Hospitals & Asylums

Digestion

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1st ed. HA-24-11-13, 2nd HA-30-10-19

Let food be thy medicine and medicine be thy food.
Hippocrates

Introduction

Humans require 0.7 to 3.7 liters of distilled or filtered **water** for drinking and cooking daily per person. The adult bladder holds about 400 mL of urine and the kidneys produce 1 liter of urine a day (McAninch '88: 34) from 4-6 liters of blood. Human beings can survive without food for thirty or forty days – about five weeks – but without water, life would end in three to five days. The average person's body is composed of approximately 70 percent water, although water content varies considerably from person to person, and one body part to another. Quality water is beneficial for virtually all disorders (Balch '00: 35). Each 24 hours about 100-200 grams of stool is evacuated (Jones et al '85: 301). The more fruit and vegetables eaten, the more feces excreted per bowel movement. Increasing the proportion of that food group can raise the weight of a bowel movement from the average 3 ½ to 7 ounces (100 to 200 grams) to as much as 178 or 18 ounces (500 grams) per day (Enders '15: 70, 71). Only 1 in 100 Western citizens have fewer than three bowel movements a week or more than three per day (Jones et al '85: 301).

A **calorie** is the heat required to raise the temperature of 1 gram of water 1ºC. The energy value of food and human energy requirements are expressed as caloric equivalents. Infants should be exclusively breast fed on a demand feeding schedule averaging 4 oz. six times per day at 1 month to 4.2 oz five times per day at 6 months when solid foods are introduced (Muscari '01: 306)(WHO '19). Sedentary calorie requirements in the United States for children 2-3 years is 1,000 calories, children 4-8 years 1200-1400 calories. Girls 9-13 1600 calories. Boys 9-13 1800 calories. Girls 14-18 years 1800 calories. Boys 14-18 years 2200 calories. Females 19-30 years 2000 calories. Males 19-30 2400 calories. Females 31-50 years 1800 calories. Males 31-50 2200 calories. Females 51+ years 1600 calories. Males 51+ years 2000 calories. Good nutrition is the foundation of health and well-being for all (Balch '00: 3)(WHO '19: 6). Everyone needs four basic nutrients – water carbohydrates, proteins and fats – as well as vitamins, minerals and other micronutrients. The human body is two-thirds water (Balch '00: 3). Fatty acids are used by the body as a source of energy and are provided for in our diet by animal fat and vegetable oils that when metabolized supply 9 cal/g. Proteins, are complex chains of amino acids, supplied chiefly by animal proteins –meat, milk, cheese and eggs – and plants such as rice and legumes and nuts, that when metabolized yield 5 cal/g. Carbohydrates are complex compounds made up

of sugars that when metabolized yield 4 cal/g.

Protein and calorie requirements vary, with pregnant and lactating women, children, teenagers and young adults and strenuous exercise requiring larger amounts. Pregnant and lactating women in emergency settings should be provided with an extra liter of water and fortified blended food commodities, in addition to the basic general ration, that are designed to provide 10–12% (up to 15%) of energy from protein and 20–25% of energy from fat. The fortified blended food should be fortified to meet two thirds of the daily requirements for all micronutrients (WHO '19: 145). Teenagers and young adults also require extra food. Cheese sandwiches. Beyond infancy a child requires about 10 percent of caloric intake in protein. Protein deficiency, especially during the first year of life, has been associate with decreased brain development and lowered IQ (Elvin-Lewis ’77: 201, 200). The amount of protein in a mother’s breast milk is 5 percent of calories. According to the World Health Organization (WHO) the human minimum protein requirement is 5 percent of total calories, according to the US Recommended Dietary Allowance for adults 10 percent of total calories. For optimum protein intake WHO recommends 10-15 percent of calories (Robbins ’01: 71, 67). Total fat intake should be less than 30 percent of total energy intake, Saturated fatty acid intake should be less than 10 percent of total energy intake. Trans-fatty acid intake should be less than 1 percent of total energy intake (WHO '19: 24). At least 1 percent of calories should come from fat. Therefore, 55-75 to 94 percent of calories in the diet should come from carbohydrates.

Calcium + vitamin D + phosphorus = Apatite. Bones and teeth contain 99 percent of all the body’s calcium and phosphorus, that is where the body gets it. For osteoporosis therapeutic and preventive measures should emphasize adequate intake of calcium (1500 mg/day), vitamin D (400-800 IU/day) and 1,000-1,250 mg/day of phosphorus (Fishman ’06: 95, 96). Calcium supplementation is recommended for postmenopausal women, to promote the formation of calcium, vitamin D and phosphorus into apatite, to reverse osteoporosis and heal bones and tooth enamel. Brush teeth within ten minutes of eating sugar. Although inadequate amounts of protein will cause loss of strength, the body cannot use excess protein, rather, it is converted into nitrogenous wastes that burden the kidneys and is eventually passed from the body, taking calcium with it. A number of studies have linked the overeating of protein to the rise in osteoporosis. Although scientists have long known that osteoporosis results from reduced calcium in the bones, they are now coming understand that one of the main causes of calcium deficiency is too much protein in the diet (Swami '06: 11). Excess calcium is also excreted in the urine. Dietary calcium is essential to fuel healthy apatite (appetite) formulation every majority carbohydrate meal. WHO may wish to edit *Essential Nutrition Actions: Mainstreaming Nutrition Through the Life-Course* (2019) to prescribe a Calcium Supplement, to prevent osteoporosis, especially for postmenopausal women (WHO '06: 103).

Doctors are expected diagnose and treat the **double-burden of malnutrition** and over-nutrition, and diet-related noncommunicable diseases, including diabetes. The 2019 guide aims to address the double burden of treating people who are underweight and overweight and provides countries with a roadmap for better interventions. Malnutrition includes stunting, wasting, underweight, micronutrient deficiencies, overweight and obesity (among both children and adults), and associated chronic conditions such as diabetes, cardiovascular disease and some cancers. Malnutrition, in one form or another, is estimated to affect one in three people globally and is linked to morbidity and mortality. Child stunting is low height-for-age. Child wasting is low weight-for-height. Child overweight means high weight-for-height. Adult obesity is defined carrying excess body fat with a body mass index equal to or higher than 30 kg/m^2. Diet is an important factor for many non-communicable conditions including heart disease, stroke, cancer,

diabetes and chronic lung disease (WHO '19: 6).

Globally, **stunting** has been declining; between 1990 and 2018, the prevalence of stunting in children aged under 5 years declined from 39.3% to 21.9%, representing a decrease in the number of children with stunting from 253.4 million to 149.0 million (14). However, global estimates mask much slower progress in Africa (42.6% to 33.1%) and South-East Asia (49.6% to 31.9%). Wasting still affects 49.5 million children aged under 5 years (7.3%) worldwide, with more than half of these children residing in South-East Asia. During this same period, overweight has been increasing; the prevalence of children considered overweight rose from 5.0% to 5.9% between 1990 and 2018, an increase of over 9 million children (from 30.9 million in 1990 to 40.1 million in 2018). Among adults, the most recent data available from 2014, indicate that 462 million are underweight, while 1.9 billion are overweight and 600 million of those (or approximately 13% of the world's population, a rate that doubled between 1980 and 2014) are obese. Adult overweight, obesity and diabetes are rising in nearly every region and country (WHO '19: 7).

Approximately 20% of patients who visit a primary physician's office have urologic problems (Alpers '10: 906). Gastrointestinal (GI) disease accounts for about 10% of general practitioner consultations, 8.5% of prescriptions and 8.3% of the cost of inpatient treatment. The GI is responsible 8.8% of days of certified incapacity to work and 10% of all deaths (Lewis and Elvin-Lewis '77: 272). In 2015 SSA estimated a total 8.1% of permanent disabilities were diseases of the digestive system (2.1%), genitourinary system (2.5%), endocrine, nutritional and metabolic diseases (2.7%) and infectious and parasitic disease (0.8%). Chronic **abdominal disease** is often first noted as colic that is intolerably painful with exercise, forcing the patient to curtail their athletic endeavor. Because of the complicated overlapping functions of the abdominal organs, lymphatic, biliary, urinary and digestive system clinical diagnosis begins by pinpointing the part of the abdomen where pain if felt, e.g. upper right quadrant pain (liver, gallbladder), epigastric pain (transverse colon, duodenum, stomach), left upper quadrant pain (pancreas, spleen), bladder pain, or flank pain (kidneys) (Beckmann et al '02: 91, 92).

Stone Breaker™ (Chanca piedra) cures urinary and gallstones overnight. Ingredients: Stonebreaker herb (*Phyllanthus niruri*), Hydrangea root (*Hydrangea arborescens*), Celery seed (*Apium graveolens*), Burdock seed (*Arctium lappa*); and other Ingredients: certified organic grain alcohol & distilled water. Stonebreaker costs around $10 bottle. Caution: Do not take during pregnancy and keep out of reach of children. Shake well before taking 40 drops in a full cup of water, three times per day. Gastrointestinal disease is a common side effect of antibiotics and NSAIDs. **Metronidazole** (Flagyl ER), patented in 1960, longtime generic antibiotic, is uniquely useful in the treatment of diarrhea and intra-abdominal infections (including ulcers, peritonitis, intra-abdominal abscess, liver abscess), because it is effective against antibiotic resistant *Clostridium difficile* and *Helicobacter pylori* and is the only antibiotic that is well-tolerated by the gut. Caution: do not take in the first trimester of pregnancy because it may cause neural tube defects. Alcohol consumers and pregnant women in the first trimester of pregnancy are probably the only people who might benefit from Vancomycin, until they are able to take definitive medicine. Metronidazole is a broad spectrum antibiotic and antiprotozoal is useful in the treatment of bone and joint infections, vaginalis, endocarditis, non-gonococcal urethritis, rosacea, tetanus and trichomoniasis. Metronidazole possesses bactericidal, amebicidal, and trichomonacidal action and has direct anti-inflammatory effects and effects on neutrophil motility, lymphocyte transformation, and some aspects of cell-mediated immunity. Spectrum of activity includes most obligately anaerobic bacteria and many protozoa. Inactive against fungi and viruses and most aerobic or facultatively anaerobic bacteria. Gram-positive anaerobes:

Clostridium, *C. difficile*, *C. perfringens*, *Eubacterium*, *Peptococcus*, and *Peptostreptococcus*. Gram-negative anaerobes: Active against *Bacteroides fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*, *B. ureolyticus*, *Fusobacterium*, *Prevotella bivia*, *P. buccae*, *P. disiens*, *P. intermedia*, *P. melaninogenica*, *P. oralis*, *Porphyromonas*, and *Veillonella*. Active against *Helicobacter pylori*, *Entamoeba histolytica*, *Trichomonas vaginalis*, *Giardia lamblia*, and *Balantidium coli.* Acts principally against the trophozoite forms of *E. histolytica* and has limited activity against the encysted form. Resistance has been reported in some *Bacteroides* and *T. vaginalis*. Stool cultures take up to six weeks for a laboratory confirmed diagnosis, therefore metronidazole should be prescribed to treat suspected bacterial or protozoal infection, except in the first trimester of pregnancy (Pagana '06: 901). Metronidazole must be prescribed to prevent deaths from *E. coli*, *Salmonella* and before fecal transplant, rather than some new antibiotic that has wormed its way into the literature. Doxycycline, clindamycin for children, pregnant and lactating women, to treat Methicillin resistant *Staphylococcus aureus,* Lyme disease, syphilis and bubonic plague; Ampicillin for pneumonia and meningitis; to complete the list of antibiotics that must be tried before alleging that it is a microbe and not the (for instance vancomycin for *C. difficile* or IV penicillin for Staph) prescribing physician, and pharmaceutical industry, who have evolved drug resistance. Metronidazole is not for use with alcohol or by women in their first trimester of pregnancy due to neural tube defects.

Anthelmintics eliminate parasitic worms. Most of the worms that affect man live unobtrusively in the intestine and do little to impair the health of the heir host. The common helminths, with an indication of the most effective drugs administered for treatment are roundworms or trematodes *Ascaris* by piperazines, *Trichinella* by prednisone, *Trichuris* or whipworms and *Strongyloides* by thiabandazole, hookworms by tetrachloroethylene, *Enterobius* or pinworms by bacitracin, tapeworms or cestodes *Taenia* spp. by niclosamide or dichlorophen and trematodes or flukes (schistosomiasis by antimony). An anthelmintic drug must have a wide margin of safety between its toxicity to the worm and its toxic side effects to the host. To be effective they should orally active, produce results in a single dose, and be cheap. Schistosome and soil-transmitted helminth (roundworms, hookworms and whipworms) infections are among the most common infections in developing countries and can cause internal bleeding, leading to anemia. They can also cause malabsorption of nutrients, diarrhea and vomiting, and loss of appetite, further damaging nutritional status. Preventive chemotherapy (deworming), using annual or biannual single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for all young children (12–23 months of age), preschool (24–59 months of age), school-age children (5–12 years) and non-pregnant women (15-49) living in areas where the baseline prevalence of any soil-transmitted infection is 20% or more among children, in order to reduce the worm burden of soil-transmitted helminths. Anthelminthic medicines must not be given during the first trimester (WHO '19).

Exclusive breastfeeding – defined as the practice of only giving an infant breast milk for the first 6 months of life – has the single largest potential impact on child mortality of any preventive intervention. Together with appropriate complementary feeding, breastfeeding has the potential to reduce mortality among children under 5 years of age by 19%. Exclusive breastfeeding reduces the risk of gastrointestinal infection and of all-cause mortality, and protects infants from respiratory infections. Exclusive breastfeeding also has a protective effect against obesity later in life. Key recommendations are to support the Baby-Friendly Hospital Initiative, monitor the *International Code of Marketing of Breast-milk Substitutes* and subsequent World Health Assembly resolutions, to limit marketing of formula milk and improve maternity protection through the workplace (e.g. 6 months of mandatory paid maternity leave and polices to encourage women to breastfeed in the workplace), to empower women to exclusively breastfeed

(WHO '19: 34-44). The United States currently does not pay for 12 weeks of maternity leave, but protects the mother from wrongful termination of employment. A woman is entitled to 14 weeks paid leave Maternity Protection pursuant to ILO Convention No. 183 (2000). Six months is 24 weeks. There is now credible medical evidence that a woman should exclusively breastfeed for the first six months. WHO has specifically explained that this justifies for 6 months of mandatory paid leave. Therefore the unemployment compensation program needs to estimate the costs of 24 weeks paid maternity protection based on the 6-months of exclusive breastfeeding ruling to update Maternity Protection ILO Convention No. 183 (2000) in WHO *Essential Nutrition Actions: Mainstreaming Nutrition Through the Life-Course* (2019).

The *State of Food Security and Nutrition in the World: Building Climate Resilience for Food Security and Nutrition* (2018) is corroborated by the *The Report of the Secretary General on SDG Progress* (Special Edition) 2019. 821 million people – approximately 1 in 9 people in the world – were **undernourished** in 2017, up from 784 million in 2015. This represents a worrying rise in world hunger for a third consecutive year after a prolonged decline. Government spending on agriculture compared to agriculture's contribution to the total economy has declined by 37 per cent; the ratio fell from 0.42 in 2001 to 0.26 worldwide in 2017. In addition, aid to agriculture in developing countries fell from nearly 25 per cent of all donors' sector-allocable aid in the mid-1980s to only 5 per cent in 2017, representing a decrease of $12.6 billion. While progress continues to be made in reducing child stunting, levels remain unacceptably high. Nearly 151 million children under five – or over 22% – are affected by stunting in 2017. Wasting continues to affect over 50 million children under five in the world and these children are at increased risk of morbidity and mortality. Furthermore, over 38 million children under five are overweight. Adult obesity is worsening and more than one in eight adults in the world – or more than 672 million – is obese (Guterres '19: 7, 8).

Improved drinking water and sewage treatment is attributed with a 20 year increase in life-expectancy. SDG Goal 6 Ensure availability and sustainable management of water and sanitation for all. Despite progress, billions of people still lack safe water, sanitation and hand-washing facilities. Data suggests that achieving universal access to even basic sanitation service by 2030 would require doubling the current annual rate of progress. Following several years of steady increases and after reaching $9 billion in 2016, ODA disbursements to the water sector declined by 2 per cent from 2016 to 2017. However, ODA commitments to the water sector jumped by 36 per cent between 2016 and 2017, indicating a renewed focus by donors on the sector. Of 172 countries, 80 per cent have medium-low implementation or better of integrated water resources management. However, 60 per cent of countries are unlikely to reach the target of full implementation by 2030 (Guterres '19). UN Water is a lye and must improve water quality statistics by dropping the soap where there is no wastewater treatment. UN Water must publish and spend their contributions on water quality testing equal or better than Environmental Protection Agency (EPA) **Primary and Secondary Drinking Water Regulation**.

The *FAO/WFP Joint Assessment of Democratic People's Republic of Korea* (2019) estimated that 10.1 million people are food insecure and in urgent need of assistance, including 7.5 million PDS dependents and 2.6 million farmers. The food gap stands at 1.36 million mt for the whole marketing year 2018/2019. 2-3 million North Koreans died from **famine** 1994-1996. The Secretary of State must pay $2.1 billion (FY 20) to restart P.L. 480 International Agricultural Assistance Program discontinued FY 18. He also owes $1.1 billion to settle UN regular budget arrears and current year contribution. $1 billion more arrears are owed dues to discrimination against United Nations Educational, Scientific and Cultural Organization and United Nations Relief (UNESCO) and Works Administration for the Relief of Palestine Refugees in the Near

East (UNRWA) FY11 and FY19. Program levels must be re-estimated from $56.0 billion FY 16, with 2.5% annual growth for all programs, 3% for P.L. 480, to **$61.6 billion FY 20**, including arrears, $60.6 billion FY 21 less $6 billion treason in *State Department, Foreign Relations and Related Organizations* for the Fiscal Year.

The unsaid law of the land, parking agricultural and urban development is '**zero net land degradation**, despite increasing population, by eliminating waste and improving land and soil quality.' By 2050 the Food and Agriculture Organization estimates the population demand for food will increase 60% from 2005. To keep net agricultural land degradation at zero, while feeding a growing population, the strategy is to increase productivity by eliminating waste and improving land and soil quality. Fruit, vegetables and grains are more efficient sources of nutrition than livestock. To improve land use efficiency and soil quality by reducing pesticide used on animal feeds, the healthy solution to the thousands of year old dispute regarding grain fattened livestock with hungry poachers wrongfully advocating the slaughter of livestock is to 'feed the people the grain and livestock the hay'. North American producers of Genetically Modified (GM) Roundup Ready crops must be clearly labelled because they are prohibited by the Convention on Biological Diversity (CBD) (1992), Cartagena Protocol on Biosafety to the CBD of 2000 and Nagoyo Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising form the Their Utilization to the CBD of 2010. Silage producers must reduce pesticide use so their grain would be fit for human consumption to increase yield, improve land and soil quality, eliminate livestock fattening with grain, improve hay quality. Government cheese could be re-cultured to eliminate waste and end the circulation of expired dairy products for six days by the food bank; government cheese is fondly remembered. The oldest grievance is the burning of the food forests by warring city-states left everyone dependent on the market-economy for their food. In 2017 an acre of National Forest was 65 times more likely to burn than an acre of National Park. To prevent agricultural fire Congress must replant the Forest Service budget in the Interior Department. Congress must protect 'urban drinking watersheds' from entry and access instead of National Scenic Rivers, to make it easy for pedestrians to camp on public lands for free pursuant to amendment of 36CFR261.58 (e, z).

Grade A farmland is flat. Urban developers also need flat land. Disputed arable low elevation valleys are to grow a mix of fruit and nut trees to camp under, in a native berry ecosystem, on private and public park-land, without the clearcutting and tilling that leaves vegetable beds too buggy for sleeping; and the chemical fertilizers, lye and concentrated animal feeding operations that leave the irrigation water un-potable. The organic certification program estimates that it takes three lean years for soil to recover from chemical farming. Homes, gardens, fields of grain, free range chickens, open range livestock and apiaries are located between orchard trees planted on the fringes of native forests. Cities must grow vertically and invest in clean energy efficient technology. Cities must protect drinking water sources and treat wastewater. Cities must re-plant native trees to absorb carbon dioxide so the people can breathe. Cities must plant fruit and nut trees to feed the population. Cities must provide free camping for pedestrians, with sidewalks and public transportation, to and from trails to surrounding wildernesses, to live in harmony with nature. To cultivate edible organic parklike settings, with a canopy, understory, and fields, **permaculture** design principles must be given land tenure. Sustainable Development Goal 2 End hunger, achieve food security and improved nutrition and promote sustainable agriculture; challenges Goal 2.4 By 2030 ensure sustainable food production systems and implement resilient agricultural practices that increase productivity and production, that help maintain ecosystems, that strengthen capacity for adaptation to climate change, extreme weather, drought, flooding and other disasters and that progressively improve land and soil quality.

I. Water

1. Clean Water

Humans require 0.7 to 3.7 liters of distilled or filtered **water-use** for drinking and cooking daily per person. The average household uses more than 500,000 liters of water per year. That's an average of 340 liters each day. 10% of water is used in the kitchen and for drinking. 30% for toilet flushing, 30% for showers and baths, 5% for cleaning and 20% for laundry. This does not include irrigating lawns and gardens. In drought stricken lands native ground-cover is encouraged to eliminate the need for watering lawns. Households use a variety of water filtration technologies, costing from $20 to nearly $1,000, that force water through a membrane and sterilize with UV light all the water used by that household at little to no extra cost. The source can be municipal water supply, well or home delivery. Care must be taken to prevent source contamination by groundwater injection of any contaminant into the water line and also be aware that drought and flood can ruin water quality. Common causes of wasted water at home include leaking faucets, faulty plumbing, and the over-use of water for watering lawns and washing cars. In arid regions it has been recommended that yards be planted with native species to conserve water demand. Livestock are responsible for somewhere between 20% and 33% of the fresh water usage in the world, and livestock, and the production of feed for them, occupy about a third of the earth's ice-free land. Irrigating farms and watering lawns account for more than half of fresh water usage and industrial contamination of the water supply.

More than 70% of the Earth's surface is covered by water. About 97.2% of all the world's water is located in the oceans. Of the other 2.8%, all but less than one-half of one percent is tied up in ice caps and glaciers. The total amount of **usable water** is only about 0.003% of the total water supply on Earth. Of all the fresh water in the world, two-thirds is underground. The underground areas of soil and rock where there is a large quantity of water are called aquifers. The places where this water comes naturally to the surface are called springs. Most bottled water (75%), including spring water and mineral water, originates as groundwater. It is filtered, sterilized with UV light and/or boiled to prevent bacterial regrowth. There is just about the same amount of water on the Earth now as there was when the Earth was formed more than four and a half billion years ago. The same water molecules have been moving about the Earth for all those years. The endless circulation of water from the atmosphere to the Earth and back to the atmosphere is called the hydrologic cycle. At any given time, about 5 liters of every 100,000 are in motion. There are three basic steps to the **hydrologic cycle**: evaporation and transpiration; condensation and precipitation; and percolation and surface runoff. The hydrologic cycle is the manner in which water from the sea, lakes, streams, rivers and moisture transpiring from the ground and plants, evaporates to be re-precipitated as rain, snow, or dew. Precipitation on land runs off in streams and rivers, and most eventually returns to the sea. Some, however, soaks into the ground, to seep downwards into the rocks as groundwater. The obvious water is that which we see on the surface in the form of lakes and streams, but groundwater makes up 97% of all fresh water in the United States. Tap water comes from either groundwater or surface water supplies.

Good **protection of water sources** is essential to the cost-effective provision of safe water. Urban drinking watersheds are protected against all trespassing to amend 36CFR261.58(z), it does not need to be re-explained that National Scenic Rivers are occupied and used for camping under 36CFR261.58 (e, z). Animal-raising operations (pigs, chicken, cattle) can be a major source of nutrient overload in water, particularly when large quantities of manure are mixed with water and sprayed on land and some of this material leaches into ground water or runs off into streams. Cattle grazing on steep slopes can increase runoff and sedimentation of streams.

Feedlots and factory farms can contaminate water with fecal matter that may carry bacteria such as *E. coli* or pathogens such as *Cryptosporidium*. Runoff triggered by rain or melting snow on cleared farmlands may wash sediment into water. Pesticides and herbicides can leach into groundwater or wash into streams or storm sewers (urban lawns, golf courses, parks and gardens are also common sources). Gravel pits or other digging operations can disturb soils, causing sediment to wash into nearby water bodies, or expose groundwater and surface water to other contaminants such as acid-generating waste rock. Cleared land for urban developments may leave soil exposed for months at a time, leading to significant amounts of sediment washing into streams. Poorly constructed or uncapped wells are common avenues by which groundwater contamination can occur. Roads, parking lots, airports and other paved surfaces can accelerate runoff into nearby waters. The faster and heavier the runoff, the more debris, including sediment and pollutants, is carried into the water. Logging and associated road building can increase erosion and turbidity and, in some cases, cause algal booms. Forest fires, like prairie grass fires, can burn off ground cover, leading to increased erosion. From cars to factories, pollutants pumped into the air can mix with rainwater or snow or be carried by wind into water bodies. A variety of chemical and other contaminants found in sewage and industrial effluents can enter water bodies that also serve as drinking water sources.

Several years ago, Flint, Michigan, decided to reopen a water treatment plant on a local river in order to stop paying to import water from Detroit. Although the water treatment facility was obviously dilapidated they opened on schedule. The facility does not seem to have passed or undergone any sort of routine water testing by a competent authority. The water initially came out brown. It caused a number of deaths from Listeria and tests showed that children had been exposed to high level of lead. Despite mounting evidence the city continued to pump water from the local river. When CDC came to investigate they were turned away. The operation continued for several years, until ultimately the town reverted to importing Detroit water, and all is well, if you have a good water filter. No religion seems to have a prayer for water, nor prescribes a method for filtering or otherwise purifying water. Even Mormon prophet Joseph Smith, who was a **water diviner** by trade, did not advocate any method of filtering, purifying or even discovering good water in his religious teachings. Smith went so far backward in his religious treatment of water, to prohibit hot drinks as being sinful like alcohol, the usual methods of preventing the most dangerous types of infectious diarrhea on the frontier. Although a fine clean cheesecloth might be useable as a water filter, there is no historical record of cloth being used to filter water. A good source, a few hours for the sediment to settle, non-toxic pipes and 19th century bleachery are all the clean drinking water pre-modern history provides. The coffee cone and filter was not invented until after the First World War and has still not come into common use filtering tap-water for use as filtered drinking and cooking water. The difference between untreated water, municipal water treatment and point-of-use filtration is the distinction between gastrointestinal infection being the leading cause of illness and frequent cause of death in least developed countries, chronic gastrointestinal disease in people who do not drink medicinal quality point-of-use filtered water in industrialized countries with improved municipal drinking water supplies, and the ability to recover stool consistency between bouts of indigestion from random particles in water, spoiled food and gastrointestinal infection. It is essential for human health that gastrointestinal patients unsatisfied with their stool quality, consumers, cooks and drinking water providers, filter potable water or purchase professionally bottled distilled or filtered spring water for human consumption. The only other essential medicine for the treatment of bacterial or protozoal intestinal, renal, abdominal, ulcerative and joint disease is **metronidazole**. The prescription for metronidazole definitely requires support against misleading antibiotic resistance propaganda regarding forgettable unproven medicines, that were recently reported to contribute to the death of patients sickened by *Salmonella* in beef products in

the US and Mexico, after the deportation of slaughter house workers, *E. coli* and also maybe cholera treated with Oral Rehydration Salts (ORS). Metronidazole is the only antibiotic that does not cause antibiotic associated colitis. Metronidazole causes neural tube defects if taken in the first trimester of pregnancy, and is therefore not highly advised for sexually active women of childbearing age, who might mistake their embryo for indigestion, but is safe for all other ages. Metronidazole is effective against both antibiotic resistant *Clostridium difficile* and *Helicobacter pylori*, the most dangerous infectious causes of antibiotic associated colitis, as well as all known urinary and gastrointestinal parasites smaller than worms, without dangerously depopulating the good gut flora. Metronidazole has a positive effect on stool quality, gastrointestinal and urinary health, even without probiotic yoghurt or supplement, that is otherwise absolutely essential for digestive health to repopulate gut flora, after consuming other antibiotics, that don't come with such a thorough guarantee of effectiveness against all bacterial and protozoal causes of abdominal infection. Nonetheless, probiotics and purified water are advised as adjuncts to metronidazole to cure infectious diarrhea.

Human beings can survive without food for thirty or forty days – about five weeks – but without water, life would end in three to five days. The average person's body is composed of approximately 70 percent water, although water content varies considerably from person to person, and one body part to another. The body's water supply is responsible for an involved in nearly every bodily process, including digestion, absorption, circulation and excretion. Water is also the primary transporter of nutrients throughout the body. Water helps maintain normal body temperature through sweating and is essential for carrying waste material out of the body. Approximately one pint of water is lost each day through exhaling. Therefore, replacing water that is continually being lost through sweating and elimination is very important. A drop in the body's water content causes a decline in blood volume. The lowering of blood volume in turn triggers the hypothalamus, which is the brain's thirst center, to send out the demand for a drink. This causes a slight rise in the concentration of sodium in the blood. These changes quickly trigger a sensation of thirst. Unfortunately, people often consume only enough liquid to quench a dry or parched throat, not enough to cover all of their water loss. As a result they can become dehydrated. Quality water is beneficial for virtually all disorders (Balch '00: 35).

The significance of clean water for drinking and cooking is often overlooked by laymen and medical professionals alike. The 20 year extension of life expectancy attributed to improved drinking water and sanitation since the dawn of the 20th century cannot be taken for granted in either developing countries where diarrheal disease remains a leading cause of disease and death or industrialized nations where 20% of the population are crudely estimated to suffer chronic gastrointestinal disease, partially from inadequately improved drinking water. Towards the end of the 19th century governments acted to close the gap between water and sanitation. In Great Britain public investment financed an expansion of sewerage systems. Life expectancy increased in the four decades after the 1880s by an astounding 15 years. By one estimate water purification alone explains half the mortality reduction in the United States in the first third of the 20th century. No other period in US history has witnessed such rapid declines in mortality rates. By 1920 almost every big city in today's industrial world had purified water. Within another decade most had built large sewage treatment plants that removed, treated and disposed of human waste in areas where it would not contaminate drinking water. British engineers led the way in sewer construction and separation of wastes from drinking water. In Great Britain public investment financed an expansion of sewerage systems. By 1920 almost every big city in today's industrial world had purified water. By 1930 most big cities had built large sewage treatment plants that removed, treated and disposed of human waste in areas where it would not contaminate drinking water. Primarily as the result of improvements in water purity and sewage

treatment, that is attributed with 20 year improvement in life expectancy, but also because of technological advancements in medical treatment, pharmaceutical drugs and government regulation between 1900 and 2000, life expectancy at birth in the United States and other industrialized nations increased from 47 to 77 years. Age adjusted life expectancy for people aged 65 increased more than 6 years during the twentieth century, in 2002 a 65 year old American woman could expect to live almost 20 more years and a man an additional 16.6 years.

Life Expectancy, Improved Drinking Water and Sanitation 2018

Area	Life Expec Tancy	Drinking Water (urban / rural)	Sanitation (urban / rural)	Area	Life Expec Tancy	Drinking Water (urban / rural)	Sanitation (urban / rural)
World	69	96.4 / 84.5	82.2 / 50.5	Kuwait	78.3	99 / 99	100 / 100
Africa				Kyrgystan	71.2	96.7 / 86.2	89.1 / 95.6
Americas				Laos	65	85.6 / 69.4	94.5 / 56
Asia	71.85			Latvia	74.9	99.8 / 98.3	90.8 / 81.5
Europe	77.2	99.5 / 97.6	94.2 / 88.1	Lebanon	77.9	99 / 99	80.7 / 80.7
Oceania	77.95	99.5 / 59.4	97.4 / 41.1	Lesotho	53	94.6 / 77	37.3 / 27.6
Afghanistan	52.1	78.2 / 47.0	45.1 / 27.0	Liberia	63.8	88.6 / 62.6	28 / 5.9
Albania	78.6	94.9 / 95.2	95.5 / 90.2	Libya	76.9	n/a	96.8 / 95.7
Algeria	77.2	84.3 / 81.8	89.8 / 82.2	Liechtenstein	82		
American Samoa	73.9	100 / 100	62.5 / 62.5	Lithuania	75.2	99.7 / 90.4	97.2 / 82.8
Andorra	82.9	100 / 100	100 / 100	Luxembourg	82.4	100 / 100	97.5 / 98.5
Angola	60.6	75.4 / 28.2	88.6 / 22.5	Macedonia	75.9	99.8 / 98.9	97.2 / 82.6
Anguilla	81.6	94.6 / n/a	97.6 / n/a	Madagascar	66.6	81.6 / 35.3	18 / 8.7
Antigua & Barbuda	76.9	97.9 / 97.9	91.4 / 91.4	Malawi	62.2	95.7 / 89.1	47.3 / 39.8
Argentina	77.5	99.0 / 100	96.2 / 98.3	Malaysia	75.4	100 / 93	98.1 / 95.9
Armenia	75.1	100 / 100	96.2 / 78.2	Maldives	76	99.5 / 97.9	97.5 / 98.3
Aruba	77.1	98.1 / 98.1	97.7 / 97.7	Mali	60.8	96.5 / 64.1	37.5 / 16.1
Australia	82.4	100 / 100	100 / 100	Malta	82.7	100 / 100	100 / 100

Austria	81.7	100 / 100	100 / 100	Marshall Islands	73.6	93.5 / 97.6	84.5/ 56.2
Azerbaijan	73	94.7 / 77.8	91.6 / 86.6	Martinique (France)	81.1	100 / 99.8	94 / 72.7
Bahamas	72.9	98.4 / 98.4	92.0 / 92.0	Mauritania	63.8	58.4 / 57.1	57.5 / 13.8
Bahrain	79.1	100 / 100	99.2 / 99.2	Mauritius	76	99.9 / 99.8	93.9 / 92.6
Bangladesh	73.7	86.5 / 87.0	57.7 / 62.1	Mayotte	79.5		
Barbados	75.7	99.7 / 99.7	96.2 / 96.2	Mexico	76.3	97.2 / 92.1	88 / 74.5
Belarus	73.2	99.9 / 99.1	94.1 / 95.2	Micronesia, Federated States of	73.4	94.8 / 87.4	85.1 / 49
Belgium	81.2	100 / 100	99.5 / 99.4	Moldova	71.3	96.9 / 81.4	87.8 / 67.1
Belize	74.7	98.9 / 100	93.5 / 88.2	Monaco	89.4	100 / n/a	100 / n/a
Benin	62.7	85.2 / 72.1	35.6 / 7.3	Mongolia	70.2	66.4 / 59.2	66.4 / 42.6
Bermuda	81.5			Montenegro		100 / 99.2	98 / 92.2
Bhutan	71.1	100 / 100	77.9 / 33.1	Montserrat	74.8	99 / 99	
Bolivia	69.8	96.7 / 75.6	60.8 / 27.5	Morocco	77.3	98.7 / 65.3	84.1 / 65.5
Bonaire, Sint Eustatius and Saba				Mozambique	54.1	80.6 / 37	42.4 / 10.1
Bosnia & Herzegovina	77.1	99.7 / 100	98.9 / 92	Namibia	64.4	98.2 / 84.6	54.5 / 16.8
Botswana	63.8	99.2 / 92.3	78.5 / 43.1	Nauru	67.8	96.5 / n/a	65.6 / n/a
Brazil	74.3	100 / 87	88 / 51.5	Nepal	71.3	90.5 / 91.8	56 / 43
British Virgin Islands	78.9		97.5 / 97.5	Netherlands	81.5	100 / 100	97.5 / 99.9
Brunei	77.5			New Caledonia	78	98.5 / 98.5	100 / 100
Bulgaria	74.8	99.6 / 99	86.8 / 83.7	New Zealand	81.4	100 / 100	
Burkina	61.8	97.5 /	50.4 / 6.7	Nicaragu	73.7	99.3/	76.5 / 55.7

Faso		75.8		a		69.4	
Burma (Myanmar)	68.6	92.7 / 74.4	84.3 / 77.1	Niger	56.3	100 / 48.6	37.9 / 4.6
Burundi	61.4	91.1 / 73.8	43.3 / 48.6	Nigeria	59.3	80.6 / 57.3	32.8 / 25.4
Cabo Verde	72.7	94 / 87.3	81.6 / 54.3	Niue		98.4 / 98.6	100 / 100
Cambodia	65.2	100 / 69.1	88.1 / 30.5	Northern Mariana Islands	75.6	97.5 / 97.5	79.7 / 79.7
Cameroon	59.4	94.8 / 52.7	61.8 / 26.8	Norway	82	100 / 100	98 / 98.3
Canada	82	100 / 99	100 / 99	Oman	75.9	95.5 / 86.1	97.3 / 94.7
Cayman Islands	81.4	97.4 / n/a	95.6 /n/a	Pakistan	68.4	93.9 / 89.9	83.1 / 51.1
Central-African Republic	53.3	89.6 / 54.4	43.6 / 7.2	Palau	73.6	97 / 86	100 / 100
Chad	57.5	71.8 / 44.8	31.4 / 6.5	Palestine	75.4	50.7 / 81.5	93 / 90.2
Channel Islands (UK)	80.55			Panama	78.9	97.7 / 88.6	83.5 / 58
Chile	79.1	99.7 / 93.3	100 / 90.9	Papua New Guinea	67.5	88 / 32.8	56.4 / 13.3
China	75.8	97.5 / 93	86.6 / 63.7	Paraguay	77.6	100 / 94.9	95.5 / 78.4
China, Hong Kong	83.1			Peru	74.2	91.4 / 69.2	82.5 / 53.2
China, Macau	84.6			Philippines	69.6	93.7 / 90.3	77.9 / 70.8
Colombia	76.2	96.8 / 73.3	85.2 / 67.9	Poland	77.9	99.3 / 96.9	97.5 / 96.7
Comoros	64.9	92.6 / 89.1	48.3 / 30.9	Portugal	80.9	100 / 100	99.6 / 99.8
Congo, Republic of	60.3	95.8 / 40	20 / 5.6	Puerto Rico (USA)	81		99.3 / 99.3
Congo,Democratic Republic of the	58.1	81.1 / 31.2	28.5 / 28.7	Qatar	79	100 / 100	98 / 98
Cook Islands	76.2	99.9 / 99.9	97.6 / 97.6	Reunion		99.2 / 97.8	98.4 / 95.3
Costa	78.9	99.6 /	95.2 /	Romania	75.6	100 / 100	92.2 / 63.3

Rica		91.6	92.3				
Cote d'Ivoire	60.1	93.1 / 68.8	32.8 / 10.3	Russia	71.3	98.9 / 91.2	77 / 58.7
Croatia	76.3	99.6 / 99.7	97.8 / 95.8	Rwanda	64.5	86.6 / 71.9	58.5 / 62.9
Cuba	78.9	96.4 / 89.9	94.4 / 89.1	Saint Helena	79.8		
Curacao	78.6			Saint Kitts & Nevis	76.2	98.3 / 98.3	
Cyprus	79	100 / 100	100 / 100	Saint Lucia	78.1	99.5 / 95.6	84.7 / 91.9
Czechia	78.9	100 / 100	99.1 / 99.2	Saint Pierre and Miquelon	80.7		
Denmark	81	100 / 100	99.6 / 99.6	Saint Vincent and the Grenadines	75.8	95.1 / 95.1	
Djibouti	64	97.4 / 64.7	59.8 / 5.1	Samoa	74.2	97.5 / 99.3	93.3 / 91.1
Dominica	77.4	95.7 / n/a	n/a	San Marino	83.4		
Dominican Republic	71.3	85.4 / 81.9	86.2 / 75.7	SaoTome e Principe	65.7	98.9 / 93.6	40.8 / 23.3
Ecuador	77.1	93.4 / 75.5	87.0 / 80.7	Saudi Arabia	75.7	97 / 97	100 / 100
Egypt	73.2	100 / 99	96.8 / 93.1	Senegal	62.5	92.9/ 67.3	65.4 / 33.8
El Salvador	75.1	97.5 / 86.6	82.4 / 60	Serbia	75.9	99.4 / 98.9	98.2 / 94.2
Equatorial Guinea	65	72.5 / 31.5	79.9 / 71	Seychelles	75.2	95.7 / 95.7	98.4 / 98.4
Eritrea	65.6	73.2 / 53.3	44.6 / 7.3	Sierra Leone	59	84.9 / 47.8	22.8 / 6.9
Estonia	77	100 / 99	97.5 / 96.6	Singapore	85.5	100 / n/z	100 / n/a
Eswatini	57.2	93.6 / 68.9	63.1 / 56	Sint Maarten (Dutch)	78.5		
Ethiopia	63	93.1 / 48.6	27.2 / 28.2	Slovakia	77.4	100 / 100	99.4 / 98.2
Falkland Islands (Malvinas)	77.9			Slovenia	81.2	99.7 / 99.4	99.1 / 99.1

Faroe Islands	80.6			Solomon Islands	75.8	93.2 / 77.2	81.4 / 15
Fiji	73.2	99.5 / 91.2	94.3 / 88.4	Somalia	53.2	69.6 / 8.9	52 / 6.3
Finland	81.1	100 / 100	99.4 / 88	South Africa	64.1	99.6 / 81.4	69.6 / 60.5
France	82	100 / 100	98.6 / 98.9	Spain	81.8	100 / 100	99.8 / 100
French Guiana		94.5 / 75.1	94.9 / 75.8	Sri Lanka	77.1	98.5 / 95	88.1 / 96.7
French Polynesia	77.5	100 /100	98.5 / 98.5	Sudan	65.8		
Gabon	68	97.2 / 66.7	43.4 / 31.5	Sudan, South		66.7 / 56.9	16.4 / 4.5
Gambia	65.4	94.2 / 84.4	61.5 / 55	Suriname	72.8	98.1 / 88.4	88.4 / 61.4
Georgia	76.6	100 / 100	95.2 / 75.9	Swaziland		93.6 / 68.9	63.1 / 56.0
Germany	80.9	100 / 100	99.3 / 99	Sweden	82.2	100 / 100	99.2 / 99.6
Ghana	67.4	92.6 / 84	20.2 / 8.6	Switzerland	82.7	100 / 100	99.9 / 99.9
Gibraltar	79.7			Syria	75.2	92.3 / 87.2	96.2 / 95.1
Greece	78.2	100 / 100	99.2 / 98.1	Taiwan	80.4		
Greenland (Denmark)	72.9	100 / 100	100 /100	Tajikstan	68.4	93.1 / 66.7	93.8 / 95.5
Grenada	74.8	99 / 95.3	97.5 / 98.3	Tanzania	63.1	77.2 / 45.5	31.3 / 8.3
Guadeloupe	80.4	99.3 / 99.8	97 / 89.5	Thailand	75.1	97.6 / 98	89.9 / 96.1
Guam	76.4	99.5 / 99.5	89.8 / 89.8	Timor-Leste	68.7	95.2 / 60.5	69 / 26.8
Guatemala	71.8	98.4 / 86.8	77.5 / 49.3	Togo	65.8	91.4 / 44.2	24.7 / 2.9
Guinea	62.1	92.7 / 67.4	34.1 / 11.8	Tokelau		n/a /100	n/a / 90.5
Guinea-Bissau	61.4	98.8 / 60.3	33.5 / 8.5	Tonga	76.6	99.7 / 99.6	97.6 / 89
Guyana	68.9	98.2 / 98.3	87.9 / 82	Trinidad & Tobago	73.4	95.1 / 95.1	91.5 / 91.5
Haiti	64.6	64.9 / 47.6	33.6 / 19.2	Tunisia	75.9	100 / 93.2	97.4 / 79.8
Holy See				Turkey	75.3	100 / 100	98.3 / 85.5
Honduras	71.3	97.4 / 83.8	86.7 / 77.7	Turkmenistan	70.7	89.1 / 34.6	77 / 49.9

Hungary	76.3	100 / 100	97.6 / 98.6	Turks & Caicos	80.1	87 / 87	81.4 / 81.4
Iceland	83.1	100 / 100	98.7 / 100	Tuvalu	67.2	98.3 / 97	86.3 / 80.2
India	69.1	97.1 / 92.6	82.6 / 28.5	Uganda	56.3	95.5 / 75.8	28.5 / 17.3
Indonesia	73.2	94.2 / 79.5	72.3 / 47.5	Ukraine	72.4	95.5 / 97.8	97.4 / 92.6
Iran	74.2	97.7 / 92.1	92.8 / 62.3	United Arab Emirates	78.7	99.6 / 100	98 / 95.2
Iraq	74.9	93.8 / 70.1	86.4 / 83.8	United Kingdom	80.9	100 / 100	99.1 / 99.6
Ireland	81	97.9 / 97.8	89.1 / 92.9	United States	80.1	99.4 / 98.2	100 / 100
Isle of Man	81.4			Uruguay	77.6	100 / 93.9	96.6 / 92.6
Israel	82.7	100 / 100	100 / 100	Uzbekistan	74.3	98.5 / 80.9	100 / 100
Italy	82.4	100 / 100	99.5 / 99.6	Vanuatu	74	98.9 / 92.9	65.1 / 55.4
Jamaica	74.5	97.5 / 89.4	79.9 / 84.1	Venezuela	76.2	95 / 77.9	97.5 / 69.9
Japan	85.5	100 / 100	100 / 100	Viet Nam	73.9	99.1 / 96.9	94.4 / 69.7
Jordan	75	97.8 / 92.3	98.6 / 98.9	Virgin Islands USA)	79.5	100 / 100	96.4 / 96.4
Kazakhstan	71.4	99.4 / 85.6	97 / 98.1	Wallis and Futuna	80		
Kenya	64.6	81.6 / 56.8	31.2 / 29.7	Western Sahara	63.8		
Kiribati	66.9	87.3 / 50.6	51.2 / 30.6	Yemen	66.2	72 / 46.5	92.5 / 34.1
Korea, Democratic People's Republic	71	99.9 / 99.4	87.9 / 72.5	Zambia	53	85.6 / 51.3	55.6 / 35.7
Korea, Republic of	82.5	99.7 / 87.9	100 / 100	Zimbabwe	61.1	97 / 67.3	49.3 / 30.8

Source: World Statistics Pocketbook 2018 ed. UN Department of Economic and Social Affairs; CIA World Factbook

Over the past twenty years many improvements have been made to provide increasing numbers of people with access to safe water. Gains in life expectancy were initially lost to the HIV/AIDS epidemic, but universal antiretroviral drug access has turned the invariably lethal disease into a

chronic condition, life-expectancy increased by 20 years in the most infected nations. It is time to redouble global efforts to provide universal access to improved drinking water and sanitation, including sewage, garbage collection and malaria vector control. In the mid-1970s only 38% of people in non-industrialized countries had access to safe water. By 1994 this had increased to 75%. While this may be considered tremendous progress, that still leaves 25% — more than 1 billion people — without access to safe sources of water. In addition, almost half the world's entire population — about 2.4 billion people — does not have an acceptable means of sanitation. One of the results of poor sanitation and unsafe water supply is diarrheal disease. Infants, young children, and the elderly are most at risk. The World Health Organization reports that there are four billion cases of diarrhea in the world every year. Of these, 2.2 million people die as a result, and most are children under five years of age. Diarrheal disease accounts for more deaths each year than AIDS and cancer combined. With a safe water supply and adequate sanitation and hygiene, the number of cases of diarrhea could be reduced by one-quarter to one-third and mortality nearly eliminated. About 34,000 people die each day worldwide because of water, feces, and dirt related diseases. They also report that, in developing countries, 80% of illnesses are water-related. In Latin America and the Caribbean, 4% of the water supply systems in rural areas are not functioning at any given time. In Asia this figure climbs to 17% and in Africa it is roughly 30%. In non-industrialized nations, wastewater goes untreated. In Asia only about 35% of wastewater is treated and in Latin America it is only 14%. In Africa treatment of wastewater is almost non-existent. Not treating wastewater causes a serious problem of environmental exposure and drinking water contamination.

In developing countries appropriate technology options in water treatment include both community-scale and household-scale point-of-use (POU) or self-supply designs. Such designs may employ solar water disinfection methods, using solar irradiation to inactivate harmful waterborne microorganisms directly, mainly by the UV-A component of the solar spectrum, or indirectly through the presence of an oxide photocatalyst, typically supported TiO_2 in its anatase or rutile phases. Despite progress in SODIS technology, military surplus water treatment units like the ERDLator are still frequently used in developing countries. Newer military style Reverse Osmosis Water Purification Units (ROWPU) are portable, self-contained water treatment plants are becoming more available for public use. The Sawyer Squeeze and coffee cone and filter are the most cost-effective methods of water filtration on the world-wide market, that might make water filtration technology affordable to poor people in developing nations.

Sustainable Development Goal (SDG) 3.9 By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination.
Goal 6 Ensure availability and sustainable management of water and sanitation for all.
6.1 By 2030, achieve universal and equitable access to safe and affordable drinking water for all.
6.2 By 2030, achieve access to adequate and equitable sanitation and hygiene for all and end open defecation, paying special attention to the needs of women and girls and those in vulnerable situations.
6.3 By 2030, improve water quality by reducing pollution, eliminating dumping and minimizing release of hazardous chemicals and materials, halving the proportion of untreated wastewater and substantially increasing recycling and safe reuse globally.
6.4 By 2030, substantially increase water-use efficiency across all sectors and ensure sustainable withdrawals and supply of freshwater to address water scarcity and substantially reduce the number of people suffering from water scarcity.
6.5 By 2030, implement integrated water resources management at all levels, including through transboundary cooperation as appropriate.

6.6 By 2020, protect and restore water-related ecosystems, including mountains, forests, wetlands, rivers, aquifers and lakes.
6.a By 2030, expand international cooperation and capacity-building support to developing countries in water- and sanitation-related activities and programs, including water harvesting, desalination, water efficiency, wastewater treatment, recycling and reuse technologies.
6.b Support and strengthen the participation of local communities in improving water and sanitation management.

The Secretary Generals Report on SDG Progress 2019 (Special Edition) reports: Despite progress, billions of people still lack safe water, sanitation and hand-washing facilities. Data suggests that achieving universal access to even basic sanitation service by 2030 would require doubling the current annual rate of progress. More efficient use and management of water are critical to addressing the growing demand for water, threats to water security and the increasing frequency and severity of droughts and floods resulting from climate change. As of the time of writing, most countries are unlikely to reach full implementation of integrated water resources management by 2030. The global population using safely managed sanitation services increased from 28 per cent in 2000 to 43 per cent in 2015 and to 45 per cent in 2017, with the greatest increases occurring in Latin America and the Caribbean, sub-Saharan Africa and East and South-East Asia. Between 2000 and 2017, the proportion lacking even a basic sanitation service decreased from 44 to 27 per cent, yet 701 million people still practiced open defecation in 2017. In 2017, some 60 per cent of people worldwide and only 38 per cent in least developed countries had a basic hand-washing facility with soap and water at home, leaving an estimated 3 billion people without basic hand-washing facilities at home (Guterres '19: 14 - 15).

In 2016, one third of all primary schools lacked basic drinking water, sanitation and hygiene services, a affecting the education of millions of schoolchildren, but particularly girls managing menstruation, and one in four health-care facilities worldwide lacked basic water services, affecting more than 2 billion people. Approximately one third of countries have medium or high levels of water stress. Almost all countries that have registered high water stress are located in North Africa and West Asia or in Central and South Asia, and these levels indicate serious water difficulties in the supply of freshwater, at least during parts of the year. Following several years of steady increases and after reaching $9 billion in 2016, ODA disbursements to the water sector declined by 2 per cent from 2016 to 2017. However, ODA commitments to the water sector jumped by 36 per cent between 2016 and 2017, indicating a renewed focus by donors on the sector. Of 172 countries, 80 per cent have medium-low implementation or better of integrated water resources management. However, 60 per cent of countries are unlikely to reach the target of full implementation by 2030. A significant effort is needed to ensure that cooperation is operational in all transboundary basins. According to data from 67 of 153 countries that share transboundary waters, the average percentage of national transboundary basins covered by an operational arrangement was 59 per cent in the period 2017–2018, with only 17 countries reporting that all their transboundary basins were covered by such arrangements (Guterres '19: 15).

For all the money they received 2016-2017, UN Water produces a very childish test of patience, rather than information on water, or disbursement of funds received. In general, most water literature on the Internet is not attributed to a human author and is consequently difficult to cite as a literary source, in the first instance. Furthermore, UN Water must disseminate information regarding particulate limits for certain chemicals that are tested for in routine water tests, like the toxic substances listed in the EPAs *Primary Drinking Water Regulations*. To improve statistics and better live in harmony with nature, the UN should stop requiring people to use soap. Source

protection is key. Drinking water sources must be protected from contamination by human bathing, dishwashing, sewage and industrial waste and must be filtered by the consumer, whether it comes directly, or is piped, from a protected watershed or from a high-tech urban water treatment facility drawing on a navigable river or lake. Natural bathing, ass and clothes washing water sources must be protected against soap, laundry detergent, insect repellant and dishwashing dregs. In the woods, in the absence of waste-water treatment, soap, especially laundry detergent, not only pollutes the water, but smells bad. As a rule, toilet paper, soap, and laundry detergent are unnecessary and ill-advised in the woods. Toilet paper must be buried deeply in the ground under at least six inches of dirt, and maybe a heavy rock or stick, to not pop up to the surface, when a wood rat smells the feces. A six inch cat-hole is minimally necessary to uphold the no open defecation provisions. Outhouses can be dug, and re-dug, in rural areas where large groups of people live for extended periods of times. Decomposed “night-soil” is used as fertilizer in China. Certain disinfectants and disinfectant byproducts levels in drinking water are tested for by the EPA's National Drinking Water Regulations.

UN Water statistics is advised to drop the soap, protect urban drinking water sources from all entry, bathing and other contamination and/or adequately test and treat navigable river or lake water, and count the growth in public restroom and sewage treatment system coverage in urban areas. Urban drinking watersheds require protection, treatment and pipelines. Residential drinking water must be professionally tested and treated to ensure improved water quality. In urban environments human waste and waste water, must be hygienically buried by a septic system (hole in the ground) or piped to a municipal sewage treatment facility, to prevent pollution of the drinking water. Soap and detergents should not be used without a wastewater treatment system because the “lye” contaminates the water and/or soil. UN Water must distribute 2017 donations to sustain contributions and improve statistics. UN Water should sell subsidized water filtration technology to individuals, families, communities and cities in developing and industrialized nations. UN Water should solicit local and mail order standard scientific testing of water for dangerous levels of certain chemical and organic particles. UN Water must advocate for rural outhouses and hygienic urban public restrooms and sewage treatment systems to protect urban drinking water from contamination. UN Water should continue encouraging regional, national, state and local governments to promulgate sensible regulations regarding the procurement of clean water, water testing and sewage treatment.

To better protect 'urban drinking watersheds' in the United States, camping on 'National Scenic Rivers' must be defended against legislative and interpretative error: 'Use and occupancy' needs to be amended; the no trespassing language is unconstitutionally vague, even wrong, to arbitrarily and capriciously restrict the free camping on the 'National Scenic Rivers', and it must be changed to specifically protect 'urban drinking watershed' from all entry and access under 36CFR261.58(e, z). Title 16 of the US Code Chapter 1 National Park Service (2013) must be restored to create a common law with Title 54 of the US Code National Park Service and Related Organizations (2014). It is the right to bear arms on the similarly extra-territorial Wildlife Refuge that must be repealed, in its entirety, from Chapter 1 National Park Service under 16USC§1a-7b. Volunteer camp hosts typically chlorinate tap-water tastefully. It takes expensive tanks, pipes and the right amount of chlorine to chemically treat water. Municipal tap-water should not contain too much chlorine or fluoride. Cities must regularly test the levels of all regulated toxic substances in tap-water, use appropriate treatment technology and abide by all state and federal regulation. Point-of-use filtration systems for public drinking fountains, restaurants and private residences are necessary to ensure everyone consumes improved drinking water. All governments must be competent to facilitate routine local and mail-order, professional, full-spectrum, water testing on-demand.

2. Water Testing

The Federal Water Pollution Act of 1972 was intended to restore and maintain the chemical, physical, and biological integrity of the Nation's waters, and to eliminate as of 1985 all discharge of pollutants into navigable waters and the ocean, to protect and propagate fish, shellfish, wildlife and recreation, to prohibit the discharge of toxic pollutants in toxic amounts, to provide for waste treatment and address point and non-point sources of pollution under 33USC§1251. The Safe Drinking Water Act of 1974, 1984 and 1996 established the National Drinking Water Advisory Council and established regulations under 42USC§300j-5. The Safe Drinking Water Act requires the U.S. Environmental Protection Agency (EPA) to set standards for drinking water quality in public water systems entities that provide water for human consumption to at least 25 people, for at least 60 days a year. A State has primary enforcement responsibility for public water systems during any period for which the Administrator determines that such State has adopted drinking water regulations that are no less stringent than the national primary drinking water regulations promulgated by the Administrator under 42USC§300g-1. Since June 19, 1986 no person may use in any pipe or plumbing fitting or fixture, any solder, or any flux. No rule may be promulgated which authorizes any underground injection which endangers drinking water sources under 42USC§300h.

The Safe Drinking Water Act divides the water pollution into two categories: "point source pollution" and "non-point source pollution". Point sources of pollution have clear requirements. They are illegal unless people have applied for and obtained a permit to discharge, called a "national pollutant discharge elimination system" or NPDES permit (in Kentucky the permit is a KPDES permit). The act defines "non-point source pollution" as everything else that causes water pollution. Non-point sources of pollution have no requirements under the law until or unless these sources impair water quality as stipulated under the Clean Water Act's total maximum daily load (TMDL) requirement. National Secondary Drinking Water Regulations are non-enforceable guidelines regarding contaminants that may cause cosmetic effect (such as skin or tooth discoloration) or aesthetic effects (such as taste, odor or color) in drinking water. EPA recommends secondary standards to water systems but does not require systems to compl. Some states may choose to adopt them as enforceable standards.

National Secondary Drinking Water Regulation

Contaminant	Maximum Contaminant Level	Contaminant	Maximum Contaminant Level
Aluminum	0.05 to 0.2 mg/L	Iron	0.3 mg/L
Chloride	250 mg/L	Manganese	0.05 mg/L
Color	15 (color units)	Odor	3 threshold odor number
Copper	1.0 mg/L	pH	6.5-8.5
Corrosivity	Noncorrosive	Silver	0.10 mg/L

Fluoride	2.0 mg/L	Sulfate	250 mg/L
Foaming Agents	0.5 mg/L	Total Dissolved Solids	500 mg/L
		Zinc	5 mg/L

Source: EPA Office of Ground Water and Drinking Water

The Environmental Protection Agency (EPA) has set the safe limit in drinking water well for arsenic at 10 parts per billion (ppb), but in many areas around the United States, levels range from 50 to 90 ppb. In some Asian countries, the levels exceed 3,000 ppb. In one recent study mice given water containing 100 ppb of arsenic had much more serious upper respiratory symptoms when exposed to the swine flu virus than those mice who had clean drinking water. Arsenic is still however used extensively as a pesticide. Many studies show a link between concentrated animal feeding operations (CAFO) and flooding, urban living, chemicals, pollution, leaky pipes, flooding, drought and other environmental factors such as brackish water, with the contamination of drinking water, gastrointestinal ailments, cancer and other diseases. EPA has set standards for over 90 contaminants organized into six groups: microorganisms, disinfectants, disinfection byproducts, inorganic chemicals, organic chemicals and radionuclides. The European Union tests for more than 45 parameters. In Canada the testing and sampling requirements of drinking water are set out by regional testing standards.

The EPA has defined pure water as “bacteriologically safe” water, and it recommends, but does not require that tap-water has pH between 6.5 and 8.5. Local water officials or local health health departments may test tap water free of charge. Typically, however, these agencies test the water only for bacteria levels, not for toxic substances. Commercial and local state university laboratories can test water for its chemical content. The Water Quality Association is prepared to answer questions about the various types of water and methods of water treatment. The EPA operates the toll-free Safe Drinking Water Hotline, which can help to locate a local office or laboratory that does certified water testing. There are also a number of laboratories that will send a self-addressed container to fill and return by mail for testing. The cost starts at thirty-five to forty dollar per tap. Results are usually available in two or three weeks. The EPA's recommended Maximum Contaminant Levels are used to understand the results of water testing. This and other water quality information is available from NSF International (formerly the National Sanitation Foundation) and the Water Quality Association (Balch '00: 38). The EPA also publishes the MCLs online.

National Primary Drinking Water Regulations

Contaminant	Type	MCL or TT (mg/L)[2]	Potential health effects from long-term exposure above MCL	Common sources of contamination in drinking water	Public Health Goal (mg/L)[2]
Acrylamide	Organic Chemical	TT[4]	Nervous system or blood problems; increased risk	Added to water during sewage/ wastewater	zero

			of cancer	treatment	
Alachlor	Organic Chemical	0.002	Eye, liver, kidney or spleen problems; anemia; increased risk of cancer	Runoff from herbicide used on row crops	zero
Alpha/photon emitters	Radionuclides	15 picocuries per Liter (pCi/L)	Increased risk of cancer	Erosion of natural deposits of certain minerals that are radioactive and may emit a form of radiation known as alpha radiation	zero
Antimony	Inorganic Chemical	0.006	Increase in blood cholesterol; decrease in blood sugar	Discharge from petroleum refineries, fire retardants, ceramics, electronics, solder	0.006
Arsenic	Inorganic Chemical	0.010	Skin damage or problems with circulatory systems, and may have increased risk of getting cancer	Erosion of natural deposits, runoff from orchards, runoff from glass and electronics production wastes	0
Asbestos (fibers >10 micrometers)	Inorganic Chemical	7 million fibers per Liter (MFL)	Increased risk of developing benign intestinal polyps	Decay of asbestos cement in water mains, erosion of natural deposits	7 MFL

Atrazine	Organic Chemical	0.003	Cardiovascular system or reproductive problems	Runoff from herbicide used on row crops	0.003
Barium	Inorganic Chemical	2	Increase in blood pressure	Discharge of drilling wastes, discharge from metal refineries, erosion of natural deposits	2
Benzene	Organic Chemical	0.005	Anemia, decrease in blood platelets, increased risk of cancer	Discharge from factories, leaching from gas storage tanks and landfills	zero
Benzo(a) pyrene (PAHs)	Organic Chemical	0.0002	Reproductive difficulties, increased risk of cancer	Leaching from linings of water storage tanks and distribution lines	zero
Beryllium	Inorganic Chemical	0.004	Intestinal lesions	Discharge from metal refineries and coal-burning factories, discharge from electrical, aerospace and defense industries	0.004
Beta photon emitters	Radionuclides	4 millirems per year	Increased risk of cancer	Decay of natural and man-made deposits of certain minerals that are radioactive and may emit forms of radiation known as	zero

				photons and beta radiation	
Bromate	Disinfection Byproduct	0.010	Increased risk of cancer	Byproduct of drinking water disinfection	zero
Cadmium	Inorganic Chemical	0.005	Kidney damage	Corrosion of galvanized pipes, erosion of natural deposits, discharge from metal refineries, runoff from waste batteries and paints	0.005
Carbofuran	Organic Chemical	0.04	Problems with blood, nervous system, or reproductive system	Leaching of soil fumigants used on rice and alfalfa	0.04
Carbon tetrachloride	Organic Chemical	0.005	Liver problems, increased risk of cancer	Discharge from chemical plans and other industrial activities	zero
Chloramines (as Cl_2)	Disinfectant	MRDL=4.0[1]	Eye/nose irritation, stomach discomfort	Water additive used to control microbes	MRDLG=4.0[1]
Chlordane	Organic Chemical	0.002	Liver or nervous system problems increased risk of cancer	Residue of banned termiticide	zero
Chlorine (Cl_2)	Disinfectant	MRDL=4.0[1]	Eye/nose irritation, stomach discomfort	Water additive used to control microbes	MRDL=4.0[1]

Chlorine Dioxide (as ClO)	Disinfectant	MRDL=0.8[1]	Anemia, infants, young children, and fetuses of pregnant women, nervous system effects	Water additive used to control microbes	MRDL=0.8[1]
Chlorite	Disinfection Byproduct	1.0	Anemia, infants, young children and fetuses of pregnant women, nervous system effects	Byproduct of drinking water disinfection	0.8
Chlorobenzene	Organic Chemical	0.1	Liver or kidney problems	Discharge from chemical and agricultural chemical factories	0.1
Chromium (total)	Inorganic Chemicals	0.1	Allergic dermatitis	Discharged from steel and pulp mills, erosion of natural deposits	0.1
Copper	Inorganic Chemical	TT[5], Action Level = 1.3	Short-term exposure: Gastrointestinal distress. Long-term exposure: Liver or kidney damage. People with Wilson's Disease should consult their personal doctor if the amount of copper in their water exceeds	Corrosion of household plumbing systems, erosion of natural deposits	1.3

			the action level		
Cryptosporidium	Microorganism	TT[7]	Short-term exposure: Gastrointestinal illness	Human and animal fecal waste	zero
Cyanide (as free cyanide)	Inorganic Chemical	0.2	Nerve damage or thyroid problems	Discharge from steel / metal factories, discharge from plastic and fertilizer factories	0.2
2,4-D	Organic Chemical	0.07	Kidney, liver or adrenal gland problems	Runoff from herbicide used on row crops	0.07
Dalapon	Organic Chemical	0.2	Minor kidney changes	Runoff from herbicide used on rights of way	0.2
1,2-Dibromo-3-chloropropane (DBCP)	Organic Chemical	0.0002	Reproductive difficulties, increased risk of cancer	Runoff/leaching from soil fumigant used on soybeans, cotton, pineapples and orchards	zero
o-Dichlorobenzene	Organic Chemical	0.06	Liver, kidney, or circulatory problems	Discharge from industrial chemical factories	0.06
p-Dichlorobenzene	Organic Chemical	0.075	Anemia liver, kidney, or spleen damage, changes in blood	Discharge from industrial chemical factories	0.075
1,2-Dichloroethane	Organic Chemical	0.005	Increased risk of cancer	Discharge from industrial chemical	zero

				factories	
1,1-Dichlorethylene	Organic Chemical	0.007	Liver problems	Discharge from industrial chemical factories	0.1
Dichloromethane	Organic Chemical	0.005	Liver problems, increased risk of cancer	Discharge from industrial chemical factories	zero
1,2-Dichloropropane	Organic Chemical	0.005	Increased risk of cancer	Discharge from industrial chemical factories	zero
Di(2-ethylhexyl) adipate	Organic Chemical	0.4	Weight loss, liver problems and possible reproductive difficulties	Discharge from chemical factories	0.4
Di(2-ethylhexyl) phthalate	Organic Chemical	0.006	Reproductive difficulties, liver problems, increased risk of cancer	Discharge from rubber and chemical factories	zero
Dinoseb	Organic Chemical	0.007	Reproductive difficulties	Runoff from herbicide used on soybeans and vegetables	0.007
Dioxin (2,3,7,8-TCDD)	Organic Chemical	0.00000003	Reproductive difficulties, increased risk of cancer	Discharge from rubber and chemical factories	zero
Diquat	Organic Chemical	0.02	Cataracts	Runoff from herbicide use	0.02
Endothall	Organic Chemical	0.1	Stomach and intestinal problems	Runoff from herbicide use	0.1
Endrin	Organic Chemical	0.002	Liver problems	Residue of banned	0.002

				insecticides	
Epichlorohydrin	Organic Chemical	TT[4]	Increased cancer risk, stomach problems	Discharge from industrial chemical factories, an impurity of some water treatment chemicals	zero
Ethylbenzene	Organic Chemical	0.7	Liver or kidney problems	Discharge from petroleum refineries	0.7
Ethylene dibromide	Organic Chemical	0.00005	Problems with liver, stomach, reproductive system or kidneys, increased risk of cancer	Discharge from petroleum refineries	zero
Fecal coliform and *E. coli*	Microbes	MCL[6]	Fecal coliform and *E. coli* are bacteria whose presence indicates that the water may be contaminated with human or animal wastes. Microbes in these wastes may cause short term effect, such as diarrhea, cramps, nausea, headaches, or other symptoms. They may pose special health	Human and aimal fecal waste	zero

			risk for infants, young children, and people with severely compromised immune systems		
Fluoride	Inorganic Chemical	4.0	Bone disease (pain and tenderness of the bones), children may get mottled teeth	Water additive which promotes strong teeth, erosion of natural deposits, discharge from fertilizer and aluminum factories	4.0
Giardia lamblia	Microbes	TT[7]	Short-term exposure; gastrointestinal illness (e.g. diarrhea, vomiting, cramps)	Human and animal fecal waste	zero
Glyphosate	Organic Chemical	0.7	Kidney problems, reproductive difficulties	Runoff from herbicide (Roundup) use	0.7
Haloacetic acids	Disinfection Product	0.060	Increased risk of cancer	Byproduct of drinking water disinfection	N/a[9]
Heptachlor	Organic Chemical	0.0004	Liver damage, increased risk of cancer	Residue of banned termiticide	zero
Heptachlor epoxide	Organic Chemical	0.0002	Liver damage, increased risk of cancer	Breakdown of heptachlor	zero
Heterotrophic plate count (HPC)	Microbes	TT[7]	HPC has no health effects, it is an analytic	HPC measures a range of bacteria that are	N/a

			method used to measure the variety of bacteria that are common in water. The lower the concentration of bacteria in drinking water, the better maintained the water system is	naturally present in the environment	
Hexachlorobenzene	Organic Chemical	0.001	Liver or kidney problems, reproductive difficulties, increased risk of cancer	Discharge form metal refineries and agricultural chemical factories	zero
Hexachlorocyclopentadiene	Organic Chemical	0.05	Kidney or stomach problems	Discharge from chemical factories	0.05
Lead	Inorganic Chemical	TT[5], Action Level = 0.015	Infants and children, delays in physical and mental development, children could show slight deficit in attention span and learning abilities, adults, kidney problems and high blood pressure	Corrosion of household plumbing systems, erosion of natural deposits	zero
Legionella	Microbes	TT[7]	Legionnaire's Disease, a type of pneumonia	Found naturally in water, multiplies in heating systems	zero

Lindane	Organic Chemical	0.0002	Liver of kidney problems	Runoff/leaching from insecticide used on cattle, lumber, and gardens	0.0002
Mercury	Inorganic Chemical	0.002	Kidney damage	Erosion of natural deposits, discharge from refineries and factories, runoff from landfills and croplands	0.002
Methoxychlor	Organic Chemical	0.04	Reproductive difficulties	Runoff/ leaching from insecticide used on fruits, vegetables, alfalfa and livestock	0.04
Nitrate (measured as Nitrogen)	Inorganic Chemical	10	Infants below the age of six months who drink water containing nitrate in excess of the MCL could become seriously ill and if, untreated, may die. Symptoms include shortness of breath and blue-baby syndrome	Runoff from fertilizer use, leaching from septic tanks, sewage, erosion of natural deposits	10
Nitrite (measured as Nitrogen)	Inorganic Chemical	1	Infants below the age of six months who drink water containing	Runoff from fertilizer use, leaching from septic tanks, sewage, erosion	1

			nitrate in excess of the MCL could become seriously ill and if, untreated, may die. Symptoms include shortness of breath and blue-baby syndrome	of natural deposits	
Oxamyl (Vydate)	Organic Chemical	0.2	Slight nervous system effects	Runoff/leaching from insecticide used on apples, potatoes and tomatoes	0.2
Pentachlorophenol	Organic Chemical	0.001	Liver of kidney problems, increased risk of cancer	Discharge from wood-preserving factories	zero
Picloram	Organic Chemical	0.5	Liver problems	Herbicide runoff	0.5
Polychlorinated biphenyls (PCBs)	Organic Chemical	0.0005	Skin changes, thymus gland problems, immune deficiencies, reproductive or nervous system difficulties, increased risk of cancer	Runoff from landfills, discharge of waste chemicals	zero
Radium 226 and Radium 228 (combined)	Radionuclides	5 pCi/L	Increased risk of cancer	Erosion of natural deposits	zero
Selenium	Inorganic Chemical	0.05	Hair or fingernail loss, numbness in fingers or toes, circulatory	Discharge from petroleum and metal refineries, erosion of natural	0.05

			problems	deposits, discharge from mines	
Simazine	Organic Chemical	0.004	Problems with blood	Herbicide runoff	0.004
Styrene	Organic Chemical	0.1	Liver, kidney, or circulatory problems	Discharge from rubber and plastic factories, leaching from landfills	0.1
Tetrachloroethylene	Organic Chemical	0.005	Liver problems, increased risk of cancer	Discharge from factories and dry cleaners	zero
Thallium	Inorganic Chemical	0.002	Hair loss, changes in blood, kidney, intestine, or liver problems	Leaching from ore-processing sites, discharge from electronics, glass and drug factories	0.0005
Toluene	Organic Chemical	1	Nervous system, kidney or liver problems	Discharge from petroleum factories	1
Total Coliforms	Microbes	5.0percent[8]	Coliforms are bacteria that indicate that other, potentially harmful bacteria may be present, such as *E. coli*	Naturally present in the environment	zero
Total Trihalomethanes (TTHMs)	Disinfection Byproduct	0.080	Liver, kidney, or central nervous system problems, increased risk	Byproduct of drinking water disinfection	N/a[9]

			of cancer		
Toxaphene	Organic Chemical	0.003	Kidney, liver, or thyroid problems, increased risk of cancer	Runoff/leaching from insecticide used on cotton and cattle	zero
2,4,5-TP (Silvex)	Organic Chemical	0.05	Liver problems	Residue of banned herbicide	0.05
1,2,4-Trichlorobenzene	Organic Chemical	0.07	Changes in adrenal glands	Discharge from textile finishing factories	0.07
1,1,1-Trichloroethane	Organic chemical	0.2	Liver, nervous system, or circulatory problems	Discharge from metal degreasing sites and other factories	0.2
1,1,2-Trichloroethane	Organic Chemical	0.005	Liver, kidney, or immune system problems	Discharge from industrial chemical factories	0.003
Trichloroethylene	Organic Chemical	0.005	Liver problems, increased risk of cancer	Discharge from metal degreasing sites and other factories	zero
Turbidity	Microbes	TT[7]	Turbidity is a measure of the cloudiness of water. It is used to indicate water quality and filtration effectiveness (e.g. whether disease-causing organisms are present). Higher turbidity levels are often	Soil runoff	N/a

			associated with higher levels of disease-causing microorganisms such as viruses, parasites, and some bacteria. These organisms can cause short term symptoms such as nausea, cramps, diarrhea and associated headaches		
Uranium	Radionuclide	30µg/L	Increased risk of cancer, kidney toxicity	Erosion of natural deposits	zero
Vinyl chloride	Organic Chemical	0.002	Increased risk of cancer	Leaching from PVC pipes, discharge from plastic factories	zero
Viruses (enteric)	Microbes	TT[7]	Short-term exposure: Gastrointestinal illness (e.g. diarrhea, vomiting, cramps)	Human and animal fecal waste	zero
Xylenes (total)	Organic Chemical	10	Nervous system damage	Discharge from petroleum factories, discharge from chemical factories	10

Source: EPA National Primary Drinking Water Regulations

[1] Definitions: Maximum Contaminant Level Goal (MCLG): The level of a contaminant in drinking water below which there is no known or expected risk to health. MCLGs allow for a margin of safety and are non-enforceable public health goals. Maximum Contaminant Level

(MCL): The highest level of a contaminant that is allowed in drinking water. MCLs are set as close to CLGs as feasible using the best available treatment technology and taking cost into consideration. MCLs are enforceable standards. Maximum Residual Disinfectant Level Goal (MRDLG): The level of drinking water disinfectant below which there is no known or expected risk to health. MRDLGs do not reflect the benefits of the use of disinfectants to control microbial contaminants. Maximum Residual Disinfection Level (MRDL): The highest level of a disinfectant allowed in drinking water. There is convincing evidence that addition of disinfectant is necessary for control of microbial contaminants. Treatment Technique (TT): A required process intended to reduce the level of a contaminant in drinking water.

[2] Units are in milligrams per liter (mg/L) unless otherwise noted. Milligrams per liter are equivalent to parts per million (ppm).

[3] Health effects are from long-term exposure unless specified as short-term exposure.

[4] Each water system must certify annually, in writing, to the state (using third-party or manufacturers certification) that when it uses acrylamide and or epichlorohydrin to treat water, the combination (or product) of dose and monomer level does not exceed the levels specified, as follows; Acrylamide = 0.05 percent dosed at 1 mg/L (or equivalent); Epichlorohydrin = 0.01 percent dosed at 20 mg/L (or equivalent).

[5] Lead and copper are regulated by a Treatment Technique that requires systems to control the corrosiveness of their water. If more than 10 percent of tap water samples exceed the action level, water systems must take additional steps. For copper, the action level is 1.3 mg/L and for lead is 0.015 mg/L.

[6] A routine sample that is fecal coliform-positive or E. coli positive triggers repeat samples – if any repeat sample is total coliform positive, the system ha an acute MCL violation. A routine sample that is a total coliform-positive and fecal coliform-negative or E. coli negative triggers repeat samples – if any repeat sample is fecal coliform-positive or E. coli positive, the system has an acute MCL violation.

[7] EPA's surface water treatment rules require systems using surface water or ground water under the direct influence of surface water to (1) disinfect their water, and (2) filter their water or meet criteria for avoiding filtration so that the following contaminants are controlled at the following levels. Cryptosporidium: 99 percent removal for systems that filter. Unfiltered systems are requires to include Cryptosporidium in their existing watershed control provisions. Giardia lamblia: 99.9 percent removal/inactivation. Viruses: 99.9 percent removal/inactivation. Legionella: No limit, but EPA believes that if Giardia and viruses are remove/inactivated, according to the treatment techniques in the surface water treatment rule, Legionella will also be controlled. Turbidity: For systems that use conventional or direct filtration, at no time can turbidity (cloudiness of water) go higher than 1 nephelometric turbidity unit (NTU) and samples for turbidity must be less than or equal to 0.3 NTU in at least 95 percent of the samples in any month. Systems that use filtration other than the conventional or direct filtration must follow state limits, which must include turbidity at no time exceeding 5 NTU. HPC: No more than 500 bacterial colonies per milliliter. Long Term 1 Enhanced Surface Water Treatment: Surface water systems or ground water systems under the direct influence of surface water serving fewer than 10,000 people must comply with the applicable Long Term 1 Enhanced Surface Water Treatment Rule provisions (e.g. turbidity standards, individual filter monitoring, Cryptosporidium removal requirements, updated watershed control requirements for unfiltered systems. Long Term 2 Enhanced Surface Water Treatment: This rule applies to all surface water systems or ground water systems under the direct influence of surface water. The rule targets additional Cryptosporidium treatment requirements for higher risk systems, and includes provisions to reduce risks from uncovered finished water storage facilities and to ensure that the systems maintain microbial protection as they take steps to reduce the formation of disinfection byproducts. Monitoring start dates are staggered by system size. The largest systems serving at

least 100,000 people will begin monitoring in October 2006 and the smallest systems serving fewer than 10,000 people will not begin monitoring until October 2008. After completing monitoring and determining their treatment bin, systems generally have three years to comply with any additional treatment requirements. Filter Backwash Recycling: The Filter Backwash Recycling Rule requires systems that recycle to return specific recycle flows through all processes of the system's existing conventional or direct filtration system or at an alternate location approved by the state.

[8] No more than 5.0 percent samples total coliform-positive in a month. (For water systems that collect fewer than 40 routine samples per month, no more than one sample can be total coliform positive per moth). Every sample that has total coliform must be analyzed for either fecal coliforms or E. coli, if two consecutive TC-positive samples, and one is also positive for E. coli or fecal coliforms, system has an acute MCL violation.

[9] Although there is no collective MCLG for this contaminant group, there are individual MCLGs for some of the individual contaminants. Haloacetic acids: dichloroacetic acid (zero); trichloroacetic acid (0.3 mg/L). Trihalomethanes: bromodichloromethane (zero); bromoform (zero), dibromochloromethane (0.06 mg/L).

Some **undesirable substances** found in water, including radon, fluoride, and arsenic, as well as iron, lead, copper and other heavy metals, can occur naturally. Other contaminants, such as fertilizers, asbestos, cyanides, herbicides, pesticides, and industrial chemicals, may leach into ground water through the soil, or into any tap water from plumbing pipes. May of these chemicals have been linked to cancer and other disorders. Water can also contain biological contaminants, including viruses, bacteria and parasites. Other substances, including chlorine, carbon, lime, phosphates, soda ash, and aluminum sulfate, are intentionally added to public water supplies to kill bacteria adjust pH and eliminate cloudiness, among other things. A study conducted by the Natural Resources Defense Council found that 18,500 of he nation's water systems (serving 45 million Americans) violated safe drinking water laws at some point during 1994 or 1995. the council's report blamed contaminate water fro some 900,000 illnesses per year, including 100 deaths. Even if the levels of individual substances in water are well within "allowable" limits, the total of all contaminants present may still be harmful to your health.

The greatest concerns about **water quality** today focus on chorine, pesticides, and parasites. Chlorine has long been added to public water supplies to kill disease-causing bacteria. However, the levels of chlorine in drinking water can be quite high, and some byproducts of chlorine are known carcinogens. The US Environmental Protection Agency is considering steps to reduce the level of chlorine in drinking water, but is facing opposition from industry groups. The EPA must publicize the tasteful proportion of chlorine to put in water, some campgrounds and municipalities sweeten water with, and others put so much the chlorine particles the water tastes bad and cause diarrhea. Pesticides pose a risk in any area where the tap water is extracted form an underground sources. These chemicals are suspected of causing, or at least contributing to metabolic disorder and an increased incidence of cancer. The pesticide problem is a particular concern in areas where agriculture is (or was) a major part of the economy. These chemicals are persistent. Residues from the pesticides used decades ago may still be present in water coming out of the tap today, and may pose a risk to health (Balch '00: 36).

Long considered a problem limited to poor, developing countries, the presence of bacteria and parasites in drinking water – especially a parasite called *Crytosporidium*, is becoming a serious problem in the United States today. In April 1993, as many as 370,000 people in and around Milwaukee, Wisconsin, were stricken by the parasite *Cryptosporidium parvum* from the city's water supply. Thousands suffered from severe diarrhea, and up to 100 deaths were attributed to

the outbreak. Users of the public water system had to boil their tap water before using it. In New York City many people with weakened immune systems charged that *Cryptosporidium* in the water made them sick, even though local officials insist that the water is safe to drink. For people with HIV and AIDS, *Cryptosporidium* can be lethal. Like cryptosporidium, *Giardia* resists the effects of chlorine. The CDC and EPA have advised that immunocompromised individuals boil tap water for at least one minute, use an appropriate filtration system or buy quality bottled drinking water (Balch '00: 36).

More than one-third of all community water systems have been cited for failure to meet the EPAs water safety standards or treatment technique, monitoring or reporting requirements. Consumer activist Ralph Nader's Center for Study of Responsive Law issued a study in 1988 entitled Troubled Waters on Tap: Organic Chemicals in Public Drinking Water Systems and the Failure or Regulation that identified over 2,100 contaminants in tap water in the United States. According to a study released in 1995, 54 million Americans drank tap water that was contaminated by feces, radiation, lead or dangerous parasites at some time between 1993 and 1994. Municipal water utilities are now required to send an assessment of the water, including information about where it comes from, any contaminants that have been found in it, and any health risk associated with substances in the water, on the water bill. There some basic warning signs of bad water. Watch for cloudiness or murkiness in water. Chlorination can cause some cloudiness, but it usually clears if the water is left to stand whereas bacterial or sedimentary cloudiness will remain. Foaming may be caused by bacterial contamination, by floating particles of sediment, or by soaps or detergents. Bacteria can be destroyed by boiling water for at last five minutes, while sediment should settle out if you let the water stand for several hours. Strange smells or tastes in water that was previously fine could mean chemical contamination. However,, many toxic hazards that work their way into water do not change its taste, smell, or appearance (Balch '00: 36, 37).

There are six main types of **water contamination**: physical, radioactive, microbiological, disinfectants and disinfection byproducts, inorganic, and organic. Physical contamination. 1. Turbidity, or cloudiness, in water is caused by the presence of suspended particle matter such as clay, silt or microscopic organisms.Turbidity is a common problem with water as a result of soil run-off. Surface waters, there- fore, are much more likely than groundwater sources to be subject to chronic or occasional problems with turbidity. Cloudy or turbid water is a problem because the particles in the water can serve as a source of nutrients and food for any bacteria, viruses or protozoa that may be in the water. In addition, because these microorganisms attach themselves to the particles in the water, and may be obscured by them, it can be difficult to determine exactly what substances are in the water. Cloudy water can also interfere with the ability of disinfectants to eliminate pathogens in the water both before and after they enter water treatment and distribution systems. Water can contain sediment, chemicals, and all sorts of impurities that affect the taste and smell of water. Salt Water is the general term for all brackish water over 1,000 ppm (mg/L) total dissolved solids (TDS). 2. Water may become contaminated with radioactive atoms (called radionuclides) from both natural and human sources. Exposure to such radionuclides is associated with a slight in- creased risk of cancer and genetic disorders. Consuming water contributes only a very small amount of our total radiation exposure. Most radionuclides in water are there naturally as a result of the decay of uranium and thorium.

Human and animal wastes are the main sources of **microorganisms**, or microbial contaminants that can cause disease in water supplies. Improperly treated sewage, bird droppings, and runoff from farms and city streets can all introduce microorganisms into the water. Protozoa are organisms that have only one cell. Some of them are very strong and, once they enter our bodies,

can be very hard to get rid of.While many bacteria in water are quite easily killed when chlorine is added at a water treatment plant, protozoa can survive and must be removed by proper coagulation and filtration. *Giardia* is the most common protozoa found in water. It causes a gastrointestinal disease known as *giardiasis* or "beaver fever," which can last for a long time. Symptoms of *Giardia* infection may include watery diarrhea, loss of appetite, dehydration, cramps and vomiting.Wilderness campers and others who drink untreated water are most susceptible to *Giardia* exposure. Another common protozoan, *Cryptosporidium* is very resistant to chlorination, but can be killed by boiling water. In humans it causes *cryptosporidiosis,* a disease with symptoms that may include diarrhea, stomach cramps and a mild fever. These symptoms typically appear two to ten days after exposure. For people with a weakened immune system, such as people having AIDS, *Cryptosporidiosis* is 80% fatal.

Viruses are tiny organisms that invade the living cells of our bodies, reproduce and invade more cells, and soon make us sick.Viruses are responsible for the colds and flu we typically catch in the winter. More serious viruses found in water include the hepatitis A virus and several viruses that cause gastrointestinal disease. Some viruses may be killed with chlorination. Others, if they adhere to larger particles in the water, may be removed with small pore membrane filters, though this is not technically feasible for treating large volumes of water. Phytoplankton are microscopic plants that live in saltwater and freshwater bodies. If there are a lot of these plants, they may make the water look green and murky. Some phytoplankton naturally produce toxins that can damage the liver or nervous system.This may pose a danger when very large numbers of these organisms are present, as may occur in small nutrient-rich lakes, ponds and dugouts. Symptoms of exposure include fever, headache, dizziness, stomach cramps, vomiting, diarrhea, skin and eye irritations, sore throat and swollen lips. People are at greatest risk of exposure to toxic phytoplankton during blooms (quick and abundant growth of plankton in one area), which typically occur in late August and September.While it is unlikely that anyone would purposely drink the green, foul-smelling water from a lake or river during a bloom, people may accidentally ingest it during recreational activities such as swimming, canoeing or water-skiing.

Bacteria are present virtually everywhere, certain types which exist in untreated water may be pathogenic (capable of causing disease in other organisms). These bacteria can cause a variety of diseases. Infants, children, the elderly, and people with weakened immune systems are most at risk of becoming ill due to ingestion of bacteria-contaminated water. *Campylobacter jejuni,* which causes gastroenteritis (inflammation of the stomach and intestines).This bacterium is typically found in human and animal wastes, including bird droppings, and often ends up in water after a heavy rainfall. *Escherichia coli.* This bacterium is naturally present in human intestines and plays an important role in digestion. However, some forms of *E. coli* can cause gastrointestinal diseases, including a severe form of diarrhea that can lead to kidney failure and death. One way that *E. coli* ends up in water is from untreated sewage particularly runoff from a concentrated animal feeding operation (CAFO). Almost all of the 2,000 strains of *Salmonella* that have been identified can cause illness to varying degrees.The species typically found in Canada are linked to gastrointestinal illness.The effects of *Salmonella* contamination range from mild, flu-like symptoms to severe infections lasting for months, and potentially ending in death. In the early 1970s, the most common cause of water-borne disease in North America was the presence of *Shigella*. However, there hasn't been a reported outbreak of illness due to this bacterium since 1975. *Shigella* can cause symptoms ranging from mild (diarrhea, vomiting) to severe (abdominal pain, fever, bloody stools).

When **chlorine** is added as a disinfectant to water with a high organic content, a number of other substances form as a result. Called "disinfection by-products," many of these substances have

been discovered to be harmful to human health. Disinfection by-products that are formed in water as a result of chlorination include trihalomethanes (THMs), haloacetates, haloacetonitriles, haloaldehydes, haloketones and halohydroxyfuranones. THMs and haloacetates are the most common by-products found in chlorinated water. The THMs most commonly found in drinking water are chloroform, bromodichloromethane, chlorodibromethane and bromoform. Brominated disinfection by-products are considered to be among the more harmful. In the interest of protecting water as it travels through the system, a small amount of chlorine sometimes continues to be added to water at various intervals during distribution.The result, however, is that the concentration of disinfection by-products may continue to increase until the water reaches our taps. Studies have shown that, from the time that water leaves the treatment plant to the time it reaches the consumer, the concentration of disinfection by- products may increase by 25 to 100%. To avoid this, many systems add ammonia to the system. The result is that the residual chlorine combines with the ammonia to form chloramine. Chloramine is a weaker but more stable disinfectant than chlorine that controls bacteria risk while producing lower levels of THMs. It is very effective at maintaining a residual level of disinfectant in drinking water systems. Smaller communities may rely on chlorination as the only treatment step. In such cases, depending on the amount of chlorine used, the type and amount of organic material found in the raw water and the time of year, the levels of disinfection by-products are often found to be elevated. In addition to cancer, there is some concern that disinfection by-products, and THMs specifically, may be linked to reproductive health effects. A study of five thousand pregnant women in California reported that there was an association between the incidence of spontaneous abortion and the consumption of tap water. In fact, women who drank five or more glasses of cold tap water containing high levels of THMs were almost twice as likely to suffer a spontaneous abortion as those women who drank less tap water.

Alternatives to chlorine disinfection include the use of disinfectants other than chlorine, such as chloramine, chlorine dioxide and ozone, and the use of non-chemical processes, such as ultraviolet light. As compared to chlorine, ozone is equally or more effective at neutralizing bacteria, viruses and protozoa. In addition, it is effective at dealing with parasites such as *Giardia* and *Cryptosporidium*, which are highly resistant to conventional chlorination treatment. In addition to microbiological contamination, ozone is effective at removing color, taste, odor, and a range of trace organics. A significant advantage of ozone over chlorine is that the use of ozone does not result in the production of chlorination by-products. Among the drawbacks of using ozone are that it is generally more expensive than chlorine and its effectiveness is short-lived as it does not have a residual effect after the water leaves the treatment plant. Another potential drawback of ozone is that it can result in the production of some by-products, including bromate and formaldehyde, both known to cause cancer.

Inorganic, or non-living, water contaminants include various metals, fluoride and nitrates. Metals may be naturally present in water, from weathering and erosion for example, or they may be present as a result of human activities, such as mining and manufacturing. In most areas of Canada, drinking water is a minor source of exposure to metals as compared with food and air. Arsenic may enter water bodies from smelting operations, the burning of coal and waste, and dumping of industrial waste water. It may be in particles in the air, which then land in the water. It may also be present as a result of natural processes, such as weathering and erosion. Uranium may be present in water as a result of natural processes, such as weathering or erosion, or as a result of human activities, such as mining and the use of fertilizers that contain phosphate. Natural uranium is weakly radioactive. However, its toxicity, especially to the kidneys, is more of a threat to human health than is its radioactivity. Like most other metals, antimony may naturally end up in source waters as a result of weathering and erosion. Human activities, such as

mining and industrial and municipal waste water discharges, also result in antimony deposits. Household piping and non-lead solders may also be a source of antimony. Studies have shown that people exposed to elevated levels of antimony in airborne particles, such as in an industrial workplace, can experience an increase in blood pressure, heart problems and ulcers. Long-term exposure is also linked to increased incidence of menstrual problems and spontaneous abortions. Fluoride is a naturally occurring chemical contaminant of many environmental water sources, and its presence is monitored by municipal water systems, particularly if it is added after treatment to meet the recommendations of dental authorities.

Levels of **lead** in untreated water are typically low and, therefore, also low in treated water. Lead may, however, make its way into tap water from coming into contact with lead pipes and fixtures in old buildings, especially structures built before the 1950s. Lead may also be present in brass fittings, such as taps, solder that connects copper tubing and that fit some plastic pipes.The use of lead in new plumbing equipment is either banned altogether or restricted. Many municipalities have undertaken programs to remove lead from the public portion of water distribution systems.This means that lead pipes, fittings and solder were replaced right up to people's private property lines. Home- owners are responsible for removing any lead-based materials on their private property,including any piping or storage tanks underground and in their homes. Research has shown that even small amounts of lead may impact on human health. Infants and children are most at risk from exposure to lead. For this reason the drinking water guidelines set acceptable levels of lead according to children's susceptibility. Exposure to small amounts of lead over an extended period of time may affect the intellectual and neurological development of the fetus, infants and young children. Lead exposure also affects blood pressure and reproductive functions in adults.

Organic contamination is comprised of pesticides, organotins, a group of organic compounds that contain tin, and volatile organic compounds.Pesticides are chemical and biological agents that are used to control pests such as weeds, insects, rodents, fungi, bacteria and viruses. Pesticides are sprayed on farm crops and animals, lawns and gardens, and golf courses. These chemicals can easily end up in our water sources. They may enter surface waters as a result of accidental spills, improper disposal of leftover chemicals, drifting on air currents for later deposition, and runoff from fields and lawns. Pesticides can also enter groundwater sup- plies by filtering through the soil where they are applied on crops and lawns, or through leachate from landfill sites. Organotins are a group of organic com- pounds that contain tin. Volatile organic compounds.Volatile organic compounds (VOCs) are among the most frequently detected organic contaminants in groundwater.VOCs are chemicals that readily evaporate and include such substances as trichloroethylene and tetrachloroethylene. These two chemicals are found in many household products and are also used as solvents by the metal-degreasing and dry-cleaning industries. VOCs are often present at high levels in the leachate from municipal landfills.The leachate may enter ground- water or surface water, thus contaminating water supplies and potentially degrading into more toxic substances. Trichloroethylene and tetrachloroethylene are potentially harmful to human health when inhaled at high concentrations.Trichloroethylene is a probable human carcinogen; tetrachloroethylene is a potential human carcinogen. The inhalation of these chemicals when showering can also be an exposure route.

Nitrates occur naturally in water, resulting from decaying plant matter. Nitrates are also a main ingredient in commercial fertilizers and can end up in water via runoff from farmers' fields, septic systems and landfills.When homeowners apply fertilizers to their lawns and gardens, up to 50% of the nitrogen in the product ends up in nearby water sources. For bottle-fed infants, water is their primary source of exposure to nitrates. (For everyone else, food is our primary source of

exposure and water is second.) When exposed to high levels of nitrates, infants have suffered from methemoglobinemia, a life-threatening condition in which body tissues don't receive the oxygen they need to survive. Symptoms may include shock, irregular heart- beat, and severe skin discoloration. Babies under three months of age are particularly at risk, as are the fetuses of women in the last three months of their pregnancy.

There are two types of **inter-laboratory comparison** projects conducted by the International Atomic Energy Association (IAEA). One is the Water Isotope Interlaboratory Comparison (WICO), which tests laboratories' ability to conduct measurements of deuterium (2H) and oxygen-18 (18O) in water samples. Measuring these isotopes accurately allows scientists to determine the age and origin of water. The other is the International Tritium Intercomparison (TRIC), which checks laboratories' ability to measure the natural radioisotope tritium (3H) in water. Tritium measurements are used to analyze water replenishment rates and to study water younger than 60 years old. TRIC checks how precise and correct these measurements are. The most recent TRIC exercise took place in 2018 with a record participation of 90 laboratories. The largest ever global inter-laboratory comparison for stable isotopes was the most recent WICO exercise in 2016 involving 235 laboratories. Its results were published in the *Rapid Communications in Mass Spectrometry* scientific journal in November 2017. Most of the laboratories involved in WICO 2016 produced acceptable to excellent results when analyzing oxygen isotopes, and about half did when analyzing deuterium. But around 5 to 6% had unacceptably poor results. The post-WICO 2016 survey of participating laboratories supports the premise that human, technical and instrumental errors are the main drivers for poor water isotope performance (Gil '19).

3. Water Treatment

Humans require 0.7 to 3.7 liters of distilled or filtered **water for drinking and cooking** daily per person. It is possible to filter this much per person, from nature or tap, with a small water purifier in a few minutes everyday. Source water must be copious and clean enough to effectively rinse off bottling equipment. The Sawyer Squeeze is the best new water filtration technology available to backpackers. The Sawyer Squeeze is advertised to be 99% effective down to 10 microns and clean 100,000 gallons of drinking water, with only routine back-flushing. A coffee cone, with an easily replaceable filter, is as good or more effective method of water filtration than older water purifying hand pumps. Most people have purchased some sort of home water filter, with varying luck. Although all water filtration systems help to produce clean drinking water, a slow, low-volume, filtration system is needed at the point-of-use, to produce minimally clean drinking water, due to source and pipe contamination. Water filtration systems are not adequate to distill fresh drinking water from salt water >1,000 parts per million (ppm) and source water must not exceed limits of 90 contaminants tested for by the EPA. Salt water contains more than 1,000 particles per million and can only be purified by distillation. Drinking water is supposed to have less than 500 ppm. Brackish water in excess of 500 ppm, but less than 1,000 ppm, is noxious to drink, will cause diarrhea, usually a morning mush, relieving all discomfort for the rest of the day, but leaving the patient anxious and digestive tract in an unhealthy way, clogged with particles, requiring many uninterrupted gallons of pure, filtered or distilled water to flush out. Basic water treatment involves both filtration to reduce particulates by 90% and UV light or boiling to prevent bacterial regrowth. Generally, filtering water twice removes 99% of contaminants.

Drinking Water Needs by Life Stage and Gender

Life Stage	Total Water (l/d)	Life Stage	Total Water (l/d)
Infants		Females	
0-6 mo.	0.7	9-13 y.	2.1
6-12 mo.	0.8	14-18 y.	2.3
Children		19-30 y.	2.7
1-3 y.	1.3	31-50 y.	2.7
4-8 y.	1.7	51-70 y.	2.7
Males		>70 y.	2.7
9-13 y.	2.4	Pregnancy	
14-18 y.	3.3	14-18 y.	3.0
19-30 y.	3.7	19-30 y.	3.0
31-50 y.	3.7	31-50 y.	3.0
51-70 y.	3.7	Lactation	
>70 y.	3.7	14-18 y	3.8
		19-30 y.	3.8
		31-50 y.	3.8

Source: Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academies Last updated September 26, 2013

Bottled water is usually classified by its source (spring, spa, geyser, public water supply, etc.), Normally, bottled is expected to contain fewer than 250 parts per million (ppm) of total dissolved solids (TDS). Spring water is potable water that comes from any underground source but not from a public community water supply. About 25 percent of bottled waters now sold come from the public water supplies, that flow into some area's household taps. If bottled water comes from a community water system, or from a municipal source, this information must appear on the label. The spring water collected and bottled is considered natural water and must have all the same properties and be of the same composition and quality as the water underground and the mineral content of the water is not altered. It may or may not ave been filtered or otherwise treated. To meet the definition of "spring water", artesian water, or artesian well water, is water drawn from a well where the water is brought to the surface by natural pressure or flow. Mineral water follows the same definition as spring water except that it is normally expected to contain more than 250 ppm of dissolved solids. If the TDS content of mineral water is below 500 ppm, the water may be labeled low mineral content. If it is greater than 1,500 ppm, the label high mineral content may be used. Purified water (defined only in US, but not in Canadian, regulations) is bottled water that has been produced by distillation, deionisation or reverse osmosis. The water can come from a spring or a public community water supply. These waters have no added minerals. When the electric charge of a molecule of water has been neutralized by the addition or removal of electrons, the resulting water is called deionized or demineralized. The deionization process removes nitrates and the minerals calcium and magnesium, in addition to the heavy metals cadmium, barium, lead, mercury and some forms of radium. Distillation involves vaporizing water by boiling it. The steam rises, leaving behind most of the bacteria, viruses, chemicals, minerals and pollutants from the water. The steam is then moved into a condensing chamber where it is cooled and condensed to become distilled water. Distilled water may contain added minerals. Flavor can be added to distilled water by adding 1 to 2 tablespoons of raw apple cider vinegar per gallon of distilled water. Lemon juice is another good flavoring agent. For added minerals mineral drops may be added to steam-distilled water. Concentrate from Trace Minerals Research is a good product for this purpose, addd 1 ¼ teaspoons of mineral drops to every 5 gallons. Carbonated bottled water is bottled water that contains natural or added

carbonation. Soda water, seltzer water and tonic water are considered soft drinks, not bottled waters (Balch '00: 40, 41).

Although **bottled water** has been available in the marketplace for many years, it wasn't until the 1970s that it started to become popular in North America. At that time, specific regulations on pre-packaged water and ice were established in the Food and Drug Regulations (Division 12). An image began to develop of bottled water as a status symbol, a lifestyle choice, a matter of convenience in our fast paced "disposable" world. Soon, due to increasing health consciousness, people began to drink bottled water as a portable beverage of choice over soft drinks, juice, beer and coffee. Then, when people first began to be concerned about the safety of their tap water, they turned to bottled water for health reasons. More recently, however, increasing health hazards and incidents related to the safety of tap water have fueled similar concerns regarding the safety of bottled water. The bottled water industry is estimated to be growing at a rate of 20% each year. Europe is, by far, the single largest market for bottled water with total consumption estimated at 27.6 billion liters per year. The US follows in distant second place, with an estimated total consumption of 11 billion liters. In 1989, Canadian bottlers sold 23 million liters of water to the US; by 1998 this figure had jumped to 272 million liters. Canadian water bottlers are now the largest suppliers of bottled water to the US. In 1995 Canadians are reported to have spent $292 million on bottled water. In 1997 the annual consumption was estimated to be 643 million liters, or 21.2 liters per person. Asia is the third largest market and is expected to grow due to its high population growth. Latin America places fourth in consumption and Canada sits in fifth position. Urban travelers should drink bottled water rather than experimenting with strange faucets. Rural travelers should bring a reverse osmosis water filter and select good water sources that have not been contaminated by large animals or industrial activity. People living near the ocean, or during periods of drought or flooding where normally good water quality is harmed, should avoid brackish water by drinking and cooking with imported bottled water.

Water that comes out of **household taps** or faucets is generally obtained, either from surface water, that has run off from ponds, creeks, streams, rivers and lakes, and is collected in reservoirs, or from ground water, water that has filtered through the ground to the water table and is extracted by means of a well. Approximately half of the tap-water in the United States coms from lakes, rivers, or other surface sources. Underground aquifers and municipal wells provide 35 percent of the tap water and the remaining 15 percent comes from private wells (Balch '00: 35). The United States has been blessed with some exceptional **underground water supplies**. The famous Dakota Sandstone, of South Dakota, at one time sustained flowing wells all the way east to the Minnesota border; but as more and more wells were drilled, this aquifer has had its pressure reduced substantially and many once flowing wells flow no more. The extensive Ogallala Formation, a huge underground lake lying beneath parts of northern Texas, Oklahoma, New Mexico, Kansas, Colorado, Nebraska, Wyoming, and South Dakota is the principal geological unit in the High Plains aquifer, which underlies 174,000 square miles. This aquifer has a maximum saturated thickness of about 1,000 feet, an average thickness of about 200 feet and contains about 3.25 billion acre-feet of drainable water. Recent count shows that more than 170,000 wells have been drilled into this aquifer for the irrigation of about 13 million acres of land that produces about 15 percent of the nation's total production of corn, wheat, cotton, and sorghum and about 38 percent of the livestock. Estimates are that about 24 million acre-feet (an acre-foot equals one foot of water, over one acre, which is 325,851 gallons) are being taken out each year. The recharge is only about three million acre feet. In places, the water in the Ogallala aquifer has dropped more than 120 feet. The U.S. Geological Survey estimates that the volume of water in storage has decreased about 166 million acre-feet up to 1980 and computer models predict a continuing loss in water. Each year it is estimated that Arizona uses 2 ½ million acre

feet more of groundwater than is replenished by natural means.

The **water-table** represents the generalized theoretical upper surface of water-saturated rocks. Rocks above the water-table are in the zone of aeration (vadose zone), because air is also present. Rocks below the water-table are saturated with water, so no air is present; this is the zone of saturation (phreatic zone). This zone passes downwards to great depths and, as it gets deeper, so the groundwater becomes more brine-like. Water near the coast is brackish; only the best groundwater can be filtered and boiled within ten miles from the ocean. Some is water squeezed out of compacting rocks, some is meteoric (rain and surface) water from above. Not all wells sunk to beneath the water-table will strike water. However, if a well is sunk through an impermeable stratum to permeable rocks beneath, water confined in those lower rocks will rise up the well to its rest level, the piezometric surface. Water-tables are not static, they fluctuate with changing seasons, rising in wet weather, falling in dry. In very dry weather, a water-table may fall so low that it falls below river level and water from the river leaks down to the water-table. Aquifer are rocks which are water-permeable; aquicludes are those which are not. Aquifers may be granular rocks of many types, particularly those sandstones and conglomerates which are sufficiently uncemented to remain permeable. Well-jointed quartzites can also be excellent water-bearing rocks, and their water is very pure.

Dug **wells** are cheap and easy to dig provided the water-table is not too deep. Pumps draw water to the surface.The water taken out is replaced with new water, often in springtime, from rainfall, melting snow and mountain streams. If too much water is pumped out of an aquifer, the spaces between the soil particles and the rocks begin to compress. Without the water to keep the spaces open, the weight of the soil and rock causes the ground to close in and the spaces are lost. Drilled wells, or boreholes, provide purer and more reliable sources of water. The bore is cased by iron pipe to prevent its walls from collapsing and to exclude water from the aerated zone and the upper part of the saturated zone. Most water boreholes are only a few hundred meters deep often much less than 200m, with a diameter of 200 mm or more. Many are drilled through an impervious stratum to reach water confined in an aquifer beneath. Water then rises up the bore to reach its rest level at the piezometric surface. Artesian conditions exist when the rest-level is above the ground surface, and the water will then flow or gush from the borehole without need of pumping. Usually, water must be pumped form the well either by hand pump, wind pump or motorized pump. Underground water is found in small openings and voids in aquifers and moves very slowly. Water is most difficult to find in areas of mica schists and phyllites where rocks are impervious and unjointed. Water occurs in the sapropelic aquifer zone, between the unaltered rock below and the completely clay-altered material above. Boreholes dug as far downslope and as far away from unweathered granitoid exposures as possible enjoy over 90% success at discovering an aquifer. The main principle in finding water is to known the geology of the area and its structure, to know what the aquifers are and where they occur and if they are subject to permanent, remedial or seasonal contamination. The problem is to find it exactly where it is wanted, at a convenient depth and in sufficient quantity to satisfy clients.

In its natural state, **groundwater** is usually quite clean and safe to drink. Water that seeps into the ground and through cracks in rock is naturally filtered by sand, soil and clay. This natural filtration process removes many microorganisms and some of the chemical contaminants that are present as a result of runoff from the land. Such filtration leaves the water cleaner than surface water. However, when groundwater becomes polluted it is very difficult to make it clean again. The amount of time that water stays under the Earth's surface varies greatly. Some groundwater stays under- ground for only a few days or a few weeks. But some water may remain under the surface as groundwater for 10,000 years or more. In comparison, the water in a river is

completely replaced with new water in about two weeks' time. Because it goes through a natural filtration process, groundwater is less likely to be contaminated with harmful microorganisms than is surface water. Some contaminants such as arsenic and nitrate are, however, more likely to be found in groundwater than in surface water. As well, surface water is more susceptible than groundwater to contamination as a result of human activity. Because it is more susceptible to bacterial and human- made contamination, surface water is typically treated at a facility before it is distributed to people in their homes and workplaces. As a rule, surface water should not be consumed without treatment. Groundwater that is at risk of contamination from surface water should be treated as if it were a surface water source. Water may also become contaminated from human sources. Human sources include garbage that is dumped into the water; chemicals that wash off lawns, roads, farms, parks and landfills and run into lakes and rivers; fuel that leaks out of underground storage tanks; and pollutants we put into the air that fall to the ground and into the water. Water treatment plants themselves can introduce substances into water. Contaminants can be absorbed by drinking or contact with skin.

There are significant differences between choosing a **water treatment device** if the source is well water versus if the source is treated municipal water. If the water source is well water, then a treatment device may be essential to, for example, soften water and remove contaminants. If the source is treated municipal water, then choosing a treatment device is a matter of choice rather than necessity. With the exception of ceramic filter and ultraviolet light devices, most home treatment systems are designed for use on water that is already treated before it arrives at individuals' homes or that is otherwise micro- biologically safe. These devices often treat only the aesthetic qualities of water. For example, they remove residual chlorine and thus improve the taste or odor of tap water. The first documented use of sand filters to purify the water supply dates to 1804, when the owner of a bleachery in Paisley, Scotland, John Gibb, installed an experimental filter, selling his unwanted surplus to the public. This method was refined in the following two decades, and it culminated in the first treated public water supply in the world, installed by the Chelsea Waterworks Company in London in 1829. Treatment for drinking water production involves the removal of contaminants from raw water to produce water that is pure enough for human consumption without any short term or long term risk of any adverse health effect. Substances that are removed during the process of drinking water treatment include suspended solids, bacteria, algae, viruses, fungi, and minerals such as iron and manganese. The processes involved in removing the contaminants include physical processes such as settling and filtration, chemical processes such as disinfection and coagulation and biological processes such as slow sand filtration.

Salt water is the general term for all water over 1,000 ppm (mg/L) total dissolved solids (TDS). Water can contain sediment, chemicals, and all sorts of impurities that affect the taste and smell of water. A combination selected from the following processes is used for municipal drinking water treatment worldwide: Softening, aeration and membranes are needed to eliminate major dissolved inorganics. Membranes are needed for minor dissolved inorganics. Pathogens are removed by sedimentation, filtration and disinfection. Major dissolved organics are removed with membranes and adsorption. Pre-chlorination for algae control and arresting biological growth. Aeration along with pre-chlorination for removal of dissolved iron when present with small amounts relatively of manganese. Turbidity and particles can be treated with coagulation / flocculation, sedimentation, or granular filtration. Coagulation for flocculation or slow-sand filtration. Coagulant aids, also known as polyelectrolytes to improve coagulation and for more robust floc formation. Sedimentation for solids separation that is the removal of suspended solids trapped in the floc. Filtration to remove particles from water either by passage through a sand bed that can be washed and reused or by passage through a purpose designed filter that may be

washable. Disinfection for killing bacteria viruses and other pathogens.

Water supplied to **domestic properties** may be further treated before use, often using an in-line treatment process. Point-of-use water treatment should be added to the faucet, if dissatisfied. Such treatments can include water softening or ion exchange. Many proprietary systems also claim to remove residual disinfectants and heavy metal ions. Home water filtration systems can provide healthy, clean drinking water that smells and tastes better. Reverse Osmosis is a process for the reduction of dissolved ions (such as salts) from water in which pressure is employed to force liquid (water) through a semi-permeable membrane, which will transmit the water but reject most other dissolved materials. When forced against the membrane surface, the dissolved materials are repelled, while the water molecules are diffused through the membrane molecule by molecule, forming purer water on the other side. Sunlight has long since been known to kill micro-organisms. The rays from the sun contain the UV *spectrum used in Ultraviolet Water Treatment Systems – although at much lower intensities. It is also referred to as either the Germicidal Spectrum or Frequency. The frequency used in killing micro-organisms is 254 nanometers (nm). The UV lamps used are designed specifically to have the highest amount of UV energy at this frequency. Filtration is a process in which water passes through a water system that may include one or more filters for the purpose of removing turbidity, taste, color, iron or odor. The design can be loose media tank-type systems or cartridge devices. In general the process may include mechanical, adsorptive, neutralizing and catalyst/oxidizing filters. Distilled water is water that has been purified by passing through one or more evaporation – condensation cycles and contains essentially no dissolved solids. Distillation requires a lot of energy to produce a small amount of purified water and is not usually sold.

There are two basic types of **home water treatment devices**: point-of-use and point-of-entry. The most common of the two types of systems, point-of-use devices are usually installed near the sink or faucet and treat only water to be used for drinking and cooking. They are called point-of-use because they are installed close to the point where the water is used. Point-of-use devices are necessary to prevent contamination of the drinking water by corrosion and sedimentation of inaccessible pipes and water supply system. Point-of-entry devices, in contrast, are installed at the point where water enters the house or building. These devices treat all incoming water, regardless of its use. Reverse osmosis systems involves forcing water through a small membrane that blocks 90% of bacteria and minerals. Reverse osmosis systems are used in portable water purifiers for hiking that cost around $50. Most systems have two additional activated carbon filters, one each on either side of the membrane, to trap any impurities that make it through the reverse osmosis membrane. Unfiltered water remains on one side of the membrane while filtered water passes through to the other side. These systems are installed most frequently under a sink, and sometimes where the water comes into the home. Reverse osmosis systems are recommended for water with a high mineral content. As they are effective at removing nitrates, they are often suitable in agricultural areas and for private water systems. An advantage of reverse osmosis systems is that the membranes last from one to eight years, depending on the quality and quantity of water being filtered.

Home Water Treatment Methods

Treatment Type	Cost	How it Works	What it Does
Activated Carbon	Faucet-mounted or pour-through unit: $20 - $60; Countertop unit:	Water is filtered through a carbon trap that absorbs the	Reduces levels of chlorine, herbicides, lead, hydrogen sulfide,

	$89 - $200; Under-sink unit: $75 - $600; Whole-house system: $499-$1,250	contaminants	and volatile organic chemicals (VOCs). Also reduces color and turbidity
Carbon filtration	Faucet-mounted unit: $25; Under-counter unit: $300 and up	Passes water through a charcoal or solid carbon block and captures contaminants. When carbon sites fill up, the cartridge is replaced.	Reduces levels of chlorine, organic chemicals, and pesticides. Also reduces bad taste and odors.
Distillation	Countertop unit: $99 - $995; Free-standing unit: $599-$1,020; Whole-house system: $799 - $4,500	Raises water temperature to boiling, leaving contaminants behind. Purified water vapor condenses to liquid.	Reduces levels of arsenic, cadmium, chromium, orin, lead, giardia cysts, nitrate and sulfate . Also reduces turbidity. Can turn salt water into drinking water.
Reverse osmosis	Countertop unit: $150 - $250; Under-sink unit: $530 - $1,500	Forces pressurized water through a contamination-rejecting membrane; sends improved water to holding tank.	Reduces levels of arsenic, cadmium, iron, chlorine, lead, giardia, giardia cysts, nitrate, radium and sulfate. Also reduces color and turbidity.
Water softener	Whole-house system: $950 - $3,500	Replaces calcium and magnesium with sodium to “soften” the water.	Reduces levels of calcium, iron and radium.

Source: Balch '00: 39

With an **activated carbon system** water passes through a filter containing granular carbon. Carbon has long been known to absorb impurities and was used by sailing ships when storing drinking water during long voyages. The carbon in the filter has been specially activated, thus increasing its capacity and tendency to attract chemicals and impurities. The carbon is often used in combination with ion exchange resins to increase the types of substances that may be removed. This is the type of filter that is often used in refillable pitchers and personal water bottles, and that is mounted onto the tap. The activated carbon system is by far the most popular choice for the average consumer. It is widely available, easy to install, and affordable. Activated charcoal systems are the least expensive filtering option, costing between $20 and $60 for the initial purchase.There are ongoing costs to replace the filters. Activated carbon systems (also referred to as activated charcoal systems, or granular activated carbon systems) can reduce, but not totally eliminate, pesticides, volatile organic compounds (VOCs), synthetic organic compounds, some radionuclides, fluoride and some metals. This type of system is best suited to areas where water comes from a treatment plant. It is not recommended for those who rely on well water. A disadvantage to this system is that the filters can actually add contaminants to the water, especially if improperly maintained. This is why it is very important to change the filters

with the frequency recommended by the manufacturer. The frequency for changing a filter depends on the amount of carbon it contains, the quality of the incoming water and the amount of water that passes through the filter. **Ceramic filter systems** are installed under a sink and attached to one faucet. They are much more expensive than activated carbon systems, which are used in refillable jugs or attached directly to the faucet. The ceramic element is designed for the removal of microorganisms. Ceramic filter systems require a lot of maintenance. They are fragile systems that need to be cleaned regularly. They are often combined with activated charcoal systems or cloth filters to remove materials such as lead.

Distilled water systems work by heating water to boiling and then cooling and condensing the steam into liquid, thus leaving behind all dis- solved minerals and bacteria. Distillation is effective at removing all non-metallic inorganics, metals, microbiological contaminants, physical contaminants, synthetic organic compounds, most pesticides and radiological contaminants. Similar to reverse osmosis units, distilled water systems can be installed either at the faucet or at the point where water enters the building. Distillation systems are most often installed at the faucet. The greatest advantage of this type of system over others is that it is the most effective at removing the largest number of chemicals. This doesn't come without significant costs, however. These systems are on the higher end of the scale when it comes to cost.They can be expensive to purchase, running to at least several hundred dollars. They are also expensive to operate as they use a lot of energy to produce only a small amount of filtered water. Another disadvantage is that the process is time-consuming, taking about eight hours to produce several liters of drinking water. the life span of the unit varies according to the type of water treated; the system lasts about 10 years with soft water but only three to four years with hard water.

Exposing water to **ultraviolet (UV) light** is effective at killing some bacteria, viruses and fungi. Lamps that contain mercury vapor are used to generate electromagnetic radiation, which acts as a disinfectant. UV light is commonly used as a disinfectant by the beverage industry. It is also commonly used in fish hatcheries to disinfect water without the use of chemicals, such as chlorine, that are harmful to fish. UV light is also used for drinking water treatment, al- though most treatment plants currently using UV are located in Europe. It is expected that increasingly more North American installations will begin using this treatment as recent research demonstrates that UV is very effective against *Giardia* and *Cryptosporidium*. Similar to ozone, however, UV light does not have a residual effect to protect water once it leaves the treatment plant. This is addressed by the addition of chlorine at low concentrations, after UV treatment, to provide residual post-treatment protection in the distribution lines. Membrane systems involve passing water through a membrane filter that has a pore size smaller than the substance being removed. Membrane filtration systems for drinking water include nano-filtration systems that remove color and THM precursors (and can also be used to soften water), ultrafiltration systems for the removal of viruses and emulsions, and micro-filtration systems for the removal of *Cryptosporidium*, *Giardia*, bacteria, iron and manganese.

Municipal water treatment is the process of cleaning the water and making sure it is safe for people to use, whether for drinking, washing,bathing or cooking. Almost every large city in the world treats its drinking water in some way. There are six basic steps in the water treatment process. Utilities use only those steps that are needed for the particular supply of water they are treating. 1. *Intake.* Water is taken from the source through a large pipe and drawn into the treatment plant. A screen at the end of the pipe prevents logs, fish, and plants from being drawn in. If the source is groundwater, the soil and rocks do the "screening" naturally as the water travels under the Earth's surface. Depending on the quality, groundwater may not require further treatment. 2. *Chemical addition.* Chemicals such as chlorine and aluminum sulphate (alum) are

added and mixed into the water. These chemicals kill bacteria in the water, improve its taste and odor, and cause any tiny particles in the water to clump together and settle. 3. *Coagulation and flocculation.* The chemicals that were added to the water cling to any substances floating in the water.The process of things sticking together like this is called coagulation.Then the particles begin to stick to each other and form larger particles.These larger particles are called floc. 4. *Sedimentation.* The water and the floc flow into a sedimentation basin.The water sits here for a time to allow the floc to settle to the bottom. In addition to removing particles from the water, this process also removes bacteria, which typically attach themselves to the particles. 5. *Filtration.* The water flows out of the sedimentation basin and into the filtration area. The water is filtered through layers of sand, gravel and other media such as anthracite or activated carbon to remove any remaining particles. 6. *Post-treatment disinfection.* The water flows from the filtration area on its way to the storage area and the distribution system. Along the way, a small amount of chlorine or other chemical disinfectant is added. The disinfectant kills any bacteria that are still in the water; a small amount remains in the water to kill any new bacteria that may be picked up while the water travels to people's homes and workplaces. 7. *Fluoridation*. Fluoride has been found to make teeth more resistant to cavities, and for this reason began to be added to drinking water in the 1940s and 1950s to achieve dental benefits. In some children, exposure to low levels of fluoride can cause moderate to severe discoloration of the teeth (fluorosis). At high levels, prolonged exposure can lead to skeletal fluorosis, a condition in which the bones become increasingly dense and brittle. Symptoms range from mild (pain and stiffness in the joints) to severe (complete rigidity of the spine, skeletal deformities, and increased risk of fractures). Water is sampled and tested at various stages throughout the treatment process. Sampling is done to make sure that all stages of the process are working properly and that the water is safe before it leaves the plant and makes it to consumers.

If **bacteria levels** in a municipality's water become too high, a "boil water advisory" may be issued for the area. Residents are typically advised to boil any water destined for cooking or drinking. A one-minute rolling boil is sufficient to kill even the most resistance pathogenic microorganisms. Microwave ovens also works, the radiation works inside the bacterial cells. Boiling water is the cheapest method of killing bacteria, and is also very effective. It is important to note, however, that boiling will only disinfect water. It will not remove most other contaminants. In some cases, for problems such as lead for example, boiling will actually concentrate the chemical. Between 1991 and 1995, Health Canada surveyed untreated and treated drinking water in 72 municipalities across Canada. Out of the 1173 samples of untreated water that they tested, 21% were contaminated with *Giardia* and 5% with *Cryptosporidium*. Out of the 423 treated water samples, 18% showed the presence of *Giardia* and 4% contained *Cryptosporidium*. Municipal water is required generally to be "softened" at the treatment plant. If your water comes from a well, however, it may have a high mineral content, also referred to as hard water. Most conditioners use an ion exchange process whereby sodium is put into the water in exchange for the calcium and magnesium that cause water hardness. This exchange process changes the chemical makeup of the water. Water softeners also remove some metals. Salt, or sodium chloride, is used to regenerate the treatment unit. Depending on the quantities and disposal techniques, disposal of the water softener salt solution back to a groundwater source may raise concerns about saltwater contamination of the aquifer. It is generally not recommended that individuals drink water directly treated by a water softener. Water to be used for drinking should by-pass the water softening system. Individuals on low-sodium diets should especially avoid softened water since the process adds sodium to the water.

Water distribution is vulnerable to toxic materials used in pipe construction, like the lead lined Roman aqueducts, decay of the pipes, and leaks and contamination of the pipes. After water is

treated it is distributed — moved from the treatment plant to people's homes and businesses. Treatment plants, reservoirs and holding tanks are built on high ground where possible. This saves energy because gravity can be relied on to naturally pull the water down from the holding areas and through the pipes to the customers. Sometimes water may be pumped uphill and then gravity is allowed to take over to feed the water back down. Similarly, pumps are used to pull water up from natural underground aquifers.They are also used in hilly places to keep water moving until it can rely on gravity once again. Water travels through large pipes called mains, or water mains. Computers are often used to control the amount of water flowing through a main at a given time. Large valves are also used to control the flow of water.Valves are like large faucet handles that can be turned off or on to varying degrees, thus regulating the water flow. If a water main breaks or there are other problems, the water for a particular area can be shut off until repairs are completed. Just as water is tested at various points in the water treatment process, it is also tested at various points in the distribution system. Sampling is done to make sure that the water is still safe when it reaches consumers. If contamination occurs within the distribution system, the testing will reveal this and steps can be taken to protect people from drinking water that isn't safe. Disinfectant is often added at various points within large distribution systems to prevent bacterial contamination.

Utilities measure the amount of water pumped each day. This is especially important when the water is drawn from a groundwater source. If too much is taken from an aquifer the ground may become too dry, compact under its own weight, and collapse, thus causing damage to any structures on the surface. Furthermore, during droughts, when wells get low, before they run dry, well water is prone to catastrophic infection by common water mold, that may cause leukemia, and other infections by *E. coli*, that elaborates toxins that can cause either infectious diarrhea or dementia depending on the strain, and other bacteria and toxic chemicals are more concentrated and pathogenic. No water treatment system is perfect. Dissatisfaction is often the result of dirty water filtration gear, that merely needs to be flushed out with reasonably good source water. Short of distillation, salty, discolored, fecal and chemical contaminated water cannot be treated, by any method of filtration. As a rule of thumb, it is best to assume that water that has been improved is 90% free of contaminants and it must filtered again to remove 99% of contaminants. Depending on the source 90% might be adequate or 99% insufficient. Discoloration and chemical contamination can only be filtered out, with certain expensive filters. Only distillation can purify "salt water".

4. Sewage Treatment

Over 75% of the nation's population is served by centralized **wastewater** collection and treatment systems. The remaining population uses septic or other onsite systems. Approximately 16,000 municipal wastewater treatment facilities are in operation nationwide. Twenty- five percent of households nationwide and one-third of the new homes being constructed are served by onsite systems. British engineers led the way in sewer construction and separation of wastes from drinking water. Towards the end of the 19th century governments acted to close the gap between water and sanitation. In Great Britain public investment financed an expansion of sewerage systems. Life expectancy increased in the four decades after the 1880s by an astounding 15 years. By one estimate water purification alone explains half the mortality reduction in the United States in the first third of the 20th century. No other period in US history has witnessed such rapid declines in mortality rates. By 1920 almost every big city in today's industrial world had purified water. Within another decade most had built large sewage treatment plants that removed, treated and disposed of human waste in areas where it would not contaminate drinking water. The relationship of cholera to water was discovered by the English physician John Snow who traced this disease from its origins in India and the path it took to Europe. Snow traced the contamination to public wells, that were bring contaminated by privy vaults in the epidemic of 1854 in London. Thus, the sewer was developed. The British engineers led the way in sewer construction and separation of wastes from drinking water. Towards the end of the 19th century governments acted to close the gap between water and sanitation. In Great Britain public investment financed an expansion of sewerage systems. By 1920 almost every big city in today's industrial world had purified water. By 1930 most big cities had built large sewage treatment plants that removed, treated and disposed of human waste in areas where it would not contaminate drinking water.

During the Neolithic period (c. 10,000B.C.E. the waste created by human activities was redressed by the movement of nomadic tribes. In the ancient world cultures developed waste treatment technologies. The City of Ur, by 3,500 B.C.E. had an average population of 65,000 people per square mile. The populace dealt with their waste by sweeping it into the streets. This caused the street levels to rise and would require, every so often the raising of the house doors. These practices were not suitable for an urban environment. Cities in the Indus basin, in current day Pakistan, from 2,500 -1,500 B.C.E. developed a high level of sanitation and had some houses with bathrooms with flushing toilets and rubbish shoots and places for rubbish were made available in public places. In the Egyptian city of Herakopolis (B.C.E 2,100) the people threw their wastes in the street but the elite made a deliberate effort to remove all wastes, organic and inorganic. Mosaic law (B.C.E. 1,300) tells "remove his own refuse and bury it in the earth". Nehemiah tells of rebuilding Jerusalem where there was a refuse gate where the city wastes were dumped and the Talmud called for the city streets to be washed daily.

In the island of Crete between 1500-1700 B.C.E. had a highly developed waste management system. They had very advanced plumbing and designed places to dispose of organic wastes. Knossos, the capital city, had a central courtyard with baths that were filled and emptied using terra-cotta pipes. They had flushing toilets, with wooden seats and an overhead reservoir. Excavations reveal four large separate drainage systems that emptied into large sewers built of stone. The Minoan royals were the last group to use flushing toilets until the re-development of that technology in 1596. The first dumps were developed by the Greeks in Athens circa 500 B.C.E. In 320 B.C.E. Athens passed the first known edict banning the disposal of refuse in the streets. By 300 B.C.E. one of the responsibilities of the Greek city-state was the removal of waste. The expenses of waste removal were covered by levees on landowners. This system

lasted 800 years, until a general breakdown in civil order. Greeks understood the relationship between water quality and public health and passed this concern to the Romans.

In the early modern period wastes were disposed of in rivers and water sources were being contaminated. These practices were brought to the New World. As developments grew into cities, the Colonies had to address the waste issues. In 1644 eighteen years after taking control of Manhattan Island "residents were directed to take all wastes out of the fort" and in 1648 a law was passed prohibiting hogs and goats from running in the streets. The major changes in waste treatment came in the 19th century. In 1860 Louis Moureas invented the septic tank however, it would not be given this name until 1895. Septic tanks at this stage were large and were used to treat sewage from communities. "the main purpose of these tanks was to removed gross solids before discharge into the nearest stream or river". Nevertheless, "effluent was largely untreated and caused pollution of rivers and streams".

Even with pre-treatment the need for disposal technology was evident. In 1869 Edward Frankland developed **trickling sand filter technology**. He devised a system consisting of six-foot high, ten-inch wide cylinders, filling each with different medias like sand and soil. He then ran sewage at different doses through the different tanks. He calculated the capabilities of the different media in purifying the wastewater. The Experimental Station at Lawrence, Massachusetts, created in 1887, by the State Board of Health worked on disposal issues. At the station in 1893 a sand bed was first used to filter effluent from a septic tank, reducing the land areas needed for sewage disposal, and the land acceptance rates were established to maintain an efficiently working sand filter.

Wastewater treatment is the process that removes the majority of the contaminants from wastewater or sewage and produces both a liquid effluent suitable for disposal to the natural environment and a sludge. Biological processes can be employed in the treatment of wastewater and these processes may include, for example, aerated lagoons, activated sludge or slow sand filters. To be effective, sewage must be conveyed to a treatment plant by appropriate pipes and infrastructure and the process itself must be subject to regulation and controls. Some waste-waters require different and sometimes specialized treatment methods. At the simplest level, treatment of sewage and most waste-waters is carried out through separation of solids from liquids, usually by sedimentation. By progressively converting dissolved material into solids, usually a biological floc, which is then settled out, an effluent stream of increasing purity is produced. Wastewater treatment is needed to protect rivers and streams for fishing, swimming and drinking water. For the first half of the 20th century, pollution in the Nation's urban waterways resulted in frequent occurrences of low dissolved oxygen, fish kills, algal blooms and bacterial contamination. Early efforts in water pollution control prevented human waste from reaching water supplies or reduced floating debris that obstructed shipping. Progress in abating pollution has barely kept ahead of population growth, changes in industrial processes, technological developments, changes in land use, business innovations, and many other factors. Increases in both the quantity and variety of goods. produced can greatly alter the amount and complexity of industrial wastes and challenge traditional treatment technology. The application of commercial fertilizers and pesticides, combined with sediment from growing development activities, continues to be a source of significant pollution as runoff washes off the land. In natural bathing areas, without wastewater treatment, one should not use soap and especially not use laundry detergent because it chemically contaminates the water in a way that is thought to harmfully alter the aquatic ecosystem and potability of filtered water and smells bad when sufficient water is not used to wash lye off. In nature, it is easy to filter water from drinking water sources and wash in the bathing area, for generations. The basic function of the

wastewater treatment plant is to speed up the natural processes by which water purifies itself. In earlier years, the natural treatment process in streams and lakes was adequate to perform basic wastewater treatment. As our population and industry grew to their present size, increased levels of treatment prior to discharging domestic wastewater became necessary. The most common form of pollution control in the United States consists of a system of sewers and wastewater treatment plants. The sewers collect municipal wastewater from homes, businesses, and industries and deliver it to facilities for treatment before it is discharged to water bodies or land, or reused. In the year 2000 approximately 208 million people in the U.S. were served by centralized collection systems.

Dissolved oxygen is a key element in water quality that is necessary to support aquatic life. A demand is placed on the natural supply of dissolved oxygen by many pollutants in waste- water. This is called biochemical oxygen demand, or BOD, and is used to measure how well a sewage treatment plant is working. Organic matter and ammonia are "oxygen-demanding" substances. Oxygen-demand- ing substances are contributed by domestic sewage and agricultural and industrial wastes of both plant and animal origin, such as those from food processing, paper mills, tanning, and other manufacturing processes. These substances are usually destroyed or converted to other compounds by bacteria if there is sufficient oxygen present in the water, but the dis- solved oxygen needed to sustain fish life is used up in this break down process. Disinfection of wastewater and chlorination of drinking water supplies has reduced the occurrence of waterborne diseases such as typhoid fever, cholera, and dysentery, which remain problems in underdeveloped countries while they have been virtually eliminated in the U.S. Infectious micro-organisms, or pathogens, may be carried into surface and groundwater by sewage from cities and institutions, by certain kinds of industrial wastes, such as tanning and meat packing plants, and by the contamination of storm runoff with animal wastes from pets, livestock and wild animals, such as geese or deer. Humans may come in contact with these pathogens either by drinking contaminated water or through swimming, fishing, or other contact activities. Modern disinfection techniques have greatly reduced the danger of water- borne disease.

Carbon, nitrogen, and phosphorus are essential to living organisms and are the chief nutrients present in natural water. Large amounts of these nutrients are also present in sewage, certain industrial wastes, and drainage from fertilized land. Conventional secondary bio- logical treatment processes do not remove the phosphorus and nitrogen to any substantial extent -- in fact, they may convert the organic forms of these substances into mineral form, making them more usable by plant life. When an excess of these nutrients overstimulates the growth of water plants, the result causes unsightly conditions, interferes with drinking water treatment processes, and causes unpleasant and disagreeable tastes and odors in drinking water. The release of large amounts of nutrients, primarily phosphorus but occasionally nitrogen, causes nutrient enrichment which results in excessive growth of algae. **Uncontrolled algae growth** blocks out sunlight and chokes aquatic plants and animals by depleting dis- solved oxygen in the water at night. The release of nutrients in quantities that exceed the affected waterbody's ability to assimilate them results in a condition called eutrophication or cultural enrichment.

Examples of inorganic and synthetic organic **chemicals** include detergents, household cleaning aids, heavy metals, pharmaceuticals, synthetic organic pesticides and herbicides, industrial chemicals, and the wastes from their manufacture. Many of these sub- stances are toxic to fish and aquatic life and many are harmful to humans. Some are known to be highly poisonous at very low concentrations. Others can cause taste and odor problems, and many are not effectively removed by conventional wastewater treatment. Heat reduces the capacity of water to retain

oxygen. In some areas, water used for cooling is discharged to streams at elevated temperatures from power plants and industries. Even discharges from wastewater treatment plants and storm water retention ponds affected by summer heat can be released at temperatures above that of the receiving water, and elevate the stream temperature. Unchecked discharges of waste heat can seriously alter the ecology of a lake, a stream, or estuary.

Whether home septic system or municipal wastewater treatment plant wastewater is subjected to similar treatment before it is finally released into the environment. The initial stage in the treatment of domestic wastewater is known as **primary treatment**. Coarse solids are removed from the wastewater in the primary stage of treatment. As wastewater enters a treatment facility, it typically flows through a step called preliminary treatment. A screen removes large floating objects, such as rags, cans, bottles and sticks that may clog pumps, small pipes, and down stream processes. The screens vary from coarse to fine and are constructed with parallel steel or iron bars with openings of about half an inch, while others may be made from mesh screens with much smaller openings. Screens are generally placed in a chamber or channel and inclined towards the flow of the wastewater. The inclined screen allows debris to be caught on the upstream surface of the screen, and allows access for manual or mechanical cleaning. Some plants use devices known as comminutors or barminutors which combine the functions of a screen and a grinder. These devices catch and then cut or shred the heavy solid and floating material. In the process, the pulverized matter remains in the wastewater flow to be removed later in a primary settling tank.

With the addition of oxygen to wastewater, masses of microorganisms grow and rapidly metabolized organic pollutants. Any excess microbiological growth could be removed from the wastewater by physical processes. Chemicals can be used to create changes in pollutants that increase the removal of these new forms by physical processes. Simple chemicals such as alum, lime or iron salts can be added to wastewater to cause certain pollutants, such as phosphorus, to **floc** or bunch together into large, heavier masses which can be removed faster through physical processes. Over the past 30 years, the chemical industry has developed synthetic inert chemicals know as polymers to further improve the physical separation step in wastewater treatment. Polymers are often used at the later stages of treatment to improve the settling of excess microbiological growth or biosolids.

After the wastewater has been screened it flows to a **sedimentation tank**. Effluent may flow into a grit chamber where sand, grit, cinders, and small stones settle to the bottom. Removing the grit and gravel that washes off streets or land during storms is very important, especially in cities with combined sewer systems. Large amounts of grit and sand entering a treatment plant can cause serious operating problems, such as excessive wear of pumps and other equipment, clogging of aeration devices, or taking up capacity in tanks that is needed for treatment. In some plants, another finer screen is placed after the grit chamber to remove any additional material that might damage equipment or interfere with later processes. The grit and screenings removed by these processes must be periodically collected and trucked to a landfill for disposal or are incinerated. With the screening completed and the grit removed, wastewater still contains dissolved organic and inorganic constituents along with suspended solids. The suspended solids consist of minute particles of matter that can be removed from the wastewater with further treatment such as sedimentation or gravity settling, chemical coagulation, or filtration. Pollutants that are dissolved or are very fine and remain suspended in the wastewater are not removed effectively by gravity settling. When the wastewater enters a sedimentation tank, it slows down and the suspended solids gradually sink to the bottom. This mass of solids is called primary sludge. Various methods have been devised to remove primary sludge from the tanks. Newer

plants have some type of mechanical equipment to remove the settled solids from sedimentation tanks. Some plants remove solids continuously while others do so at intervals.

After the wastewater has been through Primary Treatment processes, it flows into the next stage of treatment called secondary. **Secondary treatment** processes can remove up to 90 percent of the organic matter in wastewater by using biological treatment processes. The two most common conventional methods used to achieve secondary treatment are attached growth processes and suspended growth processes. In attached growth (or fixed film) processes, the microbial growth occurs on the surface of stone or plastic media. Wastewater passes over the media along with air to provide oxygen. Attached growth process units include trickling filters, biotowers, and rotating biological contactors. Attached growth processes are effective at removing biodegradable organic material from the wastewater. A trickling filter is simply a bed of media (typically rocks or plastic) through which the wastewater passes. The media ranges from three to six feet deep and allows large numbers of microorganisms to attach and grow. Older treatment facilities typically used stones, rocks, or slag as the media bed material. New facilities may use beds made of plastic balls, interlocking sheets of corrugated plastic, or other types of synthetic media. This type of bed material often provides more surface area and a better environment for promoting and controlling biological treatment than rock. Bacteria, algae, fungi and other microorganisms grow and multiply, forming a microbial growth or slime layer (biomass) on the media. In the treatment process, the bacteria use oxygen from the air and consume most of the organic matter in the wastewater as food. As the wastewater passes down through the media, oxygen-demanding substances are consumed by the biomass and the water leaving the media is much cleaner. However, portions of the biomass also slough off the media and must settle out in a secondary treatment tank.

Similar to the microbial processes in attached growth systems, **suspended growth processes** are designed to remove biodegradable organic material and organic nitrogen-containing material by converting ammonia nitrogen to nitrate unless additional treatment is provided. In suspended growth processes, the microbial growth is suspended in an aerated water mixture where the air is pumped in, or the water is agitated sufficiently to allow oxygen transfer. Suspended growth process units include variations of activated sludge, oxidation ditches and sequencing batch reactors. The suspended growth process speeds up the work of aerobic bacteria and other microorganisms that break down the organic matter in the sewage by providing a rich aerobic environment where the microorganisms suspended in the wastewater can work more efficiently. In the aeration tank, wastewater is vigorously mixed with air and microorganisms acclimated to the wastewater in a suspension for several hours. This allows the bacteria and other microorganisms to break down the organic matter in the wastewater. The microorganisms grow in number and the excess biomass is removed by settling before the effluent is discharged or treated further. Now activated with millions of additional aerobic bacteria, some of the biomass can be used again by returning it to an aeration tank for mixing with incoming wastewater.

The **activated sludge process**, like most other techniques, has advantages and limitations. The units necessary for this treatment are relatively small, requiring less space than attached growth processes. In addition, when properly operated and maintained, the process is generally free of flies and odors. However, most activated sludge processes are more costly to operate than attached growth processes due to higher energy use to run the aeration system. The effectiveness of the activated sludge process can be impacted by elevated levels of toxic compounds in wastewater unless complex industrial chemicals are effectively controlled through an industrial pretreatment program. An adequate supply of oxygen is necessary for the activated sludge process to be effective. The oxygen is generally supplied by mixing air with the sewage and

biologically active solids in the aeration tanks by one or more of several different methods. Mechanical aeration can be accomplished by drawing the sewage up from the bottom of the tank and spraying it over the surface, thus allowing the sewage to absorb large amounts of oxygen from the atmosphere. Pressurized air can be forced out through small openings in pipes suspended in the wastewater. Combination of mechanical aeration and forced aeration can also be used. Also, relatively pure oxygen, produced by several different manufacturing processes, can be added to provide oxygen to the aeration tanks. From the aeration tank, the treated wastewater flows to a sedimentation tank (secondary clarifier), where the excess biomass is removed. Some of the biomass is recycled to the head end of the aeration tank, while the remainder is "wasted" from the system. The waste biomass and settled solids are treated before disposal or reuse as biosolids.

A **wastewater lagoon** or treatment pond is a scientifically constructed pond, three to five feet deep, that allows sunlight, algae, bacteria, and oxygen to interact. Biological and physical treatment processes occur in the lagoon to improve water quality. The quality of water leaving the lagoon, when constructed and operated properly, is considered equivalent to the effluent from a conventional secondary treatment system. However, winters in cold climates have a significant impact on the effectiveness of lagoons, and winter storage is usually required. While treatment ponds require substantial land area and are predominantly used by smaller communities, they account for more than one-fourth of the municipal wastewater treatment facilities in this country. Land treatment is the controlled application of wastewater to the soil where physical, chemical, and biological processes treat the wastewater as it passes across or through the soil. The principal types of land treatment are slow rate, overland flow, and rapid infiltration. In the arid western states, pretreated municipal wastewater has been used for many years to irrigate crops. In the case of slow rate infiltration, the wastewater is applied to the land and moves through the soil where the natural filtering action of the soil along with microbial activity and plant uptake removes most contaminants. Part of the water evaporates or is used by plants. The remainder is either collected via drains or wells for surface discharge or allowed to percolate into the groundwater.

The **rapid infiltration** process is most frequently used to polish and recover wastewater effluents for reuse after pretreatment by secondary and advanced treatment processes. It is also effective in cold or wet weather and has been successfully used in Florida, northeastern and arid southwestern states. Large amounts of wastewater are applied to permeable soils in a limited land area and allowed to infiltrate and percolate downward through the soil into the water table below. If the water is to be reused, it can be recovered by wells. The **overland flow** method has been used successfully by the food processing industries for many years to remove solids, bacteria and nutrients from wastewater. The wastewater is allowed to flow down a gently-sloped surface that is planted with vegetation to control runoff and erosion. Heavy clay soils are well suited to the overland flow process. As the water flows down the slope, the soil and its microorganisms form a gelatinous slime layer similar in many ways to a trickling filter that effectively removes solids, pathogens, and nutrients. Water that is not absorbed or evaporated is recovered at the bottom of the slope for discharge or reuse.

Untreated domestic wastewater contains micro-organisms or pathogens that produce human diseases. Processes used to kill or deactivate these harmful organisms are called disinfection. Chlorine is the most widely used disinfectant but ozone and ultraviolet radiation are also frequently used for wastewater effluent disinfection. The National Pretreatment Program, a cooperative effort of Federal, state, POTWs and their industrial dischargers, requires industry to control the amount of pollutants discharged into municipal sewer systems. **Pretreatment**

protects the wastewater treatment facilities and its workers from pollutants that may create hazards or interfere with the operation and performance of the POTW, including contamination of sewage sludge, and reduces the likelihood that untreated pollutants are introduced into the receiving waters. Under the Federal Pretreatment Program, municipal wastewater plants receiving significant industrial discharges must develop local pretreatment programs to control industrial discharges into their sewer system. These programs must be approved by either EPA or a state acting as the Pretreatment Approval Authority. More than 1,500 municipal treatment plants have developed and received approval for a Pretreatment Program.

Advanced treatment technologies can be extensions of conventional secondary biological treatment to further stabilize oxygen-demanding substances in the wastewater, or to remove nitrogen and phosphorus. Advanced treatment may also involve physical-chemical separation techniques such as adsorption, flocculation/precipitation, membranes for advanced filtration, ion exchange, and reverse osmosis. In various combinations, these processes can achieve any degree of pollution control desired. As wastewater is purified to higher and higher degrees by such advanced treatment processes, the treated effluents can be reused for urban, landscape, and agricultural irrigation, industrial cooling and processing, recreational uses and water recharge, and even indirect augmentation of drinking water supplies. By providing additional biological treatment beyond the secondary stage, nitrifying bacteria present in wastewater treatment can biologically convert ammonia to the non-toxic nitrate through a process known as nitrification. Phosphorus removal can be achieved through chemical addition and a coagulation-sedimentation process discussed in the following section. Some biological treatment processes called biological nutrient removal (BNR) can also achieve nutrient reduction, removing both nitrogen and phosphorus. Most of the BNR processes involve modifications of suspended growth treatment systems so that the bacteria in these systems also convert nitrate nitrogen to inert nitrogen gas and trap phosphorus in the solids that are removed from the effluent.

A process known as **chemical coagulation-sedimentation** is used to increase the removal of solids from effluent after primary and secondary treatment. Solids heavier than water settle out of wastewater by gravity. With the addition of specific chemicals, solids can become heavier than water and will settle. Alum, lime, or iron salts are chemicals added to the wastewater to remove phosphorus. With these chemicals, the smaller particles 'floc' or clump together into large masses. The larger masses of particles will settle faster when the effluent reaches the next step--the sedimentation tank. This process can reduce the concentration of phosphate by more than 95 percent. This process produces a chemical sludge, and the cost of disposing this material can be significant. Carbon adsorption consists of passing the wastewater effluent through a bed or canister of activated carbon granules or powder which remove more than 98 percent of the trace organic substances. The substances adhere to the carbon surface and are removed from the water. To help reduce the cost of the procedure, the carbon granules can be cleaned by heating and used again.

Sewage solids, or **sludge**, when separated from the wastewater, still contain around 98 percent water. They are usually thickened and may be dewatered to reduce the volume to be transported for final processing, disposal, or beneficial use. Dewatering processes include drying beds, belt filter presses, plate and frame presses, and centrifuges. To improve dewatering effectiveness, the solids can be pretreated with chemicals such as lime, ferric chloride, or polymers to produce larger particles which are easier to remove. Digestion is a form of stabilization where the volatile material in the wastewater solids can decompose naturally and the potential for odor production is reduced. Digestion without air in an enclosed tank (anaerobic solids digestion) has the added benefit of producing methane gas which can be recovered and used as a source of energy.

Stabilization of solids may also be accomplished by composting, heat treatments, drying or the addition of lime or other alkaline materials. After stabilization, the biosolids can be safely spread on land. Heat dried biosolids pellets have been produced and used extensively as a fertilizer product for lawn care, turf production, citrus groves, and vegetable production for many years. Composting of biosolids is also a well established approach to solids management that has been adopted by a number of communities. Effective pretreatment of industrial wastes prevents excessive levels of unwanted constituents, such as heavy metals (i.e. cadmium, mercury, and lead) and persistent organic compounds from contaminating the residuals of wastewater treatment and limiting the potential for beneficial use. Incineration consists of burning the dried solids to reduce the organic residuals to an ash that can be disposed or reused.

Decentralized treatment systems include onsite systems and cluster systems. A **septic tank** and soil adsorption field is an example of an onsite system. A wastewater collection and treatment system under some form of common ownership that collects wastewater from two or more dwellings or buildings and conveys it to a treatment and dispersal system located on a suitable site near the dwellings or buildings is a cluster system. Decentralized systems include those using alternative treatment technologies like media filters, constructed wetland systems, aerobic treatment units, and a variety of soil dispersal systems. Soil dispersal systems include pressure systems such as low pressure pipe and drip dispersal systems. These systems treat and disperse relatively small volumes of wastewater, and are generally are found in rural and suburban areas. While septic tanks and soil absorption systems have significant limitations, decentralized systems can effectively protect water quality and public health from groundwater and surface water contamination if managed properly (i.e. properly sited, sized, designed, installed, operated, and maintained).

Onsite wastewater systems contain three components: a treatment unit which treats water prior to dispersal into the environment; a soil dispersal component which assures that treated water is released into the environment at a rate which can be assimilated; and a management system which assures proper long term operation of the complete system. Disinfection of the treated effluent may be provided prior to dispersal. A typical onsite system consists of a septic tank followed by an effluent distribution system. Alternative treatment systems include aerobic treatment and sand filtration systems. A septic tank is a tank buried in the ground used to treat sewage without the presence of oxygen (anaerobic). The sewage flows from the plumbing in a home or small business establishment into the first of two chambers, where solids settle out. The liquid then flows into the second chamber. Anaerobic bacteria in the sewage break down the organic matter, allowing cleaner water to flow out of the second chamber. The liquid typically discharges through a sub- surface distribution system. Periodically, the solid matter in the bottom of the tank, referred to as **septage**, must be removed and disposed of properly.

Aerobic treatment units are also used to provide onsite wastewater treatment. They are similar to septic tanks, except that air is introduced and mixed with the wastewater inside the tank. Aerobic (requiring oxygen) bacteria consume the organic matter in the sewage. As with the typical septic system, the effluent discharge from an aerobic system is typically released through a sub-surface distribution system or may be disinfected and discharged directly to surface water. Aerobic treatment units also require the removal and proper disposal of solids that accumulate in the tank. Media filters are used to provide further treatment of septic tank effluent, and provide high levels of nitrification. They can be designed to pass the effluent once or multiple times through the media bed. Media, such as sand, acts as a filter. The media is placed two to three feet deep above a liner of impermeable material such as plastic or concrete. Septic tank effluent is applied to the filter surface in intermittent doses and is further treated as it slowly trickles

through the media. In most media filters, wastewater is collected in an under-drain then either pumped back to the filter bed or to other types of treatment.

If the soil is unsuitable for the installation of a soil absorption field, alternative methods can be used to further treat or distribute the treated effluent. The most common **alternative dispersal** systems include low pressure pipe, mounds, drip disposal, and evapotranspiration beds. When soil conditions permit, the most common method to disperse septic tank or aerobic system effluent is an absorption field consisting of a series of perforated parallel pipes laid in trenches on gravel or crushed stone or as a direct discharge to the soil through trenches. When the soil is not conducive to percolation or when the groundwater level is high, a mound system is commonly used. A mound system is a distribution system constructed above the original ground level by using granular material such as sand and gravel to receive the septic tank effluent before it flows to the native soil below. The effluent flows to a dosing tank that is equipped with a pump. Here the effluent is stored until there is sufficient liquid. Once the liquid is pumped out, it moves evenly throughout the mound before reaching less permeable soil or ground water. Where soils are very thin or have reduced permeability, drip dispersal systems can be utilized. Evapotranspiration (ET) bed is an onsite dispersal system where pretreated wastewater evaporates from the soil surface or is transpired by plants into the atmosphere (EPA '04).

II. Food

1. Nutrition

Good nutrition is the foundation of health and well-being for all (Balch '00: 3)(WHO '19: 6). Everyone needs four basic nutrients – water carbohydrates, proteins and fats – as well as vitamins, minerals and other micronutrients. The human body is two-thirds water (Balch '00: 3). Doctors are expected diagnose and treat the double-burden of malnutrition and over-nutrition, and diet-related noncommunicable diseases, including diabetes (WHO '19: 6). A **calorie** is the heat required to raise the temperature of 1 gram of water 1ºC. The energy value of food and human energy requirements are expressed as caloric equivalents. Fatty acids are used by the body as a source of energy and are provided for in our diet by animal fat and vegetable oils that when metabolized supply 9 cal/g. Carbohydrates are complex compounds made up of sugars that when metabolized yield 4 cal/g. Proteins, are complex chains of amino acids, supplied in our diet chiefly by animal proteins –meat, milk, cheese and eggs – and to a lesser degree by plants such as rice and legumes and nuts, that when metabolized yield 5 cal/g. Protein requirements vary, with children, pregnant and lactating women, and men undergoing strenuous exercise requiring larger amounts. Beyond infancy a child requires about 10% of his caloric intake in protein. Protein deficiency, especially during the first year of life, has been associate with decreased brain development and lowered IQ (Elvin-Lewis ’77: 201, 200). The amount of protein in a mother’s breast milk is 5 percent of calories. According to the World Health Organization (WHO) the human minimum protein requirement is 5 percent of total calories, according to the US Recommended Dietary Allowance for adults 10 percent of total calories. For optimum protein intake WHO recommends 10-15 percent of calories (Robbins ’01: 71, 67). Total fat intake should be less than 30 percent of total energy intake, Saturated fatty acid intake should be less than 10 percent of total energy intake. Trans-fatty acid intake should be less than 1 percent of total energy intake (WHO '19: 24). Therefore, 55-75 to 94 percent of calories in the diet should come from carbohydrates. The limit for empty calories, found swiftly in excessive amounts of animal products, protein, breads and sweets, is based on estimated calorie needs by age/gender group. Physical activity increases caloric needs, so those who are more physically active need more total calories and have a larger limit for empty calories.

Age and gender	Estimated calories for those who are not physically active	
	Total daily calorie needs*	**Daily limit for empty calories**
Children 2-3 yrs	1000 cals	135
Children 4-8 yrs	1200-1400 cals	120
Girls 9-13 yrs	1600 cals	120
Boys 9-13 yrs	1800 cals	160
Girls 14-18 yrs	1800 cals	160
Boys 14-18 yrs	2200 cals	265
Females 19-30 yrs	2000 cals	260
Males 19-30 yrs	2400 cals	330
Females 31-50 yrs	1800 cals	160
Males 31-50 yrs	2200 cals	265
Females 51+ yrs	1600 cals	120
Males 51+ yrs	2000 cals	260

Source: Choosemyplate.gov * calories estimate for sedentary lifestyle, double for full-time physical labor.

The **sedentary calorie requirement** can be misleading to active pregnant and lactating women, males age 14-30, physical laborers, alcoholics and athletes, especially female athletes who can suffer osteoporosis, like everyone, and anovulation – reversible premature menopause or delayed puberty - if undernourished, require up to double the normal calorie estimate, and can often eat more without ill-effect, and are due extra-rations, as a matter of law. Pregnant and lactating women require about 25 percent more than normal. Hikers, with a heavy backpack who walk for more than eight hours a day, are hungry, they initially require more than 5,000 kcal per day before they adapt and merely consume 1 ½ to 2 times the sedentary rate, up to 5,000 kcal. 19th century loggers are said to have consumed 12,000 kcal/day. The diet for postmenopausal women and healing bones and teeth is to combine Calcium, vitamin D, and Phosphorus with the objective of making "Apatite" despite Calcium loss in the urine and feces. Authors and inactive middle aged men typically need to learn to reduce their calorie intake, by packing a lunch. The total caloric expenditure of runners completing a marathon, in three to seven hours, is difficult, if not impossible to measure accurately, and in general caloric expenditure from physical activity

requires more scientific study. However, using a treadmill it has been shown that the energy expended running is approximately 1.5kcal/kg/mile. Therefore, if a marathon were held on a motor-driven treadmill, a 50kg runner would expend 1,970 kcal, a 60kg runner 2,360 kcal, a 70 kg runner 2,750 kcal, and 80 kg runner 3,140 kcal, and so on. However marathons are not run on a treadmill, and in actual running conditions, the caloric cost is not independent of running velocity. Most marathon runners require approximately 2,400 kcal to finish the 26.2 miles. A comparison of horizontal running and hill running at the moderate velocity of 8 min/mile has been shown that an athlete running up a 6% incline will expend approximately 35% more energy than on a horizontal track, and on the downhill part of this 6% decline hill, the runner only reduces energy expenditure by 24%. The direct solar heat gain of marathon runners has been determined to be 55 kcal/m^2/hr on a sunny day with an ambient temperature of 22-23°C and relative humidity of 52-58%. For comparison, it has been reported that during desert conditions, the solar heat gain will approach 140 kcal/m^2/hr. For thin runners requiring at least 2 ½ hours to finish a marathon, an additional energy expenditure of at least 250 kcal must be utilized to cool the body. For the larger runner, who may require four hours to finish the marathon, solar heat gain may result in an energy expenditure of 400-500 kcal (Taylor '82: 38, 39).

Most long distance runners eat enough additional foodstuffs to more than double their body weight during the course of only a single year of training. When the demands of the body require repletion of the muscle and liver glycogen, carbohydrates and excess protein molecules are the only source from which the body's mechanisms can manufacture glycogen. Fat can never be converted to **glycogen**. For an endurance runner in training a proper diet should include at least 1 gm/kg/day of protein, a limitation of fat intake to no more than 20% of the caloric intake, a high percentage of the daily calories from complete carbohydrates, and an alcohol consumption that is no more than 10% of the daily caloric intake. Alcohol has a caloric index of 7 kcal/gram in comparison to 4 kcal/gram for both carbohydrates, 5 kcal for proteins and 9 kcal/gram for fats. Top men marathon runners have a percentage of body fat in the range of approximately 2% to 8%, while the top women marathon runners generally have a range of 9% to 12%. Normal hemoglobin concentrations are nearly 10% lower for women than men of the same age (Taylor '82: 60, 71, 72). Recommendations for **total weight gain during pregnancy** and the rate of weight gain per month appropriate to achieve it may be made based on a body mass index (BMI) calculated for the pre-pregnancy rate. Underweight mothers with a BMI <19.8 should gain a total of 12.7-18.2 kg (28-40 lb) at a rate of 2.3 kg (5.0 lb) every 4 weeks. Normal weight mothers with a BMI 19.8-26.9 should gain a total of 11.4-15.9 kg (25-35 lb) at a rate of 1.8 kg (4.0 lb) every 4 weeks. Overweight mothers with a BMI of 26.1-29.0 should gain a total of 6.8-11.4 kg (15-25 lb) at a rate of 1.2 kg (2.5 lb) every 4 weeks. Obese mothers with a BMI >29.0 should gain 68 kg (15 lb) at a rate of 0.9 kg (2.0 lb) every 4 weeks. Twin gestation by a normal mother requires a weight gain of 15.9-20.4 kg (35-40 lb) at a rate of 2.7 kg (6.0 lb) every 4 weeks (Beckmann et al '02: 91, 92). Pregnant and lactating women in emergency settings should be provided with an extra liter of water and fortified blended food commodities, in addition to the basic general ration, that are designed to provide 10–12% (up to 15%) of energy from protein and 20–25% of energy from fat. The fortified blended food should be fortified to meet two thirds of the daily requirements for all micronutrients (WHO '19: 145).

The composition of an average human reflects the nature of the **nutrients required in the diet**. Water is the most abundant chemical compound in living human cells, accounting for 65-90% of each cell. Each water molecule consists of two hydrogen atoms bonded to one oxygen atom, but the mass of each oxygen atom is much higher than the combined mass of the hydrogen. All organic compounds contain carbon, which is why carbon is the second most abundant element in the body. Six elements account for 99% of the mass of the human body: oxygen, carbon,

hydrogen, nitrogen, calcium, and phosphorus. Although aluminum and silicon are abundant in the earth's crust, they are found in trace amounts in the human body (Chang '07: 52). The average 70 kg adult human body contains approximately 3×10^{27} atoms and contains at least detectable traces of 60 chemical elements. About 25 of these elements are thought to play an active positive role in life and health in humans. Calcium phosphate **apatite** are inorganic compounds encountered in many different mineralized tissues, around the body in concentrations of 1.5% for calcium and 1.2% for phosphorus, but most significantly in bones and teeth (Drouet '13). Although calcium is a priority because it is lost in urine and feces, calcium can be found in green leafy vegetables and in high quantities in dairy products, and supplementation is not indicated until menopause, and to heal bones and teeth. Phosphorus is only found in animal products, mushrooms, soy and mung beans, and is not generally found in multivitamins, although it is necessary as a supplement to prevent dental caries in vegans, due to its high availability in the normal diet. Diarrhea associated with **iron deficiency anemia**, and folate, vitamin B_{12} and zinc deficiencies are the only other common supplementary concerns. Industrialized nation multivitamins need iron and those marketed for vegetarians and especially vegans, also require phosphorus.

The continuous **cellular turnover** of proteins and lipids, the loss of desquamated epithelial cells and hair, and the loss of water and electrolytes in urine and sweat means that there is a daily obligate loss of nutrients to be replaced. Additionally, nutrients are required to meet the compositional and energy demands of growth and reproduction, which increase susceptibility to malnutrition. The body is able to synthesize many of the amino acids and fatty acids it needs for protein and lipid synthesis but is dependent upon an adequate supply of essential amino acids, fatty acids, minerals and vitamins. Whereas energy requirements may be met by the catabolism of fat stores and of some protein, this is only beneficial in the management of abnormal metabolic states such as obesity. People otherwise require a certain minimum daily energy and protein intake to maintain balance, better expressed in calories. An individual's nutrient requirements cannot be predicted accurately; the metabolic and biochemical bases of nutrition and of nutrient interaction are too poorly defined, but the recommended daily allowances (RDI) are designed to meet the requirements of 97% of a healthy population, and are frequently revised (Jones et al '85: 1).

Elements in the Human Body

Element	**Percent by Mass**
Oxygen	65
Carbon	18
Hydrogen	10
Nitrogen	3
Calcium	1.5
Phosphorus	1.2
Potassium	0.2
Sulfur	0.2
Chlorine	0.2
Sodium	0.1
Magnesium	0.05

Iron, Cobalt, Copper, Zinc, Iodine	<0.05 each
Selenium, Fluorine	<0.01 each

Source: Chang '07 pg. 52

Since 1941, when the first **Recommended Daily Allowances** (RDAs) were published, they have been updated 10 times by the Food and Nutrition Board of the National Academy of Sciences.. The most recent revision was in 1989 when RDAs were determined for protein, 11 vitamins, and 7 minerals. In 1995, the Food and Nutrition Board deemed that a new, more comprehensive approach was necessary to setting dietary guidelines. So the Board replaced and expanded the current RDAs with Dietary Reference Intakes (DRIs) to provide recommended nutrient intakes for use in a variety of settings. The DRIs are actually a set of four reference values. (1) Recommended Dietary Allowance (RDA) is the average daily dietary intake of a nutrient that is sufficient to meet the requirement of nearly all (97-98%) healthy persons. (2) Adequate Intake (AI) for a nutrient is only established when an RDA cannot be determined. (3) Tolerable Upper Intake Level (UL) is the highest daily intake of a nutrient that is likely to pose no risks of toxicity for almost all individuals. As intake above the UL increases, risk increases. (4) Estimated Average Requirement (EAR) is the amount of a nutrient that is estimated to meet the requirement of half of all healthy individuals in the population. Each of these reference values distinguishes between gender and different life stages. RDAs, AIs and ULs are dietary guidelines for individuals, whereas EARs provide guidelines for groups and populations (Penland '06). Federal regulations require manufacturers to include information about the ingredients contained in a food, as well as the food's nutrition profile, somewhere on the food label. Ingredients are listed in descending order by weight. The nutrition facts panel gives a detailed accounting of how a serving of the food rates nutritionally, first by providing information about calorie count and key nutrients and then by comparing that information to reference value or standard requirements – calories, total fat in grams per serving, how much is trans-fat, saturated or unsaturated (monounsaturated or polyunsaturated) fat, cholesterol in mg, the AMA recommends that Americans eat less than 300 mg a day. Sodium guidelines encourage 2,400 mg of sodium, 1 teaspoon of salt a day or less. Total carbohydrates may be further explained in grams of sugar and grams of fiber. Protein is not much of a guide. Daily values of several different nutrients such as vitamin A, vitamin C, calcium, and iron, show how they contribute to the daily requirements set by the Food and Nutrition Board of the National Academy of Sciences (Willet '01: 192).

Recommended Dietary Allowance Water and Macronutrients

Life Stage	Total Water (l/d)	Carbo-hydrate (g/d)	Total Fiber (g/d)	Fat (g/d)	Linoleic Acid (g/d)	A-linoleic Acid (g/d)	Protein
Infants							
0-6 mo.	0.7	60	n/a	31	4.4	0.5	9.1
6-12 mo.	0.8	95	n/a	30	4.6	0.5	11.0
Children							
1-3 y.	1.3	130	19	n/a	7	0.7	13

4-8 y.	1.7	130	25		10	0.9	19
Males							
9-13 y.	2.4	130	31		12	1.2	34
14-18 y.	3.3	130	38		16	1.6	52
19-30 y.	3.7	130	38		17	1.6	56
31-50 y.	3.7	130	38		17	1.6	56
51-70 y.	3.7	130	30		14	1.6	56
>70 y.	3.7	130	30		14	1.6	56
Females							
9-13 y.	2.1	130	26		10	1.0	34
14-18 y.	2.3	130	26		11	1.1	46
19-30 y.	2.7	130	25		12	1.1	46
31-50 y.	2.7	130	25		12	1.1	46
51-70 y.	2.7	130	21		11	1.1	46
>70 y.	2.7	130	21		11	1.1	46
Pregnancy							
14-18 y.	3.0	175	28		13	1.4	71
19-30 y.	3.0	175	28		13	1.4	71
31-50 y.	3.0	175	28		13	1.4	71
Lactation							
14-18 y	3.8	210	29		13	1.3	71
19-30 y.	3.8	210	29		13	1.3	71
31-50 y.	3.8	210	29		13	1.3	71

Source: Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academies Last updated September 26, 2013

Total water includes all water contained in food, beverages, and drinking water. Based on g protein per kg of body weight for the reference body weight, e.g., for adults 0.8 g/kg body weight for the reference body weight. **Fluid replacement** during a marathon or other long distance run

is a factor in the runner's performance. Sweat rates among marathon runners of 1.09 liters/m^2/hour have been observed. Thus is a runner (world class) requires 2 ½ hours to run the 26.2 miles, then perspiration losses alone would approach five to six liters of fluid, resulting in a five to six kilogram body weight loss. A marathon runner weighing 50 to 60 kilograms could expect to lose approximately 10% of body weight in perspiration alone. However, no significant plasma volume loss is noted after prolonged exercise without fluid replacement. These findings suggest that a large portion of the body water lost through perspiration muscle come from intracellular sources to replenish the plasma volume to prevent circulatory collapse. Although plasma volume may be maintained at water losses which approach 10% of body weight, the ability to continue to cool the body to prevent hyperthermia may become impaired. When water deficits exceed 3% of the runner's body weight, even in cool environmental conditions, rectal temperature rises. Water deficits of more than 4% of body weight may lead to fatigue and loss of desire to win, which many marathon runners experience in the last few miles of the race. Sweat gland activity seems to be controlled by the frequency of cutaneous thermal receptors. The rate of change of skin temperature and the absolute skin temperature controlling perspiration rates and eventual body fluid losses can be affected by several factors. Some of these factors are running velocity, body weight, surface to volume ratio, direction and velocity of the wind, absolute ambient temperature, relative humidity, type and color of clothing, proportion of skin surface area exposed to the air, incline or decline percentage of the marathon course, amount of heat generated by exposure of the runner to direct sunlight, terrain of the marathon course, amount, type and temperature of replacement fluids, individual running efficiency, the level of training of the runner, the amount of endogenous water stored by glycogen stores in the cells, and the level of heat acclimation of the runner (Taylor '82: 26-29).

When **fluids** were ingested runners controlled their body temperature better than those with no fluid allowance. The attempt at rapid replacement of fluids, electrolytes and possible nutrients is limited by gastric emptying. Adding small amounts of glucose to water days gastric emptying when glucose concentration exceeds 139mM. Cold solutions have been shown to exit the stomach more quickly than warm solutions. Ingested solutions at 5°C were emptied from the stomach at nearly twice the rate of solutions ingested at room temperature. Gastric emptying is also enhanced by an increase in gastric volume to some degree . The rate of gastric emptying for water and hypotonic solutions increases an estimated 3.3 ml/min for every 100 ml increase until the level of 600-800 ml total content is reached whereupon additional fluid does not increase the rate of gastric emptying and pain may be induced from large gastric volume. Exercise has no effect on gastric emptying until the working efforts reach approximately 70% of maximum capacity, above which level gastric emptying is delayed. A study comparing the gastric emptying rates of water and three commercially available athletic drinks: Gatorade, Breaktime and Body Punch, found that Gatorade was 35 to 40% slower in leaving the stomach due to the glucose level (4.5gm%) (Taylor '82: 31, 32).

All living things are made up of the same basic ingredients: sugar molecules, amino aids and fats. **Sugar** molecules an be linked to form complex chains, they no longer taste sweet and are known as the carbohydrates found in bread, past or rice. The difference is that household sugar does not require so much enzymes to be broken down into such small pieces when it arrives in the small intestine that it an be absorbed directly into the bloodstream. Eating too much pure sugar at once makes blood sweeter for a while. The sugar contained in white bread is digested relatively quickly. With wholegrain bread, everything moves at a much more leisurely pace. Such bread contains particularly complex sugar chains, which have to be broken down bit by bit, and so wholegrain bread is not a sugar explosion, but a beneficial sugar store. The body has to work much harder to restore a healthy balance if a sugar onrush comes suddenly, it pumps out

large amounts of various hormones, most importantly insulin, the result is exhaustion when sugar is digested. The body loves sugary sweet treats because they save the body work, since sugar can be taken up more quickly. The same is true of warm proteins. Overeating sugar, the body stores it for later, one way is to form long, complex chains of a substance called glycogen, which is stored in the liver. Another strategy is to convert the excess sugar into fat and store it in fatty tissue, much more easily than any other foodstuff. Glycogen reserves soon used up, wherefore at least an hour of exercise is recommended to burn fat after passing through the first energy dip (Enders '15: 49-50).

Carbohydrates are traditionally divided into two categories: simple and complex. Simple carbohydrates are portrayed as bad nutrition while complex carbohydrates are highly regarded. Simple carbohydrate are sugars. The simplest simple carbohydrates are glucose (sometimes called dextrose), fructose (also called fruit sugar) and galactose (a part of milk sugar). Table sugar contains sucrose, made by joining a molecule of glucose with one of fructose, and milk contains lactose, made by joining a molecule of glucose with one of galactose. Simple carbohydrates provide energy and little else. Complex carbohydrates are more complex, long chains of linked sugars. Although there many types of complex carbohydrates in food, the main one is starch, a long chain of glucose molecules. The human digestive system can break down complex carbohydrates like starch into their component sugars. Others are quite indigestible and pass largely unchanged through the stomach and the intestines. These indigestible carbohydrates, called fiber, are an important part of diet. In the average American diet, carbohydrates contribute about half of all calories. Half of these carbohydrate calories come from just seven sources: bread (15 percent), soft drinks and sodas (9 percent), cakes, cookies, quick breads and doughnuts (7 percent), sugars syrups, and jams (6 percent), white potatoes (5 percent), ready-to-eat cereals (5 percent), and milk (5 percent). Because the simple sugar molecules are the primary fuel for the most of the body's tissues, complex mechanisms are in place to make sure that the level of glucose in the bloodstream doesn't shoot too high or drift too low. The rise in blood sugar (glucose) is followed quickly by a parallel rise in insulin. This hormone, produced by special cells in the pancreas, ushers glucose inside of muscle and other cells. As cells sponge up glucose, blood sugar levels fall first, followed closely by insulin levels. Faltering insulin production is an early sign of type 2 diabetes, which is also called non-insulin dependent or adult-onset diabetes. Resistance to insulin keeps blood sugar at high levels for longer periods and forces the pancreas to produce extra insulin in order to jam glucose into cells, and the insulin making cells in the pancreas may wear out and stop producing insulin. Four things contribute to insulin resistance: obesity, inactivity, trans-fats and Native America, Pacific Island or Asian heritage. According to the glycemic index (GI) products made from refined grains, like white bread, bagels and crackers, have a rapid and strong influence on blood sugar. Those that are less refined, such as whole-grain breads, and cereals, have relatively lower glycemic indices, as do beans, vegetables and fruits. In the Nurses' Health Study ad the Health Professionals Followup Study, participants who ate the most cereal fiber from grains (about 7.5 grams per day, the equivalent of a bowl of oatmeal and two pieces of whole wheat bread) were 30 percent less likely to develop types 2 diabetes than those who ate the least grain fiber (less than 2.5 grams per day). Eating cold breakfast cereal seems to have a protective effect on the development of diabetes, while cola beverages, white bread, white rice, French fries and cooked potatoes were all associated with increased risk of diabetes. Constipation is the number one gastrointestinal complaint in the United States accounting to more than two million physician visits a year, and $725 million in over-the-counter laxative sales. Diverticulosis is the development of tiny, easily irritated pouches inside the colon and diverticulitis, is the often painful inflammation of these pouches. Fiber from cereals, as well as from fruits and vegetables,

adds bulk to the stool and softens it. Together, these actions decrease pressure inside the intestinal tract and help prevent diverticular disease (Willet '01: 83-89, 92, 96, 97).

Grains have nourished humans since early times, but somewhere most lost touch with their goodness and must diversify their granaries and cooking styles. When storing or cooking whole grains soaking whole grains, either for a few hours or overnight helps to reduce cooking time, toasting whole grains helps intensify their nutty flavor, the best measure of doneness is tenderness, store whole grains in airtight containers in the refrigerator in the summer, cooked whole grains must be eaten within six hours without refrigeration and will keep in the refrigerator for 2 to 3 days and also freezes well. Amaranth is rich in iron and calcium, cholesterol free with a small amount of unsaturated fat. Barley has a nutty-flavor and retains a chewy texture even when cooked, a good source of protein and fiber. Brown rice gets its characteristic brown color and nutty flavor form the fact that the bran or outer layer is left on when the rice is harvested. Buckwheat is toasted and soled either whole or ground and called kasha when cooked and must be combined with other grains to make a tasty and healthy pilaf. Bulgur is a whole grain form of wheat that is steamed or boiled and ground, it is cholesterol free, high in fiber and protein. Corn is a fair source of vitamin A, is cholesterol free and rich in fiber. Couscous is not technically a whole grain but is high in protein, with 8 grams per 1 cup cooked. Flaxseed has a wonderful nutty flavor that works will in baked goods, is high in fiber and omega-3 fatty acids, that protect against heart disease and other ills. Millet is a tiny yellow-gold grain sold as bird food, eaten in Africa and Asia for its flavor and strong nutritional profile rich in thiamin and iron, providing 20-25 percent of the RDI, with significant amounts of protein, fiber and potassium. Oats are one of the world's most popular grains valued for their flavor, versatility and medical power. Oatmeal is made from whole-grain oats husked of their outer bran coating. Rolled oats are simmered for about 10 minutes. Steel cut oats are firmer and nuttier but take 40 minutes to cook and the berries contain high levels of protein to which the gluten intolerant are sensitive although it is good for the heart. Oat bran can be added to baked goods or cereal. Oat groats are whole-oat kernels that must be simmered for 30-45 minutes and can be toasted and added to baked goods. Oat flour is richer in fiber than white flour and lacks gluten the protein that helps yeast breads rise. Quinoa is a South America grain, grown in the Andes with a nutty flavor and provides a complete protein as high quality the protein found in meat and eggs. Rye is a hearty cereal grain that can grow just about anywhere. Rye flour is low in gluten (the protein that helps bread to rise), makes dense loaves of bread and is usually used in combination with a higher-protein flour like wheat or with gluten powder. Spelt is an ancient cousin of wheat but has slightly higher protein than wheat and can be tolerated by people with wheat allergies. Triticale is a slightly sweet hybrid of wheat and rye, higher in protein than wheat, but lower in gluten. Wheat berries can be soft or hard, soft wheat is low in gluten and is ground into pastry flour, hard wheat is high in gluten and is ground into bread flours. Wild rice is the seed of an aquatic grass with a stellar fiber content and nutty flavor that is cholesterol free and low in fat (Willet '01: 195-204).

Fat is the most valuable and efficient of all food particles. The atoms are combined in such a way that they concentrate twice as much energy per ounce as carbohydrates or protein. Fat is used to coat nerves, and it is this coating that makes us such fast thinkers. Some of the most important hormones in the body are made of fat, and very single ell is wrapped in a membrane made largely of fat. Unlike other nutrients, fat is not absorbed straight into the blood from the small intestine. At is not soluble in water, it would immediately clog the tiny blood capillaries in the villi of the gut and float on top of the blood in larger vessels. Fat must be absorbed via a different route, the lymphatic system. Every blood vessel inside the body is accompanies by a lymphatic vessel, even each tiny capillary in the small intestine. While blood vessels are thick

and red and pump nutrients to tissues, the lymphatic vessels are thin and filmy white in color. They drain away fluid that is pumped out of tissue and transport the immune cells. Lymphatic vessels are so slight because they do not have muscular walls like blood vessels, often working just by gravity. The reason lower legs do not fill up with fluid after a long day is that leg muscles squeeze the lymphatic vessels every step and that squeezes the fluid, known as lymph, upwards. All the body's lymph vessels converge in an impressively thick duct, known as the *ductus thoracicus*, where all the digested fat an gather without the risk of clogging. Shortly after a eating a fatty meal, there are so many tiny fat droplets in the thoracic duct that the lymph fluid is no longer transparent, but milky white. When the fat has gathered, the thoracic duct skirts the belly, passes through the diaphragm, and heads straight for the heart. There is no detoxifying in the liver, as there is for everything else digested. Detoxification of dangerous, bad fat takes place only after the heart has given the fat-laden fluid a powerful push, pumps it through the system and the droplets of fat happen to end up in one of the blood vessels of the liver (Enders '15: 50-54).

Many studies have been carried out into the beneficial effects of **olive oil** at protecting against arteriosclerosis, cellular stress, Alzheimer's and eye diseases such as macular degeneration, and also appears to have a beneficial effect on inflammatory diseases such as rheumatoid arthritis and protecting against certain types of cancer. Olive oil also has the potential to reduce body fat by blocking an enzyme in fatty tissue, known as fatty acid synthase, that likes to create fat out of spare carbohydrates. Olive oil, and other fine oils, are chemically altered by heat to capture dangerous free radical from the air, wherefore cooking oil or solid fats such as butter or hydrogenated coconut oil should be used for frying (Enders '15: 50-54). The animal fats found in meat, milk and eggs contain more arachidonic acid than vegetable fats. Arachidonic acid is converted in the body into neurotransmitters involved in the sensation of pain. Oils such as rapeseed (canola), linseed, and hempseed oil, contain more of the anti-inflammatory substance alpha-linolenic aid, while olive oil contains a substance with a similar effect called oleocanthal. Sometimes pain levels can be reduced by eating more vegetable fat than animal fat. Nutritional physiologists recommend between 25% and a maximum of 30% of daily energy requirements be filled by fat. That works to an average of 2 to 2 1/12 ounces of (55 - 66 grams) of fat a day. That means one Big Mac or eight sweet onion chicken teriyaki sandwiches from Subway (Enders '15: 54-55). For centuries it was common practice to cure meats and sausages with large quantities of nitrite salts. This gives them a pinkish red, fresh color. Use of nitrites for food preservation has been highly regulated since the 1980s, due to concerns about possible effects on human health. In the United States, sausage and cold meat products must contain no more than 156 parts per million of nitrite salt, approximately one-fifth of the level allowed twenty-five years ago. Rates of stomach cancer have fallen considerably. Today butchers use large amounts of vitamin C with small amounts of nitrites to cure their meats safely (Enders '15: 66).

Almost all dietary fats are **triglycerides** – three fatty acids bound together by a "glue" known as glycerol. There are four main categories of fatty acids – saturated, monounsaturated, polyunsaturated and trans fatty acids. Conventional wisdom is that a Mediterranean diet based in olive oil is the best for cardiovascular health. However in subsequent years expeller pressed coconut with aroma has emerged as an even more delightful and healthy oil, that is solid at room temperature and can be used to make pie crusts as well as sauté, coconut oil is in fact a saturated fat, it is a vegetable fat and is not known to have been tried by anyone with heart disease. Where Harvard implicated the potato as not being of nutritional value Hospitals & Asylums promotes the use of coconut oil. Types of fat: **Mono-unsaturated fat** is liquid at room temperature, beneficially lowers LDL, and raises HDL cholesterol; examples; olives and olive oil, canola oil, peanut oil, cashews, almonds, peanuts, and most other nuts, peanut butter, and avocados.

Polyunsaturated fats are liquid at room temperature, beneficially lower LDL and raise HDL cholesterol; examples; corn, soybean, safflower, and cottonseed oils, fish. One class of polyunsaturated fatty acid deserves attention, they are essential fats, meaning one that the boy doesn't make from scratch or from rearranging other fats, and they are needed for normal functions. Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found mainly in fish, as well as flax seeds, walnuts and canola and unhydrogenated soybean oil. Omega-3 fatty acids are important components of cell membranes throughout the body, especially in the eye, the brain and sperm cells, and are the raw materials from which some hormones are made, including those that regulate blood clotting, contraction and relaxation of artery walls and inflammation. **Saturated fats** are solid at room temperature, and unhealthily raise both LDL and HDL cholesterol; examples; whole milk, butter, cheese and ice cream, red meat, chocolate, coconuts, coconut milk and coconut oil. Trans-fat are solid or semi-solid at room temperature and raise LDL cholesterol unhealthily; examples; most margarine, vegetable shortening, partially hydrogenated vegetable oil, deep-fried chips, many fast foods, most commercial baked goods.

One carefully controlled metabolic study from Holland showed that calories from **trans fats** not only raised LDL (bad) cholesterol as much as did calories from saturated, fats, but trans fats also substantially lowered HDL (good) cholesterol. Other studies have shown that trans fats increase the amount of triglycerides and a substance called lipoprotein (a) in the bloodstream, both of which have been implicated in the causation of atherosclerosis. By 1995 in Europe, margarines were mostly free of trans fats. In the United States, trans fats in margarines decreased a bit in the 1980s and 1990s as companies began making some margarines and spreads that were higher in polyunsaturated fats, and incidentally, lower in trans-fats, while the fast-food industry switched to heavily hydrogenated vegetable oils high in trans-fats. After almost five years of study the Food and Drug Administration decided in late 1999 that it would require food labels to list the amount of trans-fats in addition to the amount of total and saturated fats. It is estimated this prevents thirty thousand or more premature heat disease death each year due to trans-fats in the food supply. Countries with lower average fat intake have lower rates of breast, colon or prostate cancer than countries with higher average fat intakes (Willet '01: 60, 61, 73, 75, 77). The steady decline in deaths due to heart disease that occurred during the 1970s and 1980s has slowed and the percentage of adult Americans with diabetes has increased almost 40 percent over the last 20 years, affecting an estimated 16 million Americans. Around the world, the number of adults with diabetes is expected to jump from 135 million in 1995 to 300 million by 2025 (Willet '01: 86).

It is known that adults need just under 1 gram of **protein** per kilogram of weight daily. That's about 8 grams for every twenty pounds, or about 50 grams for an adult woman, and 65 grams for an adult man. A cup of yogurt at lunch and a serving of chicken plus rice and beans for dinner adds up to about 60 grams of protein. Because it is so easy to get protein, it's uncommon for healthy adults to have a protein deficiency. In the average American meat-centered diet, about 15 percent of calories comes from protein. In largely vegetarian, rice-based diets that are common throughout Asia, about 12 percent of calories come from protein. Rice, a carbohydrate, is about 8 percent protein. From a global health standpoint, eating vegetable protein is a lot more efficient and kinder to the earth, than eating meat. Feeding grain to cattle in order to make steaks and hamburgers takes 50 grams of grain to make 1 gram of edible protein from beef. Protein in general has been linked to a variety of chronic diseases (Willet '01: 102-105). During digestion, most **protein** breaks down into its constituent amino acids, which are used by the body for growth and tissue replacement. Of the twenty-five amino acids, the body can synthesize all but eight. These eight “essential” amino acids exist in abundance in non-flesh foods. Dairy

products, grains, beans, and nuts are all concentrated sources of protein. Cheese, peanuts and lentils, for instance, contain more protein per ounce than hamburger, pork or porterhouse steak. Grains, beans and milk products are excellent sources of protein.

Pound for pound, many **vegetarian foods** are better sources of protein than meat. A hundred-gram portion of meat contains only twenty grams of protein. In comparison, a 100-gram portion of cheese or lentils yields twenty-five grams of protein, while a hundred grams of soybeans yields thirty-four grams of protein. Although meat provides less protein, it costs much more. A spot check in Florida in August 2005 showed sirloin steak costing $7.87 a pound, while staple ingredients for vegetarian meals averaged less than $1.50 a pound. An eight-ounce container of cottage cheese costing $1.59 provides 60 percent of the minimum daily requirement of protein. A study by Dr. Fred State of Harvard and Dr. Mervyn Hording of Loma Linda University made extensive comparisons between the protein intake of vegetarians and that of flesh-eaters. The concluded that "each group exceeded twice its requirement for every essential amino acid and surpassed this amount by a large margins for most of them. For many Americans and Europeans, protein makes up more than 20 percent of their diet, nearly twice the quantity recommended by the WHO. Although inadequate amounts of protein will cause loss of strength, the body cannot use excess protein, rather, it is converted into nitrogenous wastes that burden the kidneys and is eventually passed from the body, taking calcium with it. A number of studies have linked the overeating of protein to the rise in osteoporosis. Although scientists have long known that osteoporosis results from reduced calcium in the bones, they are now coming understand that one of the main causes of calcium deficiency is too much protein in the diet. Carbohydrates are the body's primary source of energy. Only as a last resort does the body use protein to produce energy. Too much protein actually reduces the body's energy capacity. In a series of comparative endurance tests conducted by Dr. Irving Fisher of Yale, vegetarians performed twice as well as meat-eaters. By reducing the non-vegetarians protein consumption by 20 percent, their efficiency improved by 33 percent. A study by Dr. J. Iotekyo and V. Kipan at Brussels University showed that vegetarians were able to perform physical tests two to three times longer than meat-eaters before exhaustion, and were fully recovered from fatigue in one-fifth the time needed by meat-eaters (Swami '06: 11- 12, 21 - 22).

Amino acids are linked in chains named proteins. Digestive enzymes break down these chains in the small intestine and the gut wall absorbs the amino acids. There are twenty of these amino acids and an infinite variety of ways they can be linked to form proteins. Amino acids are used to build many substances, including the DNA genetic material contained in every new cell produced. The same is true for all living things, plants and animals. That explains why all edible food produced in nature contains protein. However, maintaining a healthy meat-free diet that does not lead to nutritional deficiencies is difficult. Plants construct different proteins than animals, and they often use so little of a given amino aid that the proteins they produce are known as incomplete. When the body tries to use these to make needed amino acids, it can build the chain only until one of the amino acids runs out. Half-finished proteins are then simply broken down again, and the tiny acids are excreted in the urine or recycled in the body. Beans lack the amino acid methionine; rice and wheat (and it derivative meat substitute, seitan) lack lysine and sweetcorn is deficient in both lysine and tryptophan. Vegetarians and vegans have to be clever at combining their foods to create a complete protein. Beans may be lacking in methionine, but they are packed with lysine. A wheat tortilla with refried beans and rice will provide all the amino acids the body needs for healthy protein production. Vegetarians who eat cheese and eggs can compensate for incomplete proteins that way. People eat meals made of foodstuffs that complement each other, rich and beans, pasta with cheese, pita bread and hummus, or peanut butter on toast. Combining does not need to take place in one meal. It is

enough to take in the right combination over the course of the day. Soy, quinoa, amaranth, spirulina, buckwheat and chia seeds contain all the necessary amino acids in the necessary quantities. Tofu has a well-deserved reputation as a meat substitute, although increasing numbers of people are developing allergic reactions to it (Enders '15: 55-57). Proteins react to the heat in the hot pan and the acid in our stomach in the same way – they unfold. That means they no longer possess the clever design features that make them soluble in the liquid of the egg white, so they form solid white lumps. In this state, they an be digested far more easily in the stomach and the small intestine. Cooking food saves us the whole first burst of energy required to unfold those proteins, which would otherwise have to be expended by the stomach. By preferring cooked food, the body outsources the first part the digestive process (Enders '15: 40).

Vitamins and minerals are widely available from natural foods. They are important to maintain health and treating many diseases. One should ideally get all the vitamins and minerals needed from natural food sources to consume what could be construed as a balanced diet. There are also daily multi-vitamins and special vitamins for people recovering from a deficiency or with special needs, but there is no substitute for a healthy, balanced diet of natural foods. Recommended Dietary Allowance (RDAs) in bold type and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*) - undifferentiated. Vitamin A retinol activity equivalents (RAEs)1 RAE = 1 µg retinol, 12 µg β-carotene, 24 µg α-carotene, or 24 µg β-cryptoxanthin. Vitamin E α-Tocopherol includes RRR-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the 2R-stereoisomeric forms of α-tocopherol (RRR-, RSR-, RRS-, and RSS-α-tocopherol) that occur in fortified foods and supplements. It does not include the 2S-stereoisomeric forms of α-tocopherol (SRR-, SSR-, SRS-, and SSS-α-tocopherol), also found in fortified foods and supplements. Niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan. As dietary folate equivalents (DFE). 1 DFE = 1µg food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach. In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 µg from supplements or fortified foods in addition to intake of food folate from a varied diet. It is assumed that women will continue consuming 400 µg from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube. As cholecalciferol. 1 µg cholecalciferol = 40 IU vitamin D. Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages. Because 10 to 30 percent of older people may malabsorb food-bound B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with B_{12} or a supplement containing B_{12}.

Vitamins and Minerals, What they do, Food Source

Vitamin	**What the vitamin does**	**Significant food sources**
B1 (thiamin)	Supports energy metabolism and nerve function	spinach, green peas, tomato juice, watermelon, sunflower seeds, lean ham, lean pork chops, soy milk

B2 (riboflavin)	Supports energy metabolism, normal vision and skin health	spinach, broccoli, mushrooms, eggs, milk, liver, oysters, clams
B3 (niacin)	Supports energy metabolism, skin health, nervous system and digestive system	spinach, potatoes, tomato juice, lean ground beef, chicken breast, tuna (canned in water), liver, shrimp
Biotin	Energy metabolism, fat synthesis, amino acid metabolism, glycogen synthesis	widespread in foods
Pantothenic Acid	Supports energy metabolism	widespread in foods
B6 (pyridoxine)	Amino acid and fatty acid metabolism, red blood cell production	bananas, watermelon, tomato juice, broccoli, spinach, acorn squash, potatoes, white rice, chicken breast
Folate	Supports DNA synthesis and new cell formation	tomato juice, green beans, broccoli, spinach, asparagus, okra, black-eyed peas, lentils, navy, pinto and garbanzo beans
B12	Used in new cell synthesis, helps break down fatty acids and amino acids, supports nerve cell maintenance	meats, poultry, fish, shellfish, milk, eggs
C (ascorbic acid)	Collagen synthesis, amino acid metabolism, helps iron absorption, immunity, antioxidant	spinach, broccoli, red bell peppers, snow peas, tomato juice, kiwi, mango, orange, grapefruit juice, strawberries
A (retinol)	Supports vision, skin, bone and tooth growth, immunity and reproduction	mango, broccoli, butternut squash, carrots, tomato juice, sweet potatoes, pumpkin, beef liver
D	Promotes bone mineralization	self-synthesis via sunlight, fortified milk, egg yolk, liver, fatty fish
E	Antioxidant, regulation of oxidation reactions, supports cell membrane stabilization	polyunsaturated plant oils (soybean, corn and canola oils), wheat germ, sunflower seeds,

		tofu, avocado, sweet potatoes, shrimp, cod
K	Synthesis of blood-clotting proteins, regulates blood calcium	Brussels sprouts, leafy green vegetables, spinach, broccoli, cabbage, liver
Mineral	**What the mineral does**	**Significant food sources**
Sodium	Maintains fluid and electrolyte balance, supports muscle contraction and nerve impulse transmissions	salt, soy sauce, bread, milk, meats
Chloride	Maintains fluid and electrolyte balance, aids in digestion	salt, soy sauce, milk, eggs, meats
Potassium	Maintains fluid and electrolyte balance, cell integrity, muscle contractions and nerve impulse transmission	potatoes, acorn squash, artichoke, spinach, broccoli, carrots, green beans, tomato juice, avocado, grapefruit juice, watermelon, banana, strawberries, cod, milk
Calcium	Formation of bones and teeth, supports blood clotting	milk, yogurt, cheddar cheese, Swiss cheese, tofu, sardines, green beans, spinach, broccoli
Phosphorus	Formation of cells, bones and teeth, maintains acid-base balance	all animal foods (meats, fish, poultry, eggs, milk), mushrooms, soy and mung beans
Magnesium	Supports bone mineralization, protein building, muscular contraction, nerve impulse transmission, immunity	spinach, broccoli, artichokes, green beans, tomato juice, navy beans, pinto beans, black-eyed peas, sunflower seeds, tofu, cashews, halibut
Iron	Part of the protein hemoglobin (carries oxygen throughout body's cells)	artichoke, parsley, spinach, broccoli, green beans, tomato juice, tofu, clams, shrimp, beef liver
Zinc	A part of many enzymes, involved in production of genetic material and proteins,	spinach, broccoli, green peas, green beans, tomato juice,lentils, oysters, shrimp,

	transports vitamin A, taste perception, wound healing, sperm production and the normal development of the fetus	crab, turkey (dark meat), lean ham, lean ground beef, lean sirloin steak, plain yogurt, Swiss cheese, tofu, ricotta cheese
Selenium	Antioxidant. Works with vitamin E to protect body from oxidation	seafood, meats and grains
Iodine	Component of thyroid hormones that help regulate growth, development and metabolic rate	salt, seafood, bread, milk, cheese
Copper	Necessary for the absorption and utilization of iron, supports formation of hemoglobin and several enzymes	meats, water
Manganese	Facilitates many cell processes	widespread in foods
Fluoride	Involved in the formation of bones and teeth, helps to make teeth resistant to decay	fluoridated drinking water, tea, seafood
Chromium	Associated with insulin and is required for the release of energy from glucose	vegetable oils, liver, brewer's yeast, whole grains, cheese, nuts
Molybdenum	Facilitates many cell processes	legumes, organ meats

Source: HA

Antioxidants are a group of substances that protect tissues, cells and important compounds like proteins and DNA against the destructive power of oxygen and its relatives. Oxygen-using reactions like those needed to burn fats and carbohydrates generate many oxygen-based by-products called free radicals. Free radicals are thought to play roles in cancer, heart disease, arthritis, cataract formation, memory loss and aging. It has been estimated that the genetic material in each cell of the human body gets about ten thousand "oxidative hits" a day. The term antioxidant usually encompasses vitamin C, vitamin E, beta-carotene and other related carotenoids as well as minerals selenium (necessary to absorb vitamin E) and manganese. Actively investigated antioxidants include glutathione, coenzyme Q_{10}, lipoic acid, flavonoids, phenols, polyphenols and phytoestrogens (Willet '01: 154, 155). **Vitamin A** helps maintain the cells that line the body's interior surfaces, boosting production or white blood cells, and helping direct bone remodeling, it regulates cell growth and differentiation and the transformation of light that hits the eye's retina into electrical impulses the brain interprets as images. The

threshold appears to be in the range of the current recommended daily intakes – 5000 IU for men (the equivalent of 1,000 micrograms of retinol or 6,000 micrograms of beta-carotene) and 4,000 IU for women (the equivalent of 800 micrograms of reginol or 4,8000 micrograms of beta-carotene). Good sources of preformed vitamin A are liver, fish liver oil, eggs, and dairy products. Provitamin A comes from several carotenoids, including alpha-carotene, beta-carotene and beta-cryptoxanthin found in carrots, yellow squash, red and green peppers, spinach, kale and other green leafy vegetables. **Vitamin C** plays a role in infection control and helps make collagen, a substance needed for healthy bones, ligaments, teeth, gums, blood vessels and is involved in making several hormones and chemical messengers used in the brain and nerves. Citrus fruits prevent scurvy, a once feared disease that killed an estimated two million sailors between 1500 and 1800. The current recommended daily intake for vitamin C is 75 mg a day for women and 90 mg a day for men, with an extra 35 mg a day for smokers. There seems to be no harm in getting more, though the latest dietary reference cautions against taking megadoses above 2,000 a day. Most people get between 5 and 15 IU of **vitamin E** a day, yet it takes several hundred IUs a day to significantly block the oxidation of LDL cholesterol and the biggest inhibition happens at about 800 IUs a day. In the Nurses' Health Study and Health Professionals Follow-up Study, lower risks of heart disease in women and men in those who took vitamin E supplements of at least 100 IUs for at least two years, usually 400 IU vitamin E daily. The latest dietary reference intakes increased the recommended daily intake to 15 mg of vitamin E from food, the equivalent of 22 IU from natural source vitamin or 33 IU of synthetic form. Vitamin E is safe up to doses of 1,000 mg a day. Too much vitamin E causes a worsening of a rare eye problem known as retinitis pigmentosa and reduce the blood's ability to clot so should not be taken by people taking blood thinners (Willet '01: 158-163).

Recommended Dietary Allowance and Adequate Intakes of Vitamins

Life Stage	A retinol (µg/d)	C (mg/d)	D (µg/d)	E (mg/d)	K (µg/d)	Thiamin (mg/d)	Riboflavin (mg/d)	Niacin (mg/d)	B_6 (mg/d)	Folate (µg/d)	B_{12} (µg/d)	Pantothenic acid (mg/d)	Biotin (µg/d)	Choline (mg/d)
Infants														
0-6 mo.	400	40	10	4	2.0	0.2	0.3	2	0.1	65	0.4	1.7	5	125
6-12 mo.	500	50	10	5	2.5	0.3	0.4	4	0.3	80	0.5	1.8	6	150
Children														
1-3	300	15	15	6	30	0.5	0.5	6	0.5	150	0.9	2	8	200

y.														
4-8 y.	400	25	15	7	55	0.6	0.6	8	0.6	200	1.2	3	12	250
Males														
9-13 y.	600	45	15	11	60	0.9	0.9	12	1.0	300	1.8	4	20	375
14-18 y.	900	75	15	15	75	1.2	1.3	16	1.3	400	2.4	5	25	550
19-30 y.	900	90	15	15	120	1.2	1.3	16	1.3	400	2.4	5	30	550
31-50 y.	900	90	15	15	120	1.2	1.3	16	1.3	400	2.4	5	30	550
51-70 y.	900	90	15	15	120	1.2	1.3	16	1.7	400	2.4	5	30	550
>70 y.	900	90	20	15	120	1.2	1.3	16	1.7	400	2.4	5	30	550
Females														
9-13 y.	600	45	15	11	60	0.9	0.9	12	1.0	300	1.8	4	20	375
14-18 y.	700	65	15	15	75	1.0	1.0	14	1.2	400	2.4	5	25	400
19-30 y.	700	75	15	15	90	1.1	1.1	14	1.3	400	2.4	5	30	425
31-50	700	75	15	15	90	1.1	1.1	14	1.3	400	2.4	5	30	425

y.														
51-70 y.	700	75	15	15	90	1.1	1.1	14	1.5	400	2.4	5	30	425
>70 y.	700	75	20	15	90	1.1	1.1	14	1.5	400	2.4	5	30	425
Pregnancy														
14-18 y.	750	80	15	15	75	1.4	1.4	18	1.9	600	2.6	6	30	450
19-30 y.	770	85	15	15	90	1.4	1.4	18	1.9	600	2.6	6	30	450
31-50 y.	770	85	15	15	90	1.4	1.4	18	1.9	600	2.6	6	30	450
Lactation														
14-18 y	1200	115	15	19	75	1.4	1.6	17	2.0	500	2.8	7	35	550
19-30 y.	1300	120	15	19	90	1.4	1.6	17	2.0	500	2.8	7	35	550
31-50 y.	1300	120	15	19	90	1.4	1.6	17	2.0	500	2.8	7	35	550

Source: Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academies Last updated September 26, 2013

There are eight **B vitamins** – thiamine, niacin, riboflavin, pantothenic acid, biotin, B_6, B_{12}, and folic acid. All of these help a variety of enzymes do their jobs, ranging from releasing energy form carbohydrates and fat to breaking down amino acids and transporting oxygen and energy-containing nutrients around the body. Vitamin B_6 is a group of six related compounds mostly involved with making and breaking down amino acids, the building blocks of protein. The classic signs of too little B_6 are dermatitis, anemia, depression and confusion and convulsions

and too little B_6 means too much homocysteine and an increased risk of heart disease. One form of vitamin B_6 helps convert eh amino acid tryptophan into serotonin, an important chemical messenger used by the brain, nervous system and digestive tract. Getting too little vitamin B_{12} can cause pernicious anemia, and other problems including memory loss and dementia, muscle weakness, loss of appetite, and tingling in the arms and legs and can lead to an accumulation of homocysteine, since vitamin B_{12} is involved in converting homocysteine into the amino acid methionine. Because vitamin B_{12} is only found in animal products, deficiencies tend to crop up in strict vegetarians, also called vegans. People with inflammatory bowel disease or AIDS can have problems absorbing vitamin B_{12}, from food and drinking too much alcohol interferes with this vitamin as do a number of drugs, including some acid-neutralizing drugs used to treat ulcers, colchicine, used to treat gout and Dilantin, used to treat seizures. The current recommended daily intake for vitamin B_{12} is 6 micrograms. Liver is clearly the most efficient food source of B_{12}, delivering about 23 micrograms per ounce. Other good sources include tuna, yogurt, cottage cheese and eggs. In 1998 the Institute of Medicine's Food and Nutrition Board set the recommended daily allowance for folic acid at 400 micrograms per day. Increasing folic acid intake reduces homocysteine levels and following the federal regulation that all grain products be enriched with folic acid beginning in 198 and average blood folate levels among participants of doubled and average homocysteine levels fell by 7 percent (Willet '01: 163-166).

Determined Tolerable Upper Intake Limits for Vitamins

Life Stage	A (µg /d)	C (mg /d)	D (µg /d)	E (mg /d)	Niacin (mg /d)	B_6 (mg /d)	Folate (µg /d)	Choline (mg /d)
Infants								
0-6 mo.	600	n/a	25	n/a	n/a	n/a	n/a	n/a
6-12 mo.	600	n/a	38	n/a	n/a	n/a	n/a	n/a
Childre n								
1-3 y.	600	400	63	200	10	30	300	1.0
4-8 y.	900	650	75	300	15	40	400	1.0
Males								
9-13 y.	1700	1200	100	600	20	60	600	2.0
14-18 y.	2800	1800	100	800	30	80	800	3.0
19-30 y.	3000	2000	100	1000	35	100	1000	3.5
31-50 y.	3000	2000	100	1000	35	100	1000	3.5
51-70 y.	3000	2000	100	1000	35	100	1000	3.5

>70 y.	3000	2000	100	1000	35	100	1000	3.5
Females								
9-13 y.	1700	1200	100	600	20	60	600	2.0
14-18 y.	2800	1800	100	800	30	80	800	3.0
19-30 y.	3000	2000	100	1000	35	100	1000	3.5
31-50 y.	3000	2000	100	1000	35	100	1000	3.5
51-70 y.	3000	2000	100	1000	35	100	1000	3.5
>70 y.	3000	2000	100	1000	35	100	1000	3.5
Pregnancy								
14-18 y.	2800	1800	100	800	30	80	800	3.0
19-30 y.	3000	2000	100	1000	35	100	1000	3.5
31-50 y.	3000	2000	100	1000	35	100	1000	3.5
Lactation								
14-18 y	2800	1800	100	800	30	80	800	3.0
19-30 y.	3000	2000	100	1000	35	100	1000	3.5
31-50 y.	3000	2000	100	1000	35	100	1000	3.5

Source: Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academies Last updated September 26, 2013 n/a used instead of ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts.

A **Tolerable Upper Intake Level** (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. The UL is based on adverse effects in laboratory animals and this data could be used to set a UL for adults but not children and adolescents. The ULs for magnesium represent intake from a pharmacological agent only and do not include intake from food and water. Due to a lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, and carotenoids. In the absence of a UL, extra caution may be warranted in consuming levels above recommended intakes. Members of the general population should be advised not to routinely exceed the UL. The UL is not meant to apply to individuals who are treated with the nutrient under medical supervision or to individuals with predisposing conditions that modify their sensitivity to the nutrient. Although the UL was not determined for arsenic, there is no justification for adding arsenic to food or supplements. Although silicon has not been shown to cause adverse effects in humans, there is no justification for adding silicon to

supplements. Although vanadium in food has not been shown to cause adverse effects in humans, there is no justification for adding vanadium to food and vanadium supplements should be used with caution.

Recommended Dietary Allowance and Adequate Intakes of Minerals

Life Stage	Calcium (mg/d)	Chromium (µg/d)	Copper (µg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)	Manganese (mg/d)	Molybdenum (µg/d)	Phosphorus (mg/d)	Selenium (µg/d)	Zinc (mg/d)	Potassium (g/d)	Sodium (g/d)	Chloride (g/d)
Infants															
0-6 mo.	200	0.2	200	0.01	110	0.27	30	0.003	2	100	15	2	0.4	0.12	0.18
6-12 mo.	260	5.5	220	0.5	130	11	75	0.6	3	275	20	3	0.7	0.37	0.57
Children															
1-3 y.	700	11	340	0.7	90	7	80	1.2	17	460	20	3	3.0	1.0	1.5
4-8 y.	1000	15	440	1	90	10	130	1.5	22	500	30	5	3.8	1.2	1.9
Males															
9-13 y.	1300	25	700	2	120	8	240	1.9	34	1250	40	8	4.5	1.5	2.3
14-18 y.	1300	35	890	3	150	11	410	2.2	43	1250	55	11	4.7	1.5	2.3
19-30	100	35	900	4	150	8	400	2.3	45	700	55	11	4.7	1.5	2.3

y.	0														
31-50 y.	1000	35	900	4	150	8	420	2.3	45	700	55	11	4.7	1.5	2.3
51-70 y.	1000	30	900	4	150	8	420	2.3	45	700	55	11	4.7	1.3	2.0
>70 y.	1200	30	900	4	150	8	420	2.3	45	700	55	11	4.7	1.2	1.8
Females															
9-13 y.	1300	21	700	2	120	8	240	1.6	34	1250	40	8	4.5	1.5	2.3
14-18 y.	1300	24	890	3	150	15	360	1.6	43	1250	55	9	4.7	1.5	2.3
19-30 y.	1000	25	900	3	150	18	310	1.8	45	700	55	8	4.7	1.5	2.3
31-50 y.	1000	25	900	3	150	18	320	1.8	45	700	55	8	4.7	1.5	2.3
51-70 y.	1200	20	900	3	150	8	320	1.8	45	700	55	8	4.7	1.3	2.0
>70 y.	1200	20	900	3	150	8	320	1.8	45	700	55	8	4.7	1.2	1.8
Pregnancy															
14-18 y.	1300	29	1000	3	220	27	400	2.0	50	1250	60	12	4.7	1.5	2.3
19-	100	30	100	3	220	27	350	2.0	50	700	60	11	4.7	1.5	2.3

30 y.	0		0												
31-50 y.	1000	30	1000	3	220	27	360	2.0	50	700	60	11	4.7	1.5	2.3
Lactation															
14-18 y	1300	44	1300	3	290	10	360	2.6	50	1250	70	13	5.1	1.5	2.3
19-30 y.	1000	45	1300	3	290	9	310	2.6	50	700	70	12	5.1	1.5	2.3
31-50 y.	1000	45	1300	3	290	9	320	2.6	50	700	70	12	5.1	1.5	2.3

Source: Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academies Last updated September 26, 2013

In the United States, the official currently recommended intake of **calcium** is 1,000 mg a day from ages nineteen to fifty, 1,200 mg a day for ages fifty and over and 1,300 mg a day for pregnant or lactating women. As the body digests protein, it releases amino acids into the bloodstream, the protein, drawn mostly form the skeleton, helps neutralize these acids. A number of studies have shown the more protein consumed, the more calcium excreted in the urine. When it comes to leaching calcium from bone, animal protein is somewhat more powerful than vegetable protein. Bone and dental enamel formation and healing is a hematopoietic process whereby dietary calcium and phosphorus (found in animal products, soy and mung beans) combine to form hydroxy-apatite. A number of other vitamins and minerals are involved in smaller quantities. Vitamin D is a fat-soluble vitamin that helps the body absorb calcium to create dense bones. Women consuming more than 109 micrograms of Vitamin K a day were found by the Nurses' Health Study to have be 30 percent less likely to break a hip than women got less than that amount. Vitamin K is mainly found in green vegetables such as dark green lettuce, broccoli, spinach, Brussels sprouts, and kale. Fluoride is added to drinking water and toothpaste to fight cavities, however it creates cheap bone and has not been found to be highly effective at preventing or treating osteoporosis (Willet '01: 138-150).

Magnesium is an all-time favorite nutritional supplement. From stress to muscle cramps to premenstrual cramps to migraines, to constipation, magnesium can benefit most people. The only determining factor in the use of magnesium for inflammatory bowel disease is during diarrhea states. Magnesium can induce diarrhea states in most individuals after a certain dosage. Usually around 800 mg. Patients should take the highest dosage that they can take without getting diarrhea. In most people this lies around 600-750 mg per day in divided doses.

Magnesium can help regulate proper bowel functions, reduce stress, prevent and treat anxiety, improve sleep and prevent migraines (Black ’10: 123). Magnesium is a common element essential for hundreds of biological processes, from building substances such as DNA and proteins from scratch to releasing the energy in food, and from contracting muscles to sending signals along nerves. The current target for magnesium is 420 milligrams for men and 320 milligrams for women. **Potassium** is the most abundant positively charged particle inside the cells. The body regulates the concentration of potassium very carefully because too much or too little can cause problems. A drop in potassium levels causes fatigue, extra heartbeats and causes muscle cramps or pain. Too little potassium combined with too much sodium may also cause high blood pressure. Low potassium is also a problem for many people who take diuretics to control high blood pressure and for heavy coffee drinkers. Extra potassium can lower blood pressure. Bananas are famous for the amount of potassium they contain. Fruits and vegetables are all good sources. The metal **selenium** is a potent antioxidant, but there isn't enough of it to act directly so selenium sits at the active site of several enzymes that break down peroxides, potent oxidizing agents that are made throughout the body. Some studies of selenium show a reduction in cancer and other don't. It is important to note that selenium helps the body to absorb vitamin E. The recommended daily allowance for selenium is 55 micrograms a day for men and women and is safe up to 400 micrograms a day. **Zinc** plays a key role in immune system health, acting as an antioxidant, needed for proper vision and involved in blood clotting, wound healing and normal development of sperm. Most U.S. residents get less than the recommended daily amount of zinc – 15 milligrams for men and 12 milligrams for women. Pregnant and lactating women need extra zinc, for themselves and the child they are carrying or feeding. Children also need enough zinc and too little zinc may be one of the ways that undernourishment slows brain development and motor skills, contributes to hyperactivity and causes problems with attention. Older people need zinc for several reasons, they consume less zinc than younger people, they have trouble absorbing zinc from food and medications, especially diuretics for high blood pressure, can increase zinc excretion. Heavy drinkers, people with digestive problems such as Crohn's disease and ulcerative colitis and those with chronic infections may also need extra zinc. The biggest source of zinc is red meat and poultry (Willet '01: 170-176).

Increase **potassium** intake from food to reduce blood pressure and the risk of cardiovascular disease, stroke and coronary heart disease in adults. WHO recommends a potassium intake of at least 90 mmol/ day (3510 mg/day) for adults. WHO suggests an increase in potassium intake from food to control blood pressure in children. The recommended potassium intake of at least 90 mmol/day should be adjusted downward for children, based on the energy requirements of children relative to those of adults. Reduce **sodium** intake to reduce blood pressure and the risk of cardiovascular disease, stroke and coronary heart disease in adults. WHO recommends a reduction to below 2 g/day sodium (5 g/day salt) in adults. WHO recommends a reduction in sodium intake to control blood pressure in children. The recommended maximum level of intake of 2 g/day sodium in adults should be adjusted downward for children, based on the energy requirements of children relative to those of adults. Most people consume too much sodium through salt (corresponding to consuming an average of 9–12 g of salt per day) and not enough potassium (less than 3.5 g). High sodium intake and insufficient potassium intake contribute to high blood pressure, which in turn increases the risk of heart disease and stroke. Reducing salt intake to the recommended level of less than 5 g per day could prevent 1.7 million deaths each year. Potassium can mitigate the negative effects of elevated sodium consumption on blood pressure. Intake of potassium can be increased by consuming fresh fruit and vegetables (WHO '19: 24, 25).

All food-grade salt, used in household and food processing, should be fortified with iodine, as a safe and effective strategy for the prevention and control of iodine deficiency disorders in populations living in stable and emergency settings. **Iodized salt** has a large effect on reducing the risk of goiter, cretinism, low cognitive function, and iodine inadequacy, as indicated by low urinary iodine excretion. In some contexts, iodization of salt at the population level may cause a transient increase in the population incidence of hyperthyroidism, but not hypothyroidism. However, the beneficial effects of iodization of salt far outweigh the potential adverse effects (WHO '19: 27). The average person needs less than 1 gram of sodium a day to keep systems in good working order. The average person gets between 2 and 5 grams a meal. That's up to 15 grams, or about 4 teaspoons of salt a day. The excess is excreted but not always before it can do some damage pulling water from cells and thus increasing blood pressure. Salt is hidden in many common foods that people with high blood pressure must be aware of; examples; macaroni and cheese, 1 cup 1,343 mg of salt, canned chili with beans 1 cup 1,336 mg of salt, corned beef brisket, 3 ounces 964 mg, cottage cheese ½ cup 457 mg, canned peas 1 cup 428 mg, slice of apple pie 333 mg, American cheese one slice 300 mg (Willet '01: 173).

Determined Tolerable Upper Intake Limits for Minerals

Life Stage	Boron (mg/d)	Calcium (mg/d)	Copper (mg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)	Manganese (mg/d)	Molybdenum (µg/d)	Nickel (mg/d)	Phosphorus (g/d)	Selenium (µg/d)	Zinc (mg/d)	Sodium (g/d)	Chloride (g/d)
Infants															
0-6 mo.	n/a	1000	n/a	0.7	n/a	40	n/a	n/a	n/a	n/a	n/a	45	4	n/a	n/a
6-12 mo.	n/a	1500	n/a	0.9	n/a	40	n/a	n/a	n/a	n/a	n/a	60	5	n/a	n/a
Children															
1-3 y.	3	2500	1	1.3	200	40	65	2	300	0.2	3	90	7	1.5	2.3
4-8 y.	6	2500	3	2.2	300	40	110	3	600	0.3	3	150	12	1.9	2.9
Males															

9-13 y.	11	3000	5	10	600	40	350	6	1100	0.6	4	280	23	2.2	3.4
14-18 y.	17	3000	8	10	900	45	350	9	1700	1	4	400	34	2.3	3.6
19-30 y.	20	2500	10	10	1100	45	350	11	2000	1	4	400	40	2.3	3.6
31-50 y.	20	2500	10	10	1100	45	350	11	2000	1	4	400	40	2.3	3.6
51-70 y.	20	2000	10	10	1100	45	350	11	2000	1	4	400	40	2.3	3.6
>70 y.	20	2000	10	10	1100	45	350	11	2000	1	3	400	40	2.3	3.6
Females															
9-13 y.	11	3000	5	10	600	40	350	6	1100	0.6	4	280	23	2.2	3.4
14-18 y.	17	3000	8	10	900	45	350	9	1700	1	4	400	34	2.3	3.6
19-30 y.	20	2500	10	10	1100	45	350	11	2000	1	4	400	40	2.3	3.6
31-50 y.	20	2500	10	10	1100	45	350	11	2000	1	4	400	40	2.3	3.6
51-70 y.	20	2000	10	10	1100	45	350	11	2000	1	4	400	40	2.3	3.6

>70 y.	20	2000	10	10	1100	45	350	11	2000	1	3	400	40	2.3	3.6
Pregnancy															
14-18 y.	17	3000	8	10	900	45	350	9	1700	1	3.5	400	34	2.3	3.6
19-30 y.	20	2500	10	10	1100	45	350	11	2000	1	3.5	400	40	2.3	3.6
31-50 y.	20	2500	10	10	1100	45	350	11	2000	1	3.5	400	40	2.3	3.6
Lactation															
14-18 y	17	3000	8	10	900	45	350	9	1700	1	4	400	34	2.3	3.6
19-30 y.	20	2500	10	10	1100	45	350	11	2000	1	4	400	40	2.3	3.6
31-50 y.	20	2500	10	10	1100	45	350	11	2000	1	4	400	40	2.3	3.6

Source: Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academies Last updated September 26, 2013

Assessment of nutritional state lies in search for the subtle **signs of deficiency** and toxicity. 'Height for age' is an indication of stunting in growing children whereas 'weight for height' reflects adiposity or wasting from disease. **Dementia encephalopathy** can be caused by thiamine, nicotinamide and pyridoxine deficiency. Poor hair and hair loss can be caused by protein, zinc and copper deficiency during general severe illness. **Visual failure** (diminished dark adaptation) and xerophthalmia (dry eyes) can be caused by vitamin A and riboflavin deficiency. **Pallor** (anaemia) can be caused by iron, vitamin B_{12}, folic acid, zinc, copper, pyridoxine and protein deficiency. **Stomatitis gingivitis** can be caused by vitamin C deficiency. **Glossitis** can be caused by iron, riboflavin, nicotinamide and zinc deficiency. **Goiter** can be caused by iodine deficiency. **Leuconychia** (white nails) can be caused by protein deficiency. Fungal infections of the hands can be caused by calcium defiency. **Koilonychia** (Spoon-shaped

nails) can be caused by iron and zinc deficiency. **Skin ulceration** can be caused by deficiency in essential fatty acids and zinc. **Dermatitis** – scaly, pigmented and erythematous – can be caused by nicotinamide, riboflavin, vitamin A and essential fatty acids deficiency. **Muscle wasting** can be caused by protein calorie deficiency. **Muscle weakness** can be caused by calcium, protein, magnesium and postassium deficiency. **Liver enlargement** can be caused by protein calorie defiency. Ascites and edema can be caused by protein deficiency. 'Curly hairs' perifollicular haemorrhages and **bruising** can be caused by vitamin C deficiency. **Peripheral neuropathy** can be caused by thiamine, pyridoxine and nicotinamide deficiency. **Swollen painful joints** can be caused by vitamin C deficiency. **Ataxia** can be caused by vitamin B_{12} and vitamin E deficiency. **Hypogonadism**, weight loss and muscle weakness may be helped with multivitamins (Jones et al '85: 2, 3). **Diarrhea** can be caused by iron and vitamin B_{12} deficiency, particularly in thin vegans who don't eat iron rich dark green leafy vegetables at every meal. **Constipation** is the more common disorder with the American diet resulting in colitis, hepatoxicity, atherosclerosis, arthritis and cancer.

The five vitamins that many people don't get enough of in their diets are folic acid, vitamins B_6, B_{12}, D and E. Worldwide, about one in seven people don't get enough iron. Too little of this mineral makes it hard for red blood cells to ferry oxygen from lungs to tissues. Iron-poor blood causes one to be pale, fatigued, and mentally dull. Lack of iron stunts the growth and development of children and can damage long-term thinking skills. Iron deficiency isn't major problem in the United States, due to meat and iron fortified grain and other products. Thin vegans are frequently deficient in iron unless they eat green leafy vegetables, such as kale or nettles, every meal. The body carefully regulate the amount of iron absorbed from grains, fruits vegetables, and supplements. The iron from meat is much better absorbed than that from vegetable sources, and can lead to an over-accumulation of this mineral (Willet '01: 177, 169, 170). **Deficiencies** of most essential nutrients collectively and individually impair cell growth and division . This can be readily detected by assessing cell-mediated immunity. The peripheral lymphocyte count falls in malnutrition ($<1.2x10^9$/l) and the in-vitro lymphoblast response to a mitogen such as phytohaemagglutinin is impaired. Biochemical investigation of 'nutrient status' can be performed, but some are not available routinely in most laboratories. Serum assays are available for the estimation of most of the fat and water soluble vitamins. Serum folate levels should be performed on plasma specimens taken after fasting, otherwise red-cell folate estimations are more reliable. Plasma or serum fatty acid profiles will enable estimation of the triene-etraene ratio as an index of essential fatty acid deficiency. Vitamin K is assessed by measurement of the prothrombin time. Vitamin C status can be determined by measuring its content in leucocytes. Plasma concentrations of zinc, copper and iron can be measured but are unreliable. Leucocyte zinc concentrations may be a better criterion of tissue zinc depletion. Plasma iron-binding capacity, transferrin concentration, or ferritin levels are of value in measuring iron status. A reduced plasma transferrin level (<20 g/l) is also a sensitive index of protein malnutrition. A plasma albumin level below 35 g/l is suggestive of protein deficiency (Jones et al '85: 3, 4).

Vitamin and Mineral Deficiencies

Site	Sign or Symptom	Deficiency
Hair	Dryness	Zine
	Alopecia	Zinc
	Easy pluckability	Vitamins E and A
	Corkscrew hair	Vitamin C
	Color change	Biotin

Nails	Dystrophic	Iron
Skin	Hyperpigmentation	Niacin
	Erythema	NIcain
	Scrotal dermatitis	Niacin
	Follicular keratosis	Vitamin A
	Acneiform lesions	Vitamin A
	Xerosis	Vitamin A, linoleic acid
	Ecchymosis	Vitamins C and K
	Petechiae	Vitamins C and K
	Nasolabial seborrhea	Vitamin B_6
Eyes	Angular palpebritis	Vitamin B_2
	Bitot's spots	Vitamin A
	Conjunctival keratosis	Vitamin A
	Keratomoalacia	Vitamin A
Mouth	Glossitis	Vitamin B_{12}, niacin, folate
	Angular stomatitis	Vitamin B_2
	Cheilosis	Vitamin B_2
	Magenta tongue	Vitamin B_2
	Scarlet, raw tongue	Niacin
	Atrophic papillae	Niacin
	Swollen, bleeding gums	Vitamin C
Neurologic	Peripheral neuropathy	Thiamine, niacin, B_6
	Wernicke's encephalopathy	Thiamine
	Encephalopathy (Pellagra)	Niacin
	"Burning feet" syndrome	Patothenic acid
	Loss of deep tendon reflexes	Thiamine, vitamin B_1 & B_{12}
Musculoskeletal	Osteomalacia	Vitamin D
	Joint pain	Vitamin C
	Tender muscles	Thiamine
Hematologic	Hemolytic anemia	Vitmain E
	Macrocyctic anemia	Vitamin B_{12}, folate
	Microcytic anemia	Vitamin B_6, iron, copper
	Coagulopathy	Vitamin K
	Thrombocytopenia	Linoleic acid
Visceral	Congestive heart failure	Thiamine
	Diarrhea	Iron, folate, zinc, niacin
	Goiter	Iodine
	Hepatosplenomegaly	Zinc

Source: Thom & Daly '90: Table 59-5, Pg. 499

The presence of pallor, subcutaneous edema, skin lesions, muscle wasting and chronic diarrhea are general clinical signs of **malnutrition**. Patients with kwashiorkor will have edema, muscle wasting, sychomotor change, dyspigmentation of hair, ascites, liver enlargement and parotid gland hypertrophy. Marasmic patients demonstrate wasting of muscle and fat, but when stressed, also develop signs and symptoms seen with kwashiorkor. Vitamin deficiencies occur common in association with protein-calorie malnutrition (Thom & Daly '90: 499). Iron deficiency anemia is the most common cause of diarrhea worldwide, and is as likely to occur in animal and protein product deprived cancer and cardiac patients as in developing nations. The recommended Dietary Allowance for vitamin $B\text{-}_{12}$ is 2 micrograms, 2 millionths of a gram. Because soils have

been sprayed with chemical fertilizers and pesticides, they are devoid of the B-12 that was once abundant in the dirt. Omega-3 fats, can also be an issue. It takes twenty of today's supermarket eggs to get as much Omega-3s as are provided by a single egg from a free range chicken. Omega 3s are plentiful in flax seeds and oil, in fatty fish such as salmon, herring, mackerel and sardines, and can be found in lesser amounts in walnuts, hemp seeds, green leafy vegetables and in canola oil (Robbins '01: 91). Some 2 billion people around the world are subject to deficiencies in micronutrients. Nutritional optic neuropathy (aka deficiency optic neuropathy) is a dysfunction of the optic nerve resulting from improper dietary content of certain nutrients essential for normal functioning of the nerve fibers. Most commonly, it results from folic acid and vitamin B complex deficiency associated with malnutrition or poor dietary habits, incorrectly applied vegetarian diet, or chronic alcohol abuse. Vitamin B_{12} deficiency can cause optic neuropathy but it is very unusual to find dietary deficiency when animal products are consumed e.g. ham and sausages are significant sources of the vitamin B_{12}. If treated early, nutritional optic neuropathy can be reversed (Braine '19).

The new WHO report, *Essential Nutrition Actions: mainstreaming nutrition throughout the life course,* stresses the role of primary health care as the foundation of universal health coverage. Every $1 spent by donors on basic nutrition programs, returns $16 to the local economy, WHO said in a statement. Approximately 45 per cent of mortality in children under-five is linked to malnutrition. Breastfeeding with complimentary feeding, could reduce mortality among the under-fives by 19 per cent. Limiting salt intake to the recommended level of less than five grams daily, could prevent 1.7 million deaths per year alone. Meanwhile obesity levels continue to rise, jumping from 4.8 to 5.9 percent, for children between 1990 and 2018; an increase of nine million. When adults are accounted for, 13 per cent of the world's population are considered obese, with numbers rising in nearly every country and region. Health issues stemming from poor nourishment have seen improvements in some respects, with a global decline in stunting, for example, between 1990 and 2018 from 39.2 to 21.9 per cent, in children under-five. Intervention means health packages "need to contain robust nutrition components but countries will need to decide which interventions best support their national health policies, strategies and plans," said the UN health agency. The 2019 guide aims to address the double burden of treating people who are underweight and overweight and provides countries with a roadmap for better interventions (WHO '19).

Malnutrition includes stunting, wasting, underweight, micronutrient deficiencies, overweight and obesity (among both children and adults), and associated chronic conditions such as diabetes, cardiovascular disease and some cancers. Malnutrition, in one form or another, is estimated to affect one in three people globally and is linked to morbidity and mortality. Child stunting is low height-for-age. Child wasting is low weight-for-height. Child overweight means high weight-for-height. **Adult obesity** is defined carrying excess body fat with a body mass index equal to or higher than 30 kg/m^2. Diet is an important factor for many non-communicable conditions including heart disease, stroke, cancer, diabetes and chronic lung disease. The Global Burden of Disease Study 2013 identified "dietary risks" as constituting the largest risk factor responsible for the global burden of disease (11.3 million deaths and 241.4 million disability adjusted life years [DALYs]), with child and maternal malnutrition (1.7 million deaths and 176.9 million DALYs), and high body mass index (BMI; 4.4 million deaths and 134.0 million DALYs) not far behind. Approximately 45% of mortality in children aged under 5 years is linked to malnutrition.

Globally, **stunting** has been declining; between 1990 and 2018, the prevalence of stunting in children aged under 5 years declined from 39.3% to 21.9%, representing a decrease in the

number of children with stunting from 253.4 million to 149.0 million (14). However, global estimates mask much slower progress in Africa (42.6% to 33.1%) and South-East Asia (49.6% to 31.9%) (14). **Wasting** still affects 49.5 million children aged under 5 years (7.3%) worldwide, with more than half of these children residing in South-East Asia. During this same period, overweight has been increasing; the prevalence of children considered overweight rose from 5.0% to 5.9% between 1990 and 2018, an increase of over 9 million children (from 30.9 million in 1990 to 40.1 million in 2018). Among adults, the most recent data available from 2014, indicate that 462 million are underweight, while 1.9 billion are overweight and 600 million of those (or approximately 13% of the world's population, a rate that doubled between 1980 and 2014) are obese. Adult overweight, obesity and diabetes are rising in nearly every region and country (WHO '19: 7).

Micronutrient deficiency remains a significant public health challenge – approximately one third of the world's population (32.9%) suffers from anaemia, as of 2010 (16). The population groups most vulnerable to anaemia, as of 2016, include children under 5 years of age (41.7% with anaemia), particularly infants and children under 2 years. of age; non-pregnant women (15–49 years; 32.5% with anaemia); and pregnant women (40.1% with anaemia) (17, 18). This equates to roughly 800 million women and children with anaemia globally. Iron deficiency, a primary cause of anaemia in many settings, is estimated to affect an even larger number of people – 2 billion (19) – and, independently of the negative effects caused by anemia, is associated with delayed cognitive and behavioral development in children, as well as reduced productivity in adults and impaired cognitive functioning in women. Other prevalent micronutrient deficiencies include vitamin A and zinc. Vitamin A deficiency increases the risk of infectious morbidity and mortality from diarrhea or measles, and can cause visual impairment in children and pregnant women, as well as anaemia. Zinc deficiency is also associated with increased risk of infectious morbidity and can impair growth. Still other nutrient deficiencies, notably of calcium and folic acid, place pregnant women at risk of pregnancy complications and poor birth outcomes (WHO '19: 7, 8). WHO *Essential Nutrition Actions: Mainstreaming Nutrition Through the Life-Course* (*2019)*, encourages protein to treat osteoporosis in undernourished older people, although excess protein eliminates calcium and the omission of a prescription for routine calcium supplementation for postmenopausal women, inhibits the formation of calcium, vitamin D and phosphorus into **apatite**, wanted to heal bones and tooth enamel. Brush teeth within ten minutes of eating sugar.

The United Nations Decade of Action on Nutrition 2016–2025 focuses on action to reduce hunger and malnutrition (WHO '19: 15). The importance of adequate fetal nutrition during pregnancy and during the first 2 years of life has been well emphasized for prevention of undernutrition among children, but is also a key determinant of the later development of adult overweight and associated chronic conditions such as diabetes (WHO '19: 10). The WHO recommendation to create a healthy food environment that enables people to adopt and maintain healthy dietary practices, applicable to all countries, settings and population groups. Reduce the intake of free sugars through the life-course. In both adults and children, WHO recommends reducing the intake of free sugars to less than 10% of total energy intake. WHO suggests a further reduction of the intake of free sugars to below 5% of total energy intake. Excess calories from foods and drinks that are high in free sugars also contribute to unhealthy weight gain, which can lead to overweight and obesity. Recent evidence also shows that free sugars influence blood pressure and serum lipids, and suggests that a reduction in intake of free sugars reduces risk factors for cardiovascular diseases. Modify dietary fat intake so total fat intake should be less than 30% of total energy intake, saturated fatty acid intake should be less than 10% of total energy intake and trans-fatty acid intake should be less than 1% of total energy intake. Saturated

fatty acids and trans-fatty acids should be replaced with unsaturated fatty acids, particularly polyunsaturated fatty acids. Reducing the total fat intake to less than 30% of total energy intake helps to prevent unhealthy weight gain and reduces the risk of developing noncommunicable diseases. Consume at least 400 g, or five portions, of fruit and vegetables per day, to reduce the risk of noncommunicable diseases and helps to ensure an adequate daily intake of dietary fiber.

The need for **clinical nutritional support** is apparent in patients experiencing catabolic responses in association with major surgery, severe burns, intestinal resection or disease, or prolonged unconsciousness. The metabolic rate is increased by 10% after simple surgery, by 20% after major surgery and multiple fractures, and by over 100% for severe burns. Septicaemias induce a 13% increase in energy requirements per degree Celsius increase in core body temperature. The needs for water, electrolytes, fatty acids (linolenic acid), vitamins, minerals and trace elements are also higher than basal requirements in patents needing nutritional support. Electrolyte balance can be determined by measuring electrolyte loss in urine, drainage fluids, gastric aspirates and intestinal effluent. Nutritional support can be given either enterally (via the intestine) or parenterally (intravenously). The progress of a patient receiving nutritional support should be monitored closely. A flow chart on the patient's weight, nutrient and energy uptake, and details on electrolyte, fluid nitrogen and other laboratory values can be recorded. With this approach, nutritional deficiencies can be avoided or anticipated and the occasional problems of impaired liver function (e.g. cholestasis, and raised aminotransferases, γ- glutamyl transpeptidease and alkaline phosphatase activities) and hypophosphataemia will be detected. Hypophosphataemia occurs ore frequently with parenteral nutrition. An additional problem with both enteral and parenteral nutritional support is the evelopment of hyperglycaemia with the hazards of non-ketonic hyperosmolar coma and of dehydration secondary to glycosuria for which additional insulin can be administered subcutaneously or via an infusion. The long-term complications of nutritional support are the development of deficiencies, usually involving vitamins D and E and trace metals zinc, copper and selenium (Jones et al '85: 4-6).

If a patient has any gastrointestinal function, the **enteral route** is preferred. If the patient can cooperate by swallowing, then liquidized foods used for enteral nutrition can be given orally, in frequent sips; otherwise they can be administered continuously through a fine-bore polyvinyl catheter which is passed either nasogastrically or through a gastrostomy or jejunostomy. The continuous feeds can be dripped under gravity, and a pump is usually unnecessary. If gastrointestinal function is normal, then whole protein sources can be used in feeds, but with defective intraluminal proteolysis or short bowel syndromes, amino-acid absorption may be maximized by giving oligopeptide preparations, but these are expensive and have a high osmolality. Energy can be provided as glucose polymers, which have a low osmolality and can be hydrolysed by α-amylase and by mucosal maltase and α-dextrinase. A source of linolenic acid (or linolenic and arachidonic acids) should be added and, if lipolysis is impaired, medium-chain triacylglycerols can be used. Lipid (37 kJ/g) provides an alternative energy source to carbohydrate (17 kJ/g) and increases the palatability of the feeds for those taking them orally. Supplements of vitamins and essential minerals should be added routinely. A quarter of patients suffer some abdominal distension and discomfort. Enteral support has fewer complications and is less labour intensive than parenteral nutrition and once established, is much easier to maintain on an out-patient basis (Jones et al '85: 5).

The solutions used for **intravenous feeding** have high osmolalities and, if infused into peripheral veins, can cause thrombophlebitis. Preferably these solutions should be administered via a silicon rubber catheter, the distal end of which is passed to the superior vena cava through a subclavical/cephalic or, less frequently, an internal jugular vein. This enables the venous return

of 2-3 liters a minute to dilute the infused solution. The use of the subclavian vein carries a definite risk of pneumothorax. Therefore the cephalic vein may be preferred. The usual source for parenteral nutrition is glucose, given as hypertonic dextrose, but energy can be derived also from lipid, which has a higher energy density and is less sclerosant to the vasculature. In severe catabolic states (ie. More than 18 g nitrogen loss in 24 h), however, glucose should be used because the uptake of plasma triacylglycerol by tissues is impaired. Nitrogen is provided as crystalline α amino acids, of which 40% should be essential amino acids. Lipid is administered as 10% to 20% intralipid preparation, to which fat-soluble vitamin supplements can be added. Commercial supplements of trace elements and vitamins are added to the infusates. A recent major practical advance is that nutrients are metabolized more efficiently if given simultaneously, and this reduces insulin requirements. Furthermore, pre-mixing nutrient solutions reduces the risk of bacterial contamination. Ideally, the solutions are prepared daily, according to prescription, by a pharmacist and dispensed in sealed 'giving bags' making home parenteral nutrition a possibility in the management of severe gastrointestinal failure (Jones et al '85: 5, 6).

2. Child Nutrition

Breast milk is the most desirable complete food source for the first 6 months. It is nutritionally superior, bacteriologically safe, least allergenic and full of anti-infectious factors and immune cells. Breast feeding promotes good tooth and jaw development, it is more convenient and cost effective and it promotes close mother-infant contact. Optimal breast feeding is attained on a demand feeding schedule. Formula intake varies per infant but averages 4 oz. six times per day at 1 month to 4.2 oz five times per day at 6 months when solid foods are introduced (Muscari '01: 306). Infants should be exclusively breastfed (meaning only breast milk with no other solids or liquids given, with the exception of oral rehydration solution, vitamin/mineral drops or medicines) for the first 6 months of life, to achieve optimal growth, development and health. Exclusive breastfeeding – defined as the practice of only giving an infant breast milk for the first 6 months of life – has the single largest potential impact on child mortality of any preventive intervention. Together with appropriate complementary feeding, breastfeeding has the potential to reduce mortality among children under 5 years of age by 19%. Exclusive breastfeeding reduces the risk of gastrointestinal infection and of all-cause mortality, and protects infants from respiratory infections. Exclusive breastfeeding also has a protective effect against obesity later in life. Key recommendations are to support the Baby-Friendly Hospital Initiative, monitor the *International Code of Marketing of Breast-milk Substitutes* and subsequent World Health Assembly resolutions, to limit marketing of formula milk and improve maternity protection through the workplace (e.g. 6 months of mandatory paid maternity leave and polices to encourage women to breastfeed in the workplace), to empower women to exclusively breastfeed (WHO '19: 34-44). The United States does currently not pay for 12 weeks of maternity leave, but protects the mother from wrongful termination of employment. A woman is entitled to 14 weeks paid leave Maternity Protection pursuant to ILO Convention No. 183 (2000). Six months is however 24 weeks but there is credible medical evidence that a woman should exclusively breastfeed for the first six months and WHO as specifically called for 6 months of mandatory paid leave. Therefore the US Labor Department Unemployment Actuary is challenged to pay for 24 weeks maternity protection pursuant to the most up-to date interpretation of Maternity Protection ILO Convention No. 183 (2000), 3 weeks annual sick days Holiday with Pay ILO Convention No. 132 (1970) and Workers with Family Responsibilities Convention No. 156 (1981) and six month sabbatical every ten years, with unemployment compensation.

Term infants receiving early cord clamping (less than 1 min after birth) are at significantly higher risk of developing iron deficiency at 3–6 months of age than infants receiving delayed cord clamping. Early cord clamping in preterm infants increases the risk of necrotizing enterocolitis and intraventricular hemorrhage and the need for blood transfusions. In the past, protocols for neonatal resuscitation and active management of the third stage of labour have conflicted with the practice of delayed cord clamping. It is necessary to revise and update policies (at regional, national and local levels), curricula/textbooks and clinical protocols to include **delayed cord clamping** as part of essential newborn care. Early cord clamping (less than 1 min after birth) is not recommended unless the neonate is asphyxiated and needs to be moved immediately for resuscitation. For newborn term or preterm babies who do not require positive-pressure ventilation, the cord should not be clamped earlier than 1 min after birth. When newborn term or preterm babies require positive-pressure ventilation, the cord should be clamped and cut, to allow effective ventilation to be performed. If there is experience in providing positive-pressure ventilation without cutting the umbilical cord, ventilation can be initiated before cutting the cord. Newborn babies who do not breathe spontaneously after thorough drying should be stimulated by rubbing the back 2–3 times before clamping the cord and initiating positive-pressure ventilation. Delayed cord clamping is recommended even among women living with HIV or women with unknown HIV status (WHO '19: 33-34). Breast milk provides everything that dietary scientists believe children need to thrive, including antibodies. African children have bacteria that break down fibrous plant based foods. Japanese children have marine bacteria to help digest seafood. Children born by caesarean section take months or even longer to develop a normal population of gut bacteria, and have increased risk of allergies or asthma until age seven. Studies have shown that administering *Lactobacillus* to these children can reduce risk (Enders '15: 163).

All mothers should be supported to **initiate breastfeeding** as soon as possible after delivery, ideally within the first hour after the birth of their infant, including in facilities where maternity and newborn care is provided. Early and uninterrupted skin-to-skin contact between mothers and infants should be facilitated and encouraged as soon as possible after delivery. Place babies in skin-to-skin contact with their mothers immediately following birth, for at least an hour. Mothers should receive practical support to enable them to initiate and establish breastfeeding and manage common breastfeeding difficulties. Mothers should be enabled to position and attach their infants to the breast. Mothers should be coached on how to express breast milk as a means of maintaining lactation in the event of their being separated temporarily from their infants. Facilities providing maternity and newborn services should enable mothers and their infants to remain together and to practice rooming-in through the day and night. This may not apply in circumstances when infants need to be moved for specialized medical care. Early, focused and optimal support to initiate and establish breastfeeding has positive effects on maternal, infant and child outcomes far beyond the hospital stay. Early skin-to-skin contact and early initiation of breastfeeding increase the likelihood of any or exclusive breastfeeding for up to 3–6 months of life, as well as the overall duration of breastfeeding. Early initiation of breastfeeding has also been shown to reduce infection-specific neonatal mortality in infants. Women who are shown how to breastfeed in the immediate postnatal period are more likely to continue any or exclusive breastfeeding to 6 months of age. Begin the practice of early skin-to-skin contact in the first few minutes after delivery, while newborn assessment is occurring. Allow uninterrupted skin-to-skin contact for ideally an hour or more (WHO '19: 34-35).

Exclusive breastfeeding means, all mothers should be discouraged from giving any food or fluids to their infant other than breast milk, unless medically indicated. Almost all mothers can breastfeed successfully; however, there are a small number of health conditions of the infant or

mother that may justify that the mother does not breastfeed, either temporarily or permanently. In these cases, breast-milk substitutes are medically indicated. These conditions include the following: infants with classic galactosaemia, maple syrup urine disease or phenylketoneuria should not receive breast milk or any other milk except specialized formula milk; infants born with very low birth weight (less than1500 g) or at less than 32 weeks' gestation, or who are at risk of hypoglycemia, may need other food in addition to breast milk, for a limited period; mothers with HIV (if replacement feeding is acceptable, feasible, affordable, sustainable and safe) may justify permanent avoidance of breastfeeding. Mothers known to be living with HIV should be provided with lifelong antiretroviral therapy (ART) interventions or antiretroviral prophylaxis to reduce HIV transmission through breastfeeding. National or subnational health authorities should decide whether health services will principally counsel mothers known to be living with HIV to either breastfeed and use antiretroviral medication, or avoid all breastfeeding. The following maternal conditions may justify temporary avoidance of breastfeeding: mothers with severe illness that prevent a mother from caring for her infant; mothers with herpes simplex virus type 1 and active lesions on her breasts; mothers taking sedating psychotherapeutic drugs, anti-epileptic drugs or opioids, or combinations of these drugs; mothers taking radioactive iodine-131; mothers using topical iodine or iodophors in excess; or mothers receiving cytotoxic chemotherapy. Additional foods and fluids apart from breast milk should only be given when medically acceptable reasons exist. Facilities providing maternity and newborn services should have a clearly written breastfeeding policy that is routinely communicated to staff and parents. Breastfeeding provides optimal nutrition for the first 6 months of life and continues to provide an important nutritional contribution well beyond the first year of life. Breastfeeding protects against common children illnesses, such as diarrhea and pneumonia, supports optimal linear growth, and has been associated with higher intelligence quotient (IQ) in children. Continued breastfeeding also delays maternal fertility and is associated with reduced risk of breast and ovarian cancer, type 2 diabetes, hypertension and some cardiovascular diseases in the mother (WHO '19: 40-44).

Low-birth-weight infants, including very low-birth-weight infants (infants with birth weight between 1000 g and 1500 g), should be fed their mother's own milk. Low-birth-weight infants should be exclusively breastfed until 6 months of age. Very low-birth-weight infants who cannot be fed their mother's own milk or donor human milk and fail to gain weight with standard infant formula milk should be provided with preterm infant formula milk. Feeding low-birth-weight infants with formula milk increases the risk of mortality, severe infections and necrotizing enterocolitis, and decreases mental development scores, as compared to feeding with their mother's own milk. Feeding low-birth-weight infants with donor human milk is associated with lower incidence of infections and necrotizing enterocolitis, as compared to feeding with formula milk. Low-birth-weight infants who need to be fed by an alternative oral feeding method should be fed by cup, palladia or spoon. Feeding of low-birth-weight infants should be based on the infant's hunger cues, except when the infant remains asleep beyond 3 hours after the last feed. For very low birth-weight infants in resource-limited settings, enteral feeds of 10 mL/kg per day should be provided, preferably of expressed breast milk, starting from the first day of life, with the remaining fluid requirement met by intravenous fluid (WHO '19: 45-46).

Neonates weighing 2000 g or less at birth should be provided as close to continuous kangaroo mother care as possible. **Kangaroo mother care** involves: early, continuous and prolonged skin-to-skin contact between a mother and her neonates; frequent and exclusive breastfeeding; early discharge from hospital. Intermittent kangaroo mother care, rather than conventional care, is recommended for neonates weighing 2000 g or less at birth, if continuous kangaroo mother care is not possible. Low-birth-weight infants are at increased risk of early growth retardation,

infectious disease, developmental delay and death during infants and children. Conventional neonatal care of low-birth-weight infants is expensive and requires highly skilled staff and permanent logistic support. Kangaroo mother care reduces morbidity and mortality in low-birth-weight infants and increases breastfeeding. These recommendations do not apply to clinically unstable infants (WHO '19: 46-47).

Infants who are under 6 months of age and have a weight-for-length more than 3 z-scores below the WHO child growth standards median, or the presence of bilateral pitting edema, are considered to have severe acute malnutrition. These children should receive the same general medical care as infants with severe acute malnutrition who are 6 months of age or older. The development of **severe acute malnutrition** in infants under 6 months of age commonly reflects suboptimal feeding practices, especially breastfeeding practices, in addition to other contributing factors, including low birth weight, diarrhea, or chronic disease/disability. Feeding approaches for infants under 6 months of age with severe acute malnutrition should prioritize establishing, or re-establishing, effective exclusive breastfeeding by the mother or other caregiver. Infants with severe acute malnutrition who are admitted for inpatient care: should be given parenteral antibiotics to treat possible sepsis and appropriate treatment for other medical complications such as tuberculosis (TB), HIV, surgical conditions or disability; should be breastfed where possible. For infants with severe acute malnutrition but no edema, expressed breast milk should be given, and, where this is not possible, commercial (generic) infant formula milk or F-75 (only during the initial or stabilization phase) or diluted F-100 may be given, either alone or as the supplementary feed together with breast milk. Any infant or child with a general danger sign as defined by the Integrated Management of Children Illness (IMCI), unable to drink or breastfeed; vomits everything; has had convulsions (more than one or prolonged >15 min); lethargic or unconscious; convulsing now, should be admitted for urgent treatment and care. Infants under 6 months of age with severe acute malnutrition who do not require inpatient care should: be provided with counseling and support for optimal infant and young child feeding, based on general recommendations for feeding infants and young children, including for low-birth-weight infants; have their weight gain monitored weekly to observe changes; be referred to inpatient care if they do not gain weight, or lose weight while the mother or caregiver is receiving support for breastfeeding; have an assessment of the physical and mental health status of their mothers or caregivers and relevant treatment or support provided (WHO '19: 48-52).

Infants should be **exclusively breastfed for the first 6 months of life**, to achieve optimal growth, development and health. Thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods, while continuing to breastfeed for up to 2 years or beyond. Start at 6 months of age with small amounts of food and increase the quantity as the child gets older, while maintaining frequent breastfeeding. Gradually increase the consistency and variety of food as the infant gets older, adapting to their requirements and abilities. Increase fluid intake during illness, including more frequent breastfeeding, and encourage the child to eat soft, varied, appetizing, favorite foods. After illness, give food more often than usual and encourage the child to eat more. For the average healthy infant, meals should be provided four to five times per day, with additional nutritious snacks offered one or two times per day, as desired. Feed a variety of foods to ensure that nutrient needs are met. As needed, use fortified foods or vitamin–mineral supplements (preferably mixed with or fed with food) that contain iron. Non-breastfed infants and young children need at least 400–600 mL/day of extra fluids in a temperate climate, and 800–1200 mL/day in a hot climate. Increase fluid intake during illness and encourage the child to eat soft, varied, appetizing, favorite foods. After illness, give food more often than usual and encourage the child to eat more (WHO '19: 54-55).

All infants and children aged under 5 years presenting to primary health-care facilities should have both weight and length/height measured, in order to determine their weight-for-length/height and to classify their nutritional status according to the **WHO child growth standards**. In the United States CDC recommends WHO standards be used until 2 years when CDC standards are to be used. They are published in pdf and do not copy well into this document. With respect to identifying both wasting and overweight and obesity, it is important to relate a child's weight-for-age to their length/height, in order to correctly interpret their nutritional status. Measuring weight only can lead to misclassification of nutritional status, though measurement of height/length is not routine in many settings. he prevalence of overweight and obesity has increased sharply in recent decades, including among children and in all regions of the world. As of 2018, an estimated 40 million children aged under 5 years were overweight, with consequences for increased risk of type 2 diabetes, high blood pressure, asthma and other respiratory problems, sleep disorders and liver disease. Children with moderate or severe wasting, severe acute malnutrition or moderate stunting are at increased risk of mortality, particularly those who are severely affected (WHO '19: 56-58).

The **normal weight of a newborn** is 6 to 9 lb (2700-4000g). African-American newborns are 181 to 240 g lighter than white newborns, explaining why low birth weight is twice as common in this group. Chinese, Filipinos, Hawaiians, Japanese and Puerto Ricans also have lower mean birth weights. There is significant difference in birth weights among Native American tribes, but overall they have a higher incidence of newborns weighting 4000g or more (Muscari '01: 170, 78). In April 2006, the World Health Organization (WHO) released new international growth charts for children aged 0--59 months. Similar to the 2000 CDC growth charts, these charts describe weight for age, length (or stature) for age, weight for length (or stature), and body mass index for age. After convening an expert panel the CDC recommends that health care providers use the WHO growth standards to monitor growth for infants and children ages 0 to 2 years of age in the U.S and use the CDC growth charts for children age 2 years and older in the U.S. Breastfeeding is the recommended standard for infant feeding. The WHO charts reflect growth patterns among children who were predominantly breastfed for at least 4 months and still breastfeeding at 12 months. Breast fed infants under one month of age should be having four or more stools in a 24 hour period. Fewer than four, even if wetting frequent is considered a danger sign (Eiger '01:191). All milk, human and cow, is deficient in iron. Skim milk should be avoided until age two because it provides too few calories, an excess of protein and an inadequate amount of essential fatty acids (Eiger :196). Human milk has been implicated in HIV transmission and therefore breastfeeding should be avoided. Infants should be tested at 1 month and 4 months. There are no restrictions on daycare. The regular immunization schedule should be followed. Infants who are HIV positive should receive MMR because, unlike other live vaccines, it does not shed (Behrman '02: 446 & 450).

The best indicator of **good overall health** in an infant is steadily increasing height, weight and head and chest circumference. Growth and development are monitored by plotting measurements on a standardized growth chart, specific for boys and girls, from birth to 3 years and from 3 to 18 years. From 0 to 6 months a child grows 1 inch (2.5 cm) per month. The average 6 month old is 25 ½ inches (63.8 cm). The average 12 month old is 29 inches (72.5 cm). Birth length increases 50% by 12 months. From 0 to 5 months, the child gains 1.5 lb (682 g) per month. Birth weight doubles by 5 months. Average 6 month weight is 16 lb (727 g). Birth weight triples by 12 months. Average 12 month weight is 21.5 lb (977 g). Head circumference from 0 to 6 months increases 0.6 in (1.32 cm) per month. Average head circumference by 6 months is 17 in (37.4 cm). From 6 to 12 months head circumference increases 0.2 in (0.44) per

month. By 12 months average head circumference is 18 in (45 cm) a 33% increase and brain weight has increased two and a half times from birth measurement. The anterior fontanelle is diamond shaped; at birth, it measures 4 to 5 cm (about 2 in) at widest part and closes between 12 and 18 months. The posterior fontanelle is triangular; at birth, it measure 0.5 to 1 cm (about ½ in) at widest part and closes by 2 months (Muscari '01: 12-13).

The **dramatic growth** of infants during the 1st year of life (e.g, a three-fold increase in weight and a two-fold increase in length) and continued growth, albeit at slower rates, from 1 yr of age through adolescence impose unique nutritional needs. Expressed per unit of body weight, the normal infant requires approximately three times more energy than the adult. This reflects primarily the higher metabolic rate of the infant vs. the adult. The protein requirement of the normal infant and growing child is also greater per unit of body weight than that of the adult. In addition it is thought that the infant requires a higher proportion of essential amino acids than the adult. These include the amino acids recognized as essential (or indispensable) for the adult (i.e., leucine, isoleucine, valine, threonine, methionine, phenylalanine, tryptophan, lysine and histidine) as well as cysteine, tyrosine and perhaps, arginine. In general, human milk protein and all proteins currently used in infant formulas contain adequate amounts of all essential amino acids, including cysteine, tyrosine and arginine. Although the amino acid composition of human milk protein is considered ideal, the total protein content of human milk, though quite variable, averages only approximately 1.0 g/gL. Thus, on average, about 200 mL/kg/24 hr must be ingested to meet the current RDA for protein. Although the normal newborn infant is thought to have sufficient stores of iron to meet requirement for 4-6 months, iron deficiency is common during infancy. If protein intake is adequate, vitamin deficiencies are rare; if not, deficiencies of nicotinic acid and choline, which are synthesized, respectively, from tryptophan and ethionine, may develop. The normal infant's absolute requirement for water probably is 75-100 mL/kg/24 hr (Muscari '01).

The **double burden of malnutrition** – where undernutrition and over-nutrition can exist simultaneously in the same household or individual – means that both undernutrition and overweight need to be reliably identified by public health approaches. At primary health-care facilities, children aged under 5 years who are identified as obese should be assessed and an appropriate management plan should be developed. All obese children and their caregivers should be assessed and a comprehensive care plan should be developed to address underlying risk factors, promote weight reduction and healthy practices, and provide psychosocial support. Assessment should include screening for early indicators of metabolic syndrome, e.g. raised blood pressure for age, or hyperglycemia/insulin resistance or signs of hyperlipidemia. Children with a mid-upper arm circumference <115 mm or weight for height/length more than 3 z-scores below the WHO growth standards median, or with any degree of bilateral pitting edema are considered to have severe acute malnutrition. These children should be referred for full assessment at a treatment centre for the management of severe acute malnutrition. Severe acute malnutrition (undernutrition) affects nearly 20 million children under 5 years of age worldwide (primarily in south Asia and sub-Saharan Africa) and is estimated to contribute to approximately 1 million child deaths each year. Early identification of severe acute malnutrition (undernutrition) is important for initiating treatment and minimizing the risk of complications (WHO '19: 57-59).

Children who are identified as having **severe acute malnutrition** should first be assessed with a full clinical examination to confirm whether they have medical complications and whether they have an appetite. Children who have appetite (pass the appetite test) and are clinically well and alert should be treated as outpatients. Children who have medical complications, severe edema

generalized to the feet, legs, arms and face, or poor appetite (fail the appetite test), or who present with one or more Integrated Management of Children Illness (IMCI) danger signs, unable to drink or breastfeed; vomits everything; has had convulsions (more than one or prolonged >15 min); lethargic or unconscious; convulsing now, should be treated as inpatients. F-75 therapeutic milk is recommended for use as the therapeutic food in the stabilization phase of inpatient management of children with severe acute malnutrition. F-100 therapeutic milk may be used as the therapeutic food in the rehabilitation phase of inpatient management of children with severe acute malnutrition. Children aged 6–59 months with severe acute malnutrition who are admitted to hospital (inpatient care) can be transferred to outpatient care when their medical complications, including edema, are resolving and they have good appetite, and are clinically well and alert (WHO '19: 59-60).

Children aged over 6 months with **severe acute malnutrition**, appetite and no medical complications can be managed in the community. Children with uncomplicated severe acute malnutrition, not requiring to be admitted and who are managed as outpatients, should be given a course of oral antibiotic such as amoxicillin. Children with severe acute malnutrition should be provided a ready-to-use therapeutic food (RUTF) in amounts adjusted to their weight. Children aged 6–59 months with severe acute malnutrition should receive the daily recommended nutrient intake of vitamin A throughout the treatment period. Children with severe acute malnutrition (undernutrition) should be provided with about 5000 IU vitamin A daily, either as an integral part of therapeutic foods or as part of a multi-micronutrient formulation. If they are given therapeutic foods that are not fortified as recommended in WHO specifications, and vitamin A is not part of other daily supplements, they should be given a high dose of vitamin A (50 000 IU, 100 000 IU or 200 000 IU, depending on age) on admission to a treatment program. Children should be offered safe drinking water to drink at will and breastfeeding should be continued and offered ad libitum. Children being managed as outpatients should be followed up weekly by a skilled health-care worker. Children who fail to respond, or who develop medical complications, should be assessed by an experienced health-care worker and referred for inpatient care. Given the overlap in presentation of severe acute malnutrition (undernutrition) and HIV infection and AIDS in children, especially in poor areas, strong links between community-based management of severe acute malnutrition and AIDS programs are essential. Voluntary counseling and testing should be available for children with severe acute malnutrition and for their mothers. At the same time, children who are known to be living with HIV and who develop severe acute malnutrition should have access to therapeutic feeding to improve their nutritional status. Children with severe acute malnutrition should only be discharged from treatment when their weight-for-height/length has increased to 2 z-score or less below the WHO child growth standards median and they have had no edema for at least 2 weeks, or their mid-upper-arm circumference is 125 mm or more and they have had no edema for at least 2 weeks (WHO '19: 61-64).

Infants and children aged 6–59 months with **moderate acute malnutrition**, determined as a mid-upper arm circumference 115 mm or more and less than 125 mm or weight-for-height/length between 2 and 3 z-scores below the WHO child growth standards median, without edema. Infants and children aged 6–59 months with moderate acute malnutrition need to consume nutrient-dense foods to meet their extra needs for weight and height gain and functional recovery. Supplementary foods are specially formulated foods, in ready-to-eat or milled form, which are modified in their energy density, protein, fat or micronutrient composition to help the nutritional requirements of specific populations. Children with moderate acute malnutrition require increased intake of energy and essential nutrients. The dietary management of children with moderate acute malnutrition should be based on optimal use of locally available foods. In settings where food is scarce or where some nutrients are not sufficiently available through local

foods, specially formulated supplementary foods have been used to treat children with moderate acute malnutrition. Animal-source foods are more likely to meet the amino acid and other nutrient needs of recovering children. Plant-source foods, in particular legumes or a combination of cereals and legumes, also contain high-quality proteins, although they also contain some anti-nutrients such as phytates, tannins or inhibitors of digestive enzymes, which may limit the absorption of some micronutrients, particularly minerals. Nutrient-dense foods are those high in nutrients relative to their caloric content, i.e. they have a relatively high content of vitamins, minerals, essential amino acids and healthy fats. Examples of nutrient-dense foods include animal source foods, beans, nuts, and many fruits and vegetables (WHO '19: 64-65).

3. Diet

Diet, in the sense of Hippocrates, is a complete regime. Nutrition should be regarded as a remedy, prescribed as to kind and quantity or items to be forbidden (Gerson '90: 139). There are diets for weight loss, idiopathic bowel disease, heart health and cancer. Healthy nutrition is achieved with a **balanced diet** containing adequate, but not too much, calories, in the right proportion of water, fat, protein, carbohydrates, and all the vitamins and minerals, on a daily basis. Total fat intake should be less than 30 percent of total energy intake. Saturated fatty acid intake should be less than 10 percent of total energy intake. Trans-fatty acid intake should be less than 1% of total energy intake (WHO '19: 24). There is not really a well-established rule regarding the minimum intake of fat, but some fat, as well as fiber, is essential for stool quality; ie. bread and butter with vegetable soup; avocado, olive and coconut oil are fine sources of small quantities fat, greater than 1 percent but less than 5 percent of caloric intake. The amount of protein in a mother's breast milk is 5 percent of calories. According to the World Health Organization (WHO) the human minimum protein requirement is 5 percent of total calories, according to the US Recommended Dietary Allowance for adults 10 percent of total calories. Legumes and peanut butter contain more protein per gram than steak. For optimum protein intake WHO recommends 10-15 percent of calories (Robbins '01: 71, 67). Therefore, 55-75 percent to 90-94 percent of calories in the diet should come from carbohydrates.

Carbohydrates always contain some protein, wheat contains too much protein, rice and other grains are reliable carbohydrates, that can be eaten in proportionally large quantities, all the time. Rice and beans make a complete protein; amaranth and quinoa provide all the essential amino acids needed to make all proteinaceous enzymes. Potatoes, sweet potatoes and bananas are also carbohydrates. Having minimally treated calorie and protein deficiency, with sufficient carbohydrates, flavor, balance and fullness, is best achieved with trace amounts of calorie rich fatty acids and large servings of light vegetables to treat micronutrient deficiency, especially oft-excreted calcium, found in leafy green and cruciferous vegetables, meat and dairy. Potatoes and milk, or milk and grain such as granola, oats or cereal, are the simplest balanced meals. Animal foods would provide a balanced diet, because they are composed of all the same elements, in nearly exactly the same proportion, as in the human body, but the consumer gets atherosclerosis before they can eat enough calories, because there is too much protein and the human lymphatic system that digests fat, is not detoxified by the liver, like protein and carbohydrates.

The documentary *Game Changers* (2018) explains that **plant based diets** do not pollute blood plasma, provide more than enough protein, and are proven by many winning world class athletes to improve performance. Why exercise to digest toxic fats, when one can exercise to win with a plant-based diet? However, world class athletes seem to take less joy from their food than their athletic performance, and winning diets are not well explained. There is deep concern that people who cannot afford professional nutritional support staff and extremely high food budgets,

for breakfast bean, rice and vegetable burritos, fruit smoothies with kale, and pancakes, fancy salads, grains, legumes, trail mix, peanut butter sandwiches and non-soy meat substitutes like seitan, do not eat their fill of plant products, as needed to avoid caloric, protein, iron, calcium and other micronutrient deficiencies. Sedentary industrial and intellectual work and relaxation, is also better tolerated on a light plant based diet, to avoid consuming too many calories and specifically to avoid being overwhelmed by atherosclerosis from too much saturated animal fat or trace amounts of trans-fat or cheap vegetable oil. While weight reduction diets for fat people often involve fasting, and always involve expending more calories than consumed, the most important dietary issue for all people, especially, sedentary, overweight and obese people is to get sufficient exercise to work up an appetite. For sedentary workers this means scheduling the time, usually in the early morning, to minimally perform or exceed, a formal athletic training program, on a daily basis e.g. Marine Corp **physical fitness test** (PFT), 50 crunches, 50 push-ups and three mile run; age adjusted down to 40 crunches and push-ups and three-mile run. The ability to perform more than 100 consecutive crunches and push-ups can be achieved, by performing 250 in 5 sets of 50 in quick succession. For obese and crippled people this means a half an hour or more a day of extra-hard labor walking, due to extra weight, pain and difficulty in mobility. Fatty, adipose tissue is a fine source of nutrition, if a little toxic, and slow to metabolize. Fat quickly turns into large muscles. Sedentary obese people must become body builders and open up to outdoor activities and cardiovascular exercise. Five hours between meals are recommended. With a little practice, overweight people are able to hike and perform physical labor longer without eating than thin people. For those who are merely overweight or recovering from injury, a walk to run strategy reduces the amount of time it takes to digest a sedentary diet, and work up a healthy appetite, from two hours of walking to as little as a three mile run in half an hour, a day, or increase distance to an athletic three to five hour 26.2 mile marathon or superb 24 hour 100 mile ultra-marathon. Do not exercise with more than a fist-full of food in the stomach, or without some undigested water, carbohydrates, protein and calcium.

The Food Guide Pyramid was developed by the U.S. Department of Agriculture (USDA) in 1992, it is updated every five years. For daily exercise and weight control the Dietary Guidelines for Americans are to eat servings of whole grain foods at most meals 5-11 times a day, vegetables 3-6 times a day, fruits 2-3 times a day, nuts and legumes, 1-3 times a day, fish, poultry eggs 0-2 times a day, dairy or calcium supplement (green leafy vegetables), 1-2 times a day, and to use sparingly red meat, butter, white rice, white bread, potatoes, pasta and sweets. More than 200 studies have shown that people who eat plenty of fruits and vegetables decrease their chances of having heart attacks or strokes, of developing a variety of cancers, or of suffering from constipation or other digestive problems. Since the early 1960s, the proportion of Americans who are moderately overweight has stayed the same, hovering just over 30 percent. The number of obese people however has increased dramatically to almost one-quarter of Americans, costing $50 billion a year on medical care for obesity and its complications (Willet '01: 15-24, 36). In 2004 the Center for Disease Control (CDC) reported that at least 1/3 of all deaths in the United States were related to poor diet and lack of physical activity (Black ’10: 162).

Body Mass Index

BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Height (inches)	Body Weight (pounds)																
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287

Source: National Heart, Lung and Blood Institute BMI Table 1; Table 2 Obese BMIs > 35 - 54

More than one billion adults worldwide are overweight, and at least 300 million of these are clinically **obese**. Body mass index (BMI) s a measure which takes into account a person's weight

and height to gauge total body fat in adults. Someone with a BMI of 26 to 27 is about 20 percent overweight, which is generally believed to carry moderate health risks. A BMI of 30 and higher is considered obese. According the National Center for Health Statistics, who have been tracking obesity problems for over four decades, between 1962 and 2000 the number of obese Americans, with a BMI in excess of 30%, grew from 13% to an alarming 31% of the population. 63% of Americans are overweight with a BMI in excess of 25.0 in all 50 states. Childhood obesity in the United States has more than tripled in the past two decades. The U.S. Surgeon General estimates obesity is responsible for 300,000 death every year. The Global Strategy on Diet, Physical Activity and Health 2003 reports that chronic diseases are now the major cause of death and disability worldwide. **Noncommunicable conditions**, including cardiovascular diseases (CVD), diabetes, obesity, cancer and respiratory diseases, now account for 59% of the 56.5 million deaths annually and 45.9% of the global burden of disease. Half of the 17 million deaths resulting from chronic disease were from (CVD). Relatively few risk factors – high cholesterol, high blood pressure, obesity, smoking and alcohol – cause the majority of the chronic disease burden. Conversely, relatively few factors benefit a person's health and longevity – a balanced diet, exercise, and freedom from stress.

Desirable Weights For Men Over 25				*Desirable Weights For Women Over 25*			
Height	Frame			Height	Frame		
	Small	Medium	Large		Small	Medium	Large
5' 2"	112-120	118-129	126-141	4' 10"	92-98	96-107	104-119
5' 3"	115-123	121-133	129-141	4' 11"	94-101	98-110	105-122
5' 4"	118-126	124-138	132-148	5' 0"	96-104	101-103	109-125
5' 5"	121-129	127-139	135-152	5' 1"	99-107	104-118	112-128
5' 6"	124-133	134-147	142-161	5' 2"	102-110	107-119	115-131
5' 7"	128-137	134-147	142-161	5' 3"	105-113	110-127	118-134
5' 8"	132-141	138-152	147-168	5' 4"	108-118	113-126	121-138
5' 9"	138-145	142-158	151-170	5' 5"	111-119	116-130	125-142
5' 10"	140-150	146-160	155-174	5' 6"	114-123	120-135	129-146
5' 11"	144-154	150-165	159-179	5' 7"	118-127	124-139	133-150
6' 0"	148-158	154-170	164-184	5' 8"	122-131	128-143	137-154
6' 1"	152-162	158-175	168-189	5' 9"	126-135	132-147	141-158
6' 2"	156-167	162-180	173-194	5' 10"	130-140	138-151	145-163
6' 3"	160-171	167-185	178-199	5' 11"	134-144	140-155	149-168
6' 4"	164-175	172-190	182-204	6' 1"	138-148	144-159	153-173

The best way to **lose weight** is to take in fewer calories than burned and to aim for a weight loss of about 1 or 2 pounds a week. Exercise most days of the week for at least 30 minutes. This is the most effective way to lose weight. Diet is extremely important. Nutrition is all about the study of food and how our bodies use food as fuel for growth and daily activities. The macro-nutrients, or "big" nutrients include proteins, carbohydrates, and fats. The micro-nutrients, or "little" nutrients are the vitamins and minerals needed to be healthy. Calories are the basic unit of food energy. A healthy diet consists exclusively of fruit, vegetables and whole grains. Meat, bread and dairy products are luxury foods that are excessively fattening and should be avoided most of the time, although the fats, proteins, vitamins and minerals are important in moderation. Sweets, junk food, fast food, fried food, processed foods such as hydrogenated fats and oils (trans-fats), white flour, white rice and bread, and high fructose corn syrup, should be avoided all

of the time. To determine proper caloric intake to achieve a desired weight. First, determine a desired weight according to the following tables: Multiply this weight by 15 calories per pound if sedentary and 20 calories if moderately active to determine proper caloric intake to maintain stasis. Finally, from this amount, subtract 500 calories per day to lose an estimated pound per week. Children and young adults need slightly more calories and elderly people slightly less.

Patterns of food intake and culinary virtuosity vary. Along with our great ape cousins, humans are derived from herbivorous primate predecessors. But climates change, food sources decline. Over millennia, dental and intestinal anatomies change. Prior to emergence as erectile species, humans shared with other great apes the predilection for plant foods with energy-rich, ripe fruits as haute cuisine. During the oscillating climatic times of the Pleistocene, humans came out into the savannah. Meat was then a beneficial supplement to diet, but not a replacement for fruit and fibre. This dietary arrangement is mirrored in current hunter-gatherer tribes. A mixed diet of starch-rich plant foods supplemented with meat provided a reasonably adequate source of calories. Plant foods include vitamins and minerals that aid a multitude of physiologic processes. Some of these serve as co-factors for DNA repair enzymes, especially the flavonoids, antioxidant functions that shut off the major route to DNA damage and mutation. Our Stone Age ancestors may have obtained two-thirds of their calorie or energy intake via wild fruit and vegetables and one-third from lean, wild game and fowl, supplemented with eggs and fish. In contrast, the average adult American obtains more than half the average daily intake of calories via cereal, milk products and nutrition-less sweeteners and refined foods. Only 17 percent now derives from fruit and vegetables. Some 28 percent of calorie intake is now provided by domesticated meat sources, many of which are rich in polyunsaturated fats. One-third of Americans and almost as many Western Europeans are clinically obese. 25 percent of young American women in their 20s are obese. Colon cancer worldwide shows a strong association with total red meat intake. Lowered risk of colon cancer has been shown to significantly linked with vegetable consumption. Meat proteins subjected to high-temperature pyrolysis (burnt) generate carcinogens, including mutagenic amines, as natural breakdown produces of organic combustion. Fat dripping from barbecued steaks down onto the charcoal is fired back up onto the meat as a chemical cocktail rich in carcinogenic benzo(a)pyrene and other noxious polycylic hydrocarbon (Greaves '00:185-189). The healthiest nutritional strategy includes maintaining a stable, healthy weight; replacing trans fats with healthy fats; substituting whole-grain carbohydrates for refined-grain carbohydrates; trade red meat for nuts, beans, chicken and fish; eating plenty of vegetables and fruits; using alcohol in moderation and taking a daily multivitamin (Willet '01: 179).

The basic diets are vegan, vegetarian, lacto-ovo-vegetarian but sick people with food allergies or dose related toxicities may need to eliminate certain grains, fruits, vegetables, processed foods and chemical additives from the diet as well. The most common allergies are fructose, gluten and lactose. Peanut allergies are notorious. A **vegetarian** is someone who does not eat meat. A **lacto-ova vegetarian** is someone whose diet includes milk and eggs. This type of vegetarian diet is well accepted and proven to be healthy in children, heart patients should however not eat eggs that are high in cholesterol, much lower in egg whites. Eggs are as good as meat as a source of vitamins and minerals found only in animal products and are a fairly powerful medicine for the reversal of vegan diet induced diarrhea, anemia, osteoporosis and dental cavities, not to be taken daily if there is any cardiac intolerance. A **lacto-vegetarian** is someone who includes milk and milk products in their diet but not eggs or foods that have eggs in them. This diet is a healthy diet for children and because a long term vegan diet requires supplementation to keep the stool firm and prevent cavities a lacto-vegetarian diet provides the minimal amounts of animal product nutrition necessary to sustain gastrointestinal health in vegans over the long term. Two dairy products are particularly safe and effective source of

animal nutrition, cheese aged over two months does not tend to cause intolerance because the lactose has converted to lactic acid, and probiotic yoghurt and drinks supply the gut with friendly bacterial cultures that comprise 30% of healthy fecal volume and protect against bad bacteria. Vegetarian cultures, including the Hunza, Seventh Day Adventists, and various Indian sects, have a long history. Among these communities, vegetarianism is firmly grounded in a cultural setting, sufficient nutritional knowledge is embedded in daily and yearly rituals, ensuring continued health. In the United States, the Seventh Day Adventists were the first large group to develop and maintain a healthy vegetarian lifestyle (Yntema '95: 40, 41, 68).

About 75% of patients with **idiopathic bowel disease** believe their symptoms are related to what they eat. However, only a very rare occasion can they identify specific foods that are likely culprits in an attack of symptoms. Often the blame is assigned more or less on the basis of prejudice or on a single unfortunate instance, in the absence of any other proof. Although there is no master list of universally forbidden foods, various sugars (lactose and fructose) may have an impact on symptoms. Other foods may be culprits as well, specifically, eggs and beef have been associated with unpleasant symptoms. Elimination diets will not be diagnostic or even effective in the patient who gets symptoms only infrequently. Patients who suffer symptoms infrequently should be directed to be less introspective about infrequent episodes. If you are convinced your diarrheal symptoms are diet related, you should keep a food diary for 3 weeks. Carefully note everything ingested and every symptom perceived during the period - food, beverages, mints, gum and medications. If a food or food group looks like a likely suspect, then a diet absolutely devoid of that substance should be tried for 5 to 7 days (Newman '11: 34, 40). The **dietary elimination strategies** shown to alleviate symptoms of irritable bowel syndrome (IBS) and functional dyspepsia (FD) are (1) eliminate gluten from wheat, rye and barley grains (2) avoid lactose from milk and dairy products (3) reduce fructose (4) reduce saturated fats (5) reduce protein (6) reduce insoluble fiber (7) avoid caffeine and alcohol in favor of water and (8) eat frequent small meals (grazing) (Newman '11: 134). Foods that commonly cause reactions in individuals suffering from inflammatory conditions, namely CD, are (1) wheat and sometimes gluten as a constituent of wheat and other grains such as barley and spelt (2) dairy (3) sugar (4) potatoes (5) tomatoes (6) eggplant (7) peppers (8) paprika (9) cayenne (10) tobacco. Smoking may not cause the disease but can certainly aggravate symptoms (Black '10: 62, 65).

Foods to Avoid and Include with Irritable Bowel Syndrome

Potentially problematic foods to avoid	Foods and spices to include
Wheat or maybe all gluten	Cold water fish
Dairy	Nuts and seeds if tolerated
Sugar	8-10 glasses of filtered water daily
Potatoes	Fiber after disease is managed
Eggplant	Flax seeds or walnut oil in salads
Tomatoes	Lean hormone free meat
Peppers	Hormone free eggs
Paprika	Vegetables, steamed if sensitive to digestion
Cayenne	Fruits, steamed if sensitive digestion
Fiber in early stages of disease	Nutritional powders
Caffeine	Tumeric
Chocolate	Ginger
Alcohol	Rosemary
Carbonated drinks and soda	Garlic and garlic powder

Artificial sweeteners	Cinnamon
Artificial additives and preservative	Cilantro
Fried foods	Parsley
Dried fruit	Basil
Limit gas-producing foods such as cabbage family vegetables (broccoli, cabbage, cauliflower and Brussels sprouts) legumes, onions and chives.	

Source: Black '10: 172

No one diet is completely right for everyone with inflammatory bowel disease. Keep a food diary to find out which foods cause problems for you. Some people may have problems digesting legumes, fiber-rich foods, raw salads, spices, additives, preservative, fried foods, and others. By steaming or cooking most foods, it reduces the live enzyme content of the food and makes it significantly easier on your digestion if you are suffering. Sometimes inflammatory bowel disease sufferers who suffer from gas, diarrhea, constipation and other ailments who have tried high fiber diets and failed, may want to try a low fiber diet initially while inflammation is being treated and reduced. Low fiber doesn't mean that vegetables need to be omitted form the diet. Make sure to include vegetable juices without pulp, potatoes without skin, alfalfa sprouts, beets, green/yellow beans, carrots, celery, and cucumber without the peel, eggplant if it doesn't cause reactions, lettuce, mushrooms, green/red peppers, squash and zucchini. Many grains can be omitted considering they add to the fiber load and also are acidic for the system. Avoid vegetables from the cruciferous family such as broccoli, cauliflower, Brussels sprouts, cabbage, and kale, Swiss chard, etc. Clean proteins are acceptable such as chicken, turkey, fish and eggs. Avoid all nuts and seeds unless they are ground into butters. A small amount of rice should be okay as long as it doesn't worsen symptoms. Include some fruits in your diet such as apples as long as they are in a sauce form or steamed until soft and tender, apricots, bananas, cantaloupe, grapes, honeydew melon, peaches and watermelon. Avoid dried fruits and raw fruits except bananas. Filtered water is extremely important if you are in this stage, as it will keep everything moving in the body. Drink at least 8-10 glasses of filtered water daily. Smoothies are an excellent way to keep nutrition up while using a low fiber diet until gastrointestinal inflammation decreases (Black '10: 167, 168).

A growing number of Americans are **avoiding dairy products,** meat, and animal products in general. Since the 1950s US dairy farmers have produced more milk than can be sold on the market, Monsanto developed affordable **recombinant Bovine Growth Hormone** (rBGH), brand name Prosilac which contaminates as much as 90 percent of milk products, not labeled organic or rBGH free. Milk from cows that have been injected with Monsanto genetically engineered rBGH contains 2 to 10 times as much IGF-1 (insulin-like growth factor) as normal cow's milk. This pushed prostate cancer risk for men over 60 years of age with high IGF-1 8 times greater than men with low levels, and the risk of pre-menopausal breast cancer was 7 times greater. IGF-1 is not destroyed in pasteurization. Cows treated with rBGH have a 25 percent increase in udder infections (mastitis) and a 50 percent increase in lameness. To counter the health problems among cows injected with rBGH more antibiotics are used. American consumers overwhelmingly support the labeling of milk products produced with rBGH. But the FDA has said such labeling would unfairly stigmatize rBGH milk as less healthy. Because as much as 90 percent of milk products, not labeled organic or rBGH-free, contain rBGH. Although lactose intolerance is estimated at 10 percent amongst people of Caucasian descent, it is much higher in other races, 90-100 percent in Asians, 65-70 percent in Africans, 65-70 percent in Italians, and 50-60 percent in Hispanics. Countries with the highest levels of dairy products have the highest

levels of osteoporosis – Finland, Sweden, United States and England. The hip fracture rate for African-Americans, who consume more than 1,000 mg of calcium a day, compared with black South Africans is 9 times greater. Calcium intake in rural China is one-half that of people in the US but the bone fracture rate is one-fifth of that in the US. There are no antibiotics in soy milk. Although 80% of soy products products in the United States are genetically modified (GM). Soy milk is cholesterol-free, while cow's milk contains 34 mg of cholesterol per cup. 44 percent of children with chronic constipation so intractable that it can't be treated successfully by laxatives, are cured by switching from cow's milk to soy milk. While the average American estimates that 1 percent of the world population does not drink milk the actual number is 65 percent (Robbins '01: 335, 336, 99, 343, 104, 107).

There is no denying the logic and effectiveness of homeopathic remedies, such as **chamomile tea**, for digestive disorders. IBD Soothing GI Tea Peppermint and Chamomile. IBD Gas Relief Tea 1 part ground fennel seeds, 1 part ground fenugreek seeds, 1 part althaea (marshmallow) root, 1 part slippery elm bark (Black '10: 143-144). **Bitters** are useful herbs that function to stimulate gastric function in addition to liver function and detoxification, they help to control blood sugar, and they aid in stress relief due to their stimulation of the parasympathetic nerves in the gastrointestinal tract. They are helpful in IBD patients because they stimulate mucosal immunity and function to create balance of inflammation within the GI tract and they may help to repair mucosal wall damage caused by inflammation. Examples of bitters include licorice, peppermint, calendula, dandelion, artichoke leaf, blessed thistle, angelica, motherwort, wormwood, bitter orange peel, lemon peel, gentian root, mugwort, goldenseal, *Casara sagrada*, hops chamomile and yarrow (Black '10: 139). *Hepatica nobilis* of the Ranunculaceae is reputed to cure all liver and bilious difficulties. The Houma Indians, boiled roots from *Solidago nemoralis* (goldenrod) for a tea to cure yellow jaundice. In the 19th century physicians used dandelion roots (*Taraxacum offinale*). In England *Euonymus europaeus* was used for liver afflictions. Native American Indians used Rumex verticillatus (swamp dock) for jaundice, *Salix lucida* (red willow) for removing bile from the stomach, and *Zanthoxylum clava-herculis* (toothache tree) for obstructions of the liver. Fruit from *Emblica officinalis* in the Euphorbiaceae, which is very rich in vitamin C, is considered a good liver tonic in India. The use of dandelion appears in disparate sources (Lewis and Elvin-Lewis '77: 289). Stone Breaker (*Chanca piedra*) works overnight for both gallstones and urinary stones and should be immediately prescribed to avoid surgery.

Turmeric, or curcumin, can be used as a spice in foods or can be taken in therapeutic doses either through tincture form or capsule fork. Curcumin has significant anti-inflammatory properties and very high antioxidant capability making it a superb nutrient to use in any gastrointestinal condition, inflammation related condition, and to use preventatively to ward off cancer and chronic illness. In people who have ulcerative colitis, studies have shown that curcumin supplements, when compared with placebo, reduced the number of relapses by about fifty percent. **Ginger** can be used for gastrointestinal irritation and inflammation. Ginger tea is helpful in settling the stomach and can also be helpful in nausea. The tea should be used at 3 cups daily. **Garlic** is also a useful supplement especially if there is concern that there is yeast, bacterial or parasitic overgrowth. Garlic is anti-inflammatory, blood thinning, antimicrobial, and anti-cancer. Garlic supplements need to be taken with the odor to get the best effect. If your stomach, family members and co-workers can handle it, the best way to take garlic is to eat while cloves (Black '10: 135, 136). **Yucca** is a plant native to Mexico and Southwestern United states. Yucca has been known in folk medicine as a treatment of arthritis and inflammatory ailments. Native American Tribes and native people of Mexico have proclaimed many uses of Yucca that have dated back hundred s of years. Yucca is comprised of many phytochemicals that make it

special for use in many conditions. Resveratrol is an important anti-inflammatory agent that helps reduce aging and helps to keep inflammation under control. The phenolic compounds in yucca also act as anti-oxidants or free radical scavengers which act to reduce damage and inflammation caused by free radicals, thereby reducing damage and aging of tissues, joints, organs etc. Yucca is more often used in patients who have inflammatory bowel issues or gastrointestinal distress that coincides with arthritis. Yucca is also high in saponins, which play a part in complexing with the cholesterol molecule in the body aiding in cholesterol lowering. This cholesterol lowering effect was demonstrated more than 45 years ago. Yucca dosage should be two 500 mg tablets or capsule 2-3 times per day. Start with a lower dosage and increase if no result is seen. Yucca can also be found as a tea. The usual dosage for tea is 3-5 cups per day (Black '10: 136-137).

Herbal Remedies for Gastroenteritis

Vitamin	**Indication**
B3 (niacin)	Supports energy metabolism, skin health, nervous system and digestive system. Found in spinach, potatoes, tomato juice, lean ground beef, chicken breast, tuna (canned in water), liver and shrimp.
B12	Used in new cell synthesis, helps break down fatty acids and amino acids, supports nerve cell maintenance. meats, poultry, fish, shellfish, milk, eggs and *Bifidobacterium* spp. that manufacture it. Supplement needed to prevent chronic diarrhea in vegans.
Minerals	**Indication**
Chloride	Maintains fluid and electrolyte balance, aids in digestion. Found in salt, soy sauce, milk, eggs and meats.
Chromium	Associated with insulin and is required for the release of energy from glucose. Found in vegetable oils, liver, brewer's yeast, whole grains, cheese and nuts.
Culinary Herb	**Indication**
Sweet basil *Ocimum basilicum*	Sweet basil is known for its flavor, scent, and is widely used in stews, pestos and as a garnish for tomatoes. It eases gas and stomach cramps and relieves nausea and vomiting, nervous irritability, fatigue, depression, anxiety and insomnia.
Cinnamon *Cinnamomum* spp.	Respected digestive aid, particularly in cases of overeating, bloating and sluggish digestion. One of the best herbs around for stabilizing blood sugar levels. Powerful antiseptic, with antiviral and antifungal properties.
Garlic *Allium sativum*	Garlic is not only tasty, it is the herb of choice for treating colds, flus, sore throats and poor or sluggish digestion. It stimulates the production of white blood cells, boosting immune function and is a potent internal and external antiseptic, antibacterial, and antimicrobial agent effective for treating many types of infection, including several forms of antibiotic-resistant strains of bacteria. It helps to maintain healthy blood cholesterol and helps prevent blood platelet aggregation, making it the herb of choice for many circulatory issues and lowers blood sugar levels in Type 2 diabetes. Garlic can irritate and burn sensitive skin, cause heartburn, stomach distress, provoke anger and should be avoided by nursing mothers as it can cause colick.
Ginger *Zingiber officinale*	Ginger lowers blood level triglycerides linked to diabetes and heart disease. Ginger rivals anti-nausea drugs for chemotherapy, without side

	effects. Antiseptic properties useful for treating gastroenteritis.
Sage *Salvia officinalis,* 750 *Salvia* spp.	Sage is a superb aid in the digestion of rich, fatty meat. It also lowers cholesterol levels and is a bitter tonic for the liver. It rebuilds vitality and strength during long-term illness. Sage tea is a warming, bracing drink, nice mixed with mint or rosemary and lemon balm.
Turmeric *Curcuma longa*	Used in both Ayurvedic and traditional Chinese medicine as a remedy for jaundice and other liver and gallbladder disorders.
Black Pepper	Indicated for poor digestion.
Cardamon	In Ayurvedic medicine, it is considered on the safest and best digestive aids with ginger and turmeric.
Dill	Dill is an effective and well known remedy for digestive complaints, gas and hiccups, with powerful antispasmodic properties. Sooths colicking babies.
Aloe Vera *Aloe barbadensis*	Effective to soothe digestive irritation and inflammation, such as stomach ulcers and colitis.
Burdock *Arctium lappa*	Burdock is a specific remedy for the liver, like dandelion.
Calendula *Calendula officinalis*	Helpful for treating gastrointestinal problems such as ulcers (mixed with marsh mallow root) and cramps (mixed with valerian or cramp bark), indigestion (mixed with peppermint) and diarrhea (alone or mixed with blackberry root).
Chamomile *Chamaemelum nobile, Matricaria recutita* and related species	Approved in the pharmacopoeias of 26 countries to treat conditions ranging from colic and indigestion to muscle spasms, tension, inflammation, and infection. Chamomile flowers have rich amounts of azulene, a volatile oil with a range of active principles that serve as anti-inflammatory and antifever agents, useful in the treatment of arthritis, and other inflammatory conditions of the nervous and digestive systems. Useful for going into a deep, restful sleep. Chamomile is a popular remedy for calming colic and childhood digestive issues. Some people are allergic to chamomile.
Dandelion *Taraxacum officinale*	Encourages optimal digestion, with a rich supply of bitter compounds that, having stimulated receptor sites on the tongue, signal the digestive tract. The root also stimulates the production of bile, which in turn helps break down cholesterol and fat. Strong effect is not appropriate for all cases of liver disease. Some people are allergic to the milky latex of dandelion flowers and stems.
Goldenseal *Hydrastis canadensis*	Because of its rich bitter compounds, goldenseal is also helpful in treating, liver, gallbladder and digestive problems. The root makes a very bitter tea, people generally prefer it in tincture or capsule form.
Lemon balm *Melissa officinalis*	A tea made of lemon balm and chamomile is an excellent remedy for stomach distress and nervous exhaustion.
Licorice *Glycyrrhiza glabra*	. Herb of choice for soothing irritated and inflamed tissue such as in cases of sore throat, bronchial inflammation and stomach and bowel irritation. It is very helpful for both gastric and peptic ulcers.
Marsh Mallow *Althaea officinalis*	Because of its sweet flavor and rich mucilaginous properties marshmallow is a popular medicine for soothing all manner of inflamed tissue, specifically of the respiratory and digestive systems and skin. Neutralizes excess acid in the stomach, which is useful for stomach ulcer.
Peppermint	Peppermint is renowned as a digestive aid and is the herb of choice for

Mentha piperata	relieving nausea and gas. As an antispasmodic, it helps muscles relax and can reduce stomach cramping and spasms, and its clean, refreshing flavors is welcome after a bout of indigestion or vomiting. A drop or two of peppermint essential oil in a cup of warm water quickly removes the foul taste and odor left after stomach upset. It's a common ingredient in toothpastes, mouthwashes, and chewing gum, as well as cleaning products and disinfectants. Peppermint also has anodyne properties useful Try tea made with equal parts of chamomile and peppermint for indigestion and headaches caused by indigestion.
Plantain *lantago major, P. lanceolata, P. psyllium*	Used for all manner of liver problems, including poor digestion and assimilation, hepatitis, jaundice, skin eruptions and eruptive personalities (too much heat in the body).
Spearmint *Mentha spicata*)	Spearmint is a mild digestive aid and is lovely as a before-dinner aperitif or after-dinner digestif.
Yarrow *Achillea millefolium*	Yarrow is bitter and bitter herbs stimulate liver function and aid in digestion by stimulating the secretion of digestive enzymes.
Probiotics	**Indication**
Bifidobacterium animalis DN-173 010, (1)	General health, GI health
Bifidobacterium lactis Bb-12	General health, GI health, viral diarrhea, eczema
Bifidobacterium lactis HN019, DR10	General health, GI health, viral diarrhea
Lactobacillus acidophilus NCFM	General health, GI health, viral diarrhea, colds & respiratory virus
Lactobacillus casei DN-114 001, (2)	General health, GI health, irritable bowel syndrome, viral diarrhea
Lactobacillus casei Shirota	General health, GI health, inflammatory bowel disease, antibiotic-associated diarrhea, allergy, autoimmunity
Lactobacillus fermentum RF-14	General health, vaginal yeast infection, urinary tract infection
Lactobacillus plantarum 299v	General health, GI health, viral diarrhea, colds & respiratory virus
Lactobacillus reuteri SD2112, ING1, MM53, ATCC 55739, (3)	General health, GI health, viral diarrhea, colds & respiratory virus
Lactobacillus rhamnosus GG, LGG, (4)	General health, GI health, inflammatory bowel disease, irritable bowel syndrome, viral diarrhea, antibiotic-associated colitis, *C. difficile* diarrhea, travelers' diarrhea, eczema, autoimmunity
Lactobacillus rhamnosus GR-1	General health, vaginal yeast infection, urinary tract infection
Lactobacillus	General health, GI health

rhamnosus HN001, DR20	
Saccharomyces boulardii Iyo	General health, GI health, inflammatory bowel disease, irritable bowel syndrome, Viral diarrhea, Antibiotic-associated diarrhea, *C .difficile* diarrhea, Traveler's diarrhea

Source: Gladstar '12; Huffnagle '07: 263

Food historians speculate that **yogurt** was first made accidentally, when milk was left inside goatskin bags and fermented by wild bacteria. These days, yogurts are commercially manufactured by a process that's considerably less spontaneous. The milk, which can come from any milk-producing animal, is first pasteurized (ie. Heated sufficiently to kill any harmful bacteria- and then bacterial cultures are added to ferment it. According to FDA regulations, products sold as yogurt in the United States must be fermented with *Lactobacillus bulgaricus* and *Streptococcus thermophiles*, referred to as yogurt starters. The starter bacteria digest lactose (milk sugar) and other carbohydrates int eh milk, producing lactic acid and other acids that give yogurt its characteristic tart taste. The acids also react chemically with milk proteins, causing the milk to thicken. In addition, since harmful bacteria can't grow in an acidic environment, the acids protect the milk from contamination. On top of these useful effects are all the health benefits from probiotic bacteria and from metabiotics, the metabolic products that probiotic bacteria produce. Yogurt also contains lactoferrin, a prebiotic found in milk. After fermentation, fruit, jam, or other flavorings may be added or blended into the yogurt. Some manufacturers add fiber, which boosts the reviotic content. The best way to ensure that yogurt contains probiotics is to select a product with the "live and active cultures" seal from the National Yogurt Association (NYA). This indicates that the yogurt contains 100 million viable bacteria per gram at the time of manufacture, the equivalent of more than **20 billion per 8 ounce serving**. Some yogurts with live bacteria don't carry the NYA seal, instead their lavels may read "contains active yogurt cultures" or "contains living yogurt cultures". But avoid yogurts that simply sya "made with active cultures". Such a yogurt may have been heat-treated after fermentation, in which case the bacteria would no longer by alive. All yogurts with live bacteria contain the straters *Lactobacillus bulgaricus* and *Streptococcus thermohilus*. However, some manfuactuerers add other bacteria to their yogurts, including the probiotics *L. acidophilus, Bifidobacterium animalis, L. casie, L. reuteri*, and others. Check the label All foods fermented by probiotic bacteria contain metabiotics – even foods that have been heated after fermentation, so that the bacteria themselves are no longer alive. Bacteriocins are natural antibiotics that bacteria make to help themselves survive. These antibiotics aren't harmful to the bacteria that make them, but they kill or inhibit other bacteria. The bacteriocins produced by probiotic bacteria help shift the microbial balance in their own favor. Fermented foods, such as yogurt, cheese, sourdough bread, and sauerkraut, contain bacteriocins, thanks to the lactic acid bacteria in them (Huffnagle '07: 210, 211).

Probiotics work to neutralize the dental and gastrointestinal side-effects of such highly effective medicine as antibiotics, vegan diet and NSAIDs. Unlike antibiotics, the supplements have no adverse side effects. An effective oral dose should be at least 25 billion probiotic organisms. A person can consume a trillion without ill effect. Eating tinkers with the microbial balance. Depending on the foods, certain microbes get nutrients while making others go hungry. Prebiotics offer a cornucopia of healthy, delectable options. The chief sources are fruits, vegetables and whole grains. Prebiotics are also found in certain fats, herbs and spices, red wine and dark chocolate. Dietary fiber is the best-known prebiotic. The body can't digest fiber and turn it into fuel. But probiotic microbes thrive on it. Fiber is a form of carbohydrate, just like sugar and starch. But the human body doesn't produce enzymes that can break it down. When

consuming foods containing fiber, the fiber passes right through our digestive tract. It provides no calories, vitamins or minerals. However, that doesn't mean it's useless. Along the way, fiber performs extremely valuable functions. One of the most important is that it serves as prebiotic, selectively supporting probiotic microbes in our gut.

Fiber takes many different forms, but all of them can be grouped into two general categories – insoluble and soluble – depending on what happens when they're mixed with water. **Insoluble fiber** acts like a sponge: it holds water but doesn't dissolve. **Soluble fiber** heaves like a powder, absorbing water and forming a gel. Most plant foods contain both kinds of fiber, though one or the other may predominate, and both types are important or health. However, only soluble fiber acts as a prebiotics. Insoluble fiber is sometimes called roughage, because it's coars and bulky – characteristics that make important contributions to digestion and good health. Insoluble fiber stimulates the intestines, helping food move through them, preventing not only constipation, but also conditions caused by straining and pressure in the colon, such as hemorrhoids, and diverticulosis (a disorder in which infection-prone pouches form on the intestinal wall). When soluble fiber absorbs water, it forms a sticky gel. This turns out to be useful for appetite control. When eating something that contains both sugar and soluble fiber, say an apple, its soluble fiber slows the release of its sugar. Take away the fiber, as with clear apple juice and sugar enters the blood more rapidly Both types of fiber offer bulk to satisfy the appetite with fewer calories. Soluble fiber also helps lower blood cholesterol levels. The sticky gel absorbs cholesterol and bile acids in the intestines. Bile acids are essential for digesting fats, they're made from cholesterol by the liver. Normally, any excess is reabsorbed by the body and recycled. But when bile acids are absorbed by soluble fiber, they get removed from the body as wastes. This forces the liver to produce more, which uses up cholesterol (Huffnagle '07: 202, 270).

Two types of soluble fiber,- oligosaccharides and inulin – are particularly helpful to probiotic bacteria. Oligosaccharides are a form of soluble fiber found in vegetables. Human can't digest them, but probiotic microbes can. One oligosaccharide, fructooligosaccharide (FOS), is a particularly effective **prebiotic**. And a form of FOS called short-chain fructo-oligosaccharide (scFOS) is being considered as a possible sweetener in food, because it has a sweet taste. Inulin is another excellent prebiotic fiber. It's found in many vegetables, but the major sources of inulin in the American diet are wheat, onions, and green bananas. The microflora of breastfed and bottle-fed babies are different, which may help explain the health advantages of breastfeeding. Some manufacturers have begun to add probiotic bacteria to **infant formula**, and research suggests that babies benefit. Another promising approach is to add the following prebiotics: **Oligosaccharides**, these soluble fibers are a negligible part of cow's milk, but abundant in human breast milk. **GMP**, the prebiotic peptide is found in milk and milk curds, but not in whey. Infant formula is commonly whey-based, so it usually lacks GMP. **Alpha-lactalbumin**, between 20 and 25 percent of the protein in human milk is alpha-lactalbumin; in cow's milk it's only 2 to 5 percent. Studies suggest that as a baby digests alpha-lactalbumin, beneficial peptides form temporarily and act against harmful bacteria. This could help explain why breastfeeding offers protection againt infection. When babies consume formula in which these prebiotics are adjusted to match human breast milk, they develop a microflora that's high in *Bifidobacerium* and otherwise similar to that of breastfed babies (Huffnagle '07: 271, 281).

Dietary fiber is plant-derived material comprising non-starch polysaccharides (NSP) such as cellulose. Whereas these substances are resistant to digestion by human intestinal enzymes, they are metabolized to differing extents by the intestinal microflora; for example, pectin and hemicellulose can be degraded totally, cellulose partially and lignin virtually not at all. In the large bowel, the anaerobic microflora metabolize fibre to gases (CO_2, H_2, and CH_4) and the short-

chain organic acids, all of which can be absorbed and then metabolized systemically. The availability of fibre as a metabolizable substrate in the colon stimulates growth of microflora. Increased fecal bulk decreases intra-colonic pressure and intestinal transit time, and so increases the frequency and ease of defecation. In general, unrefined cereal foods are more effective fecal bulking agents than fruit or vegetables. Wheat bran is used in the management of constipation, diverticular disease and irritable bowel syndrome. The average fibre content of a Western diet is 20 g per day, compared with 130-150 g per day in some areas of Africa. The short-chain fatty acids from fibre in a typical western diet provide less than 10% of the daily energy requirements, but the higher fibre intakes in African and Asian diets contribute proportionately more to the energy balance. There is usually a bacterial population in the lower ileum, but it is in the colon that the intestinal microflora flourish, anaerobes (such as *Bacteroides fragilis*) outnumbering aerobes by 1000 to 1. Fecal bacteria assist in the metabolism of bilirubin and bile acids and in the synthesis of vitamins K, B_{12}, thiamin and riboflavin. The bacterial content of feces, along with desquamated cells and secretions, contribute at least half of the protein (>10 g) and fat (>7 g) found in stools.

The presence of intestinal gas can be a source of discomfort. The adult has 30-300 ml of gas in the gut at any one time. Much of this is acquired by air swallowing and in food; an egg for example, contains 80% by volume of air. **Flatulence,** excessive gas in the stomach or intestine, can be relieved by Apiaceae, *Anethum graveolens* (dill), *Foeniculum vulgare* (fennel), *Piminella anisum* (anise), Aracea, *Acorus calamus* (sweet flag), Lamiaceae, *Hedeoma pulegioides* (American pennyroyal), *Mentha piperita* (peppermint), *M. spicata* (spearmint), *Monarda fistulosa* (wild bergamot), *M. punctate* (horsemint), *Posmarinus officinalis* (rosemary), Zingiberaceae, *Zingiber officinale* (ginger). The reason for the distressing behavior of beans in the intestinal tract is the presence of complex sugars (oligosaccharides) triggers the creation of the major component of the gas produced in wind breaking, which is nothing more complex than methane. Ordinarily, when a bean germinates, it secretes the enzyme galactosidase, which breaks down oligosaccharides (Lewis and Elvin-Lewis ’77: 294-295). Excessive eructation (**belching**) is commonly due to behaviorual problems such as excessive air swallowing or to consumption of antacids or carbonated drinks which release carbon dioxide in the stomach. Gastric and intestinal stasis and bacterial overgrowth allow the production in the small bowel of unusual gases which may cause foul eructations. The volume and composition of flatus depends on the amount of unabsorbed carbohydrate, lipid and protein presented for fermentation by the colonic microflora and upon the predominant bacterial type. Nitrogen and carbon dioxide are the predominant gases, with very little oxygen; the amount of hydrogen and methane varies according to the diet (Jones et al '85: 201-203).

Fiber is often considered a laxative. Fiber is divided into two categories – soluble and insoluble. Insoluble fiber is comprosed of cellulose and other indigestible carbohydrates in one form or another. Foods rich in insoluble fiber are wheat bran, potato skins, legumes, and flax seeds. Soluble fiber is found in oat bran, rolled oats, barley and psyllium seed husks, often called ispaghula in British literature. Some plants are rich in inulin, an interesting low-calorie sugar that is included in the category of soluble fiber. Inulin is loaded with a type of sugar called fructan, which contains a lot of fructose in complex molecules and may be an offending agent in severe bloating. Inulin is found abundantly in bananas and the Jerusalem artichoke. The most widely used bulk laxatives are made of the soluble fiber psyllium seed husks and are marketed as Metamucil, Citrucel or Prodiem. The usual doses of these agents are measured in tablespoons or milliliters, generally 1 to 3 tablespoons (15 to 45 milliliters) per day. This group of agents should be swallowed with a glass or two of water (Newman ’11: 51). Enemas and prune juice treat constipation.

Fructose is a simple sugar found in abundance in many foods, including apples, pears, cherries, dates, melons, prunes, plums, artichokes, eggplant, squash, tomatoes, mustard, and ketchup, among many others. Fructose is not as reliably absorbed as glucose, and if malabsorbed, it will remain in the digestive system and be fermented. Probably the single biggest source of fructose in the North American diet is table sugar, or sucrose, which is half glucose and half fructose. Table sugar does not cause unpleasant GI symptoms, because of the presence of glucose eases the absorption of fructose. Table sugar causes dental caries. For several centuries, the most important sweetening agent used in North America and Europe was the sucrose that came from sugar beets and sugar cane. However, because of the uncertainty of sugar supplies form sugar cane grown in tropical countries facing political problems, the food industry developed high-fructose corn syrup (HFCS) as a reliable supply of a palatable sweetener. This produce contains glucose and fructose in ratios similar to what is found in sucrose, but the two sugars are present as separate molecules and their behavior in the gut may be different from when they are linked together as sucrose (Newman ’11: 37). As the result of the influx of sugar during the Columbian exchange in the 1500s the incidence of dental caries increased from 10% to 95% of the population. In general, an alternative sweetener to table sugar should be used, but it is not wise to consume the synthetic sugar substitutes, food should be sweetened with honey and fruit. **Honey** is slightly cariogenic and unpalatable to people with dental caries, but is a conservative sweetener for people, accepting of their appetite for sweets and concomitant need to brush the teeth within ten minutes of consumption to avoid tooth decay, who wish to avoid table sugar. **Raisins**, are an ideal sweetener, for instance, to make pancakes sweet enough to be enjoyed without syrup or tooth brushing.

The best approach to preventing heart disease and cancer is the tried-and-true combination of exercise and eating a healthy diet (Mooney '07: 76). Meat centered diets are are almost always high in fat and low in fiber, resulting in a slow transit time through the colon and allowing toxic wastes to do their damage. True carnivores move raw meat through their digestive tract quickly, within about three hours. Humans, with their long digestive tracts, take between twelve and eighteen hours to process and digest flesh. Because the environment of the digestive tract is warm and moist, the meat rot and creates free radicals – unstable destructive oxygen atoms atoms that can cause cancer, premature aging, and other degenerative conditions. William Cestelli, MD, former director of the Framingham Heart Study, of the National Health, Lung and Blood Institute writes, “A low-fat, plant-based diet would not only lower the heart attack rate about eighty five percent, but would lower the cancer rate sixty percent.” (Swami '06: 4).

A **vegan diet** is necessary to treat atherosclerosis. The small portions of animal products tolerated by the American Medical Association, American Heart Association and other cardiologists help to prevent death, but allowing the consumption of any fat and cholesterol whatsoever, perpetuates the painful and life-threatening atherosclerosis. Anyone suffering angina pectoris should keep a strictly vegan diet – brown rice and vegetables boiled in water is a nutritious staple that can be eaten twice a day perhaps with green salad with vinaigrette dressing, and a large fruit salad for breakfast. A vegan is someone who avoids all animal products; milk, eggs and all dairy products and by-products as well as all foods that contain these ingredients. The vegetable protein tolerance for heart disease is much higher than for cancer but complete vegetable proteins found in wheat gluten and vegetable combinations such as rice and beans and beans and corn can be cardiotoxic and should be avoided or minimized to less than 10% of meal mass. A vegetarian or lacto-ovo-vegetarian (including eggs) diet should be used as maintenance once a person has achieved an ideal weight.

Human teeth, like those of all herbivores, are designed for grinding and chewing. Humans lack the sharp canine teeth designed for tearing flesh that are characteristic of all carnivores. Meat-eating animals generally swallow their food without chewing it, so they require neither molars nor sideways-moving jaws. The human hand, is better suited to harvesting fruit and vegetables than to killing prey. Carnivorous animals can metabolize almost unlimited amounts of cholesterol and fat without adverse effect. In experiments with dogs, up to half a pound of butterfat was added to their daily diet over a period of two year, producing absolutely no change in their serum cholesterol level. Herbivorous creatures have a very limited ability to deal with any cholesterol or saturated fat. Fatty deposits (plaque) accumulate on the inner walls of the arteries, producing a condition known as atherosclerosis, or hardening of the arteries. Because the plaque deposits constrict the flow of blood to the hearts, the potential for heart attacks strokes, and blood clots is tremendously increased. As early as 1961, the Journal of the American Medical Association stated that 97 percent of heart disease in the United States could be prevent by a vegetarian diet. These findings are supported by an American Heart Association report that high-saturated fat diets cause heart disease. There is a 3-4 percent drop in the risk of heart disease for every one percent decrease in blood cholesterol. Blood cholesterol levels of vegetarians are 14 percent lower and the risk of death from heart disease or vegetarians compared to non-vegetarians one-half (Swami '06: 1-4).

Remedies for Cardiovascular Conditions

Drug	Indication
Statins	HMG-CoA reductase inhibitors (statins): Used to prevent cholesterol buildup in the coronary arteries. Can also prevent the inflammatory response that could cause atheromatous plaques to rupture in the heart and precipitate a heart attack. Side effects include muscle and liver injury.
Vitamin	
Niacin vitamin B3 (nicotinic acid), cholestyramine, gemfibrozil, clofirate:	Used to treat high cholesterol and high triglycerides.
Vitamin E	Antioxidant, regulation of oxidation reactions, supports cell membrane stabilization. Found in polyunsaturated plant oils (soybean, corn and canola oils), wheat germ, sunflower seeds, tofu, avocado and sweet potatoes.
Vitamin K	Synthesis of blood-clotting proteins, regulates blood calcium Found in Brussels sprouts, leafy green vegetables, spinach, broccoli and cabbage.
Mineral	Indication
Selenium	Antioxidant. Works with vitamin E to protect body from oxidation. Found in grains.
Culinary Herb	Indication
Garlic *Allium sativum*	Garlic, antibiotic, helps to maintain healthy blood cholesterol and prevent blood platelet aggregation, making it the herb of choice for many circulatory issues and lowers blood sugar levels in Type 2 diabetes
Ginger *Zingiber officinale*	Ginger lowers blood level triglycerides linked to diabetes and heart disease.
Rhododendrum	Antioxidant, blocks carcinogen absorption and 20% of fat

caucasium	absorption through intestines. Increases energy in heart muscles and uric acid excretion. Relaxes blood vessels, lowers blood pressure.
Rosemary *Rosmarinus offinalis*	Rosemary is a circulatory stimulant useful for the treatment of poor circulation and low blood pressure.
Sage *Salvia officinalis*	Sage is a superb aid in the digestion of rich, fatty meat. It also lowers cholesterol levels and is a bitter tonic for the liver. It rebuilds vitality and strength during long-term illness. Sage tea is a warming, bracing drink, nice mixed with mint or rosemary and lemon balm.
Hawthorne *Crataegus laevigata*	Hawthorn is considered the herb supreme for the heart. The berries, leaves and flowers are rich in bioflavonoids, antioxidants, and procanidins, which feed and tone the heart. Hawthorn works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy cholesterol levels. Hawthorn is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorn doesn't store in the body and isn't accumulative in action, it's important to take on a regular basis if using as a heart tonic. Hawthorn also helps to stabilize collagen and support the health and repair of ligaments, tendons and muscles. Hawthorn strengthens capillaries and heals bruises. The berries are tasty and often enjoyed in syrups, jams and jellies or dried infusions.
Lemon balm *Melissa officinalis*	Remedy for heart disease (and heartache), depression and anxiety, nervous disorders and a host of viral and bacterial infections. Paralesus called lemon balm the "elixir of life" and Dioscorides used it for "sweetening the spirit". In the 1600s herbalist John Evelyn wrote "balm is sovereign for the brain, strengthening the memory and powerfully chasing away melancholy". Because it's so delicious lemon balm is often prepared as tea, but it is also tasty as a culinary herb. Lemon balm is considered a thyroid inhibitor, those suffering from hypothyroidism or low thyroid activity should use it only under the guidance of a health care practitioner.
Valerian *Valeriana officinalis*	Valerian has a tonic effect on the heart and is especially recommended in cases of irregular heartbeat and anxiety that affects the heart. It is often combined infusion with hawthorne berry to treat high blood pressure and irregular heartbeat. For those people for whom valerian works, it works well. Some people find it irritating and stimulating, rather than relaxing.

Source: Gladstar '12; Brown '04: 82, 83

Hawthorne (*Crataegus laevigata*) is considered the herb supreme for the heart. The berries, leaves and flowers are rich in bioflavonoids, antioxidants, and procanidins, which feed and tone the heart. Hawthorn works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy

cholesterol levels. Hawthorn is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorn doesn't store in the body and isn't accumulative in action, it's important to take on a regular basis if using as a heart tonic. Hawthorn also helps to stabilize collagen and support the health and repair of ligaments, tendons and muscles. Hawthorn strengthens capillaries and heals bruises. The berries are tasty and often enjoyed in syrups, jams and jellies or dried infusions. The best strategy to procure hawthorne involves harvesting some of the flowers and enough berries to make pancakes, syrups and jams with enough left over to dry and make hawthornberry tea infusions year round. Other cardiac stimulants and tonics include *Apocynum cannabinum* (dogbane), *Asarum canadense* (American wild ginger) is however not a highly recommended substitute for *Zingiber officinale, Asclepia spp* (milkweeds), *Crateagus tomoentosa* (hawthorn), *Euonymus atropurpureus* (wahoo or burning bush), *Heuchera* spp. (alum root) Ilex opaca (American Holly), *Ipomoea leptophylla* (bush morning glory), *Monarda* spp. (horsemint), *Veratrum californicum* (hellebore), *Veratrum viride* (green hellebore), and *Viola* spp. (violet) (Elvin-Lewis '77: 192).

Besides a vegan diet, an athletic level of cardiovascular exercise and sporadic prophylaxis with NSAIDs, antibiotics and antifungal drug to cure rheumatic complaints and achieve higher levels of athletic performance hopefully transcending concerns about health to develop beautiful large strong muscles, even on rainy days or when crippled by an idiopathic disorder. **Statin** cholesterol lowering drugs are an essential medicine for reducing the risk of death from heart attack or ischemic stroke but recovery is not given as a reason for discontinuing statin use. Statin drugs reduce the risk of death in patients with hyperlipidemia by around 50 percent and the stroke risk by 30 percent but the reasons given for quitting statins does not include a cure. Nitrates and Nitrites can be effective at restoring normal blood flow within 5 minutes and lead to a complete recovery from angina pectoris or congestive heart failure in some patients, it should be tried in an office visit to see if a prescription is wanted. The treatment of congestive heart failure would be much improved with the use of the supreme herb for the heart - **Hawthorne** leaves, berries and flowers as an herbal tea infusion, tincture or syrup are good for the heart and kidneys. Hawthorne works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy cholesterol levels. Hawthorne is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorn doesn't store in the body and isn't accumulative in action, it's important to take on a regular basis if using as a heart tonic (Gladstar '12).

Data gathered on diet and cancer shows certain classes of fruits and vegetables seem to work against specific cancers. Mouth and throat cancer are treated with carrots, citrus fruits, green vegetables and turmeric. Lung cancer is treated with carrots, leafy green vegetables and possibly tomatoes. Stomach cancer is treated with carrots, leafy green vegetables, tomatoes and garlic. Bladder cancer is treated with cruciferous vegetables like broccoli. Colon and rectal cancer are treated with raw and green vegetables, especially those high in the vitamin folic acid (sometimes called folate). Breast cancer is treated with carrots. Prostate cancer responds will to tomatoes and cooked and processed tomato products more than two times a week. Among more than one hundred thousand men and women participating in the Nurses' Health Study and the Health Professionals Follow-up Study, it was found that eating about thirty servings of fruits and vegetables a week was associated with a 30 percent lower risk of the most common kind of stroke (ischemic stroke). One extra serving of fruits or vegetables day decreases the chances of having an ischemic stroke by about 6 percent, with most benefit accruing from eating broccoli,

spinach, kale, romaine lettuce, and citrus fruit or juice. An innovative study called DASH (Dietary Approaches to Stop Hypertension) showed that eating more fruits and vegetables can substantially lower blood pressure, especially when they are part of a diet low in animal fat and without salt (Willet '01: 119, 120).

The evidence that regular intake of **fresh vegetables and fruit** reduces cancer risk is very persuasive. A greater emphasis on diets enriched for these foods as well as fibre content, reduced in animal fat, and especially with diminished overall calorie content would make much sense and bring other health benefits, particularly if combined with a generally less sedentary, more calorie burning lifestyle (Greaves '00: 259). In 1980 the National Cancer Institute Committee on Diet, Nutrition and Cancer suggested a diet which is likely to afford optimal protection from cancer is low in fat, low in calories, low in salt, high in fiber and high in fruits and green and yellow vegetables. In Western countries who derive as much as half of their total dietary calories from fats, experience a high mortality from cancer of the breast (in postmenopausal women), colon ovaries, prostate, pancreas and womb, compared to Japanese people, who typically derive much less of their calories from fat. On the other hand Japanese diets contain more salt than conventional Western diets, and this is reflected in a higher incidence of cancer of the stomach in the Japanese population. The influence of diet on cancer has been extensively studied in experimental animals. Rodents that have unlimited access to food develop cancer more frequently and also have shorter life spans in general, than animals with a diet that is restricted in calories, and these animals are relatively more resistant to the carcinogenic effect of known cancer-causing chemicals added to their diet. Despite the fact that fruits and vegetables contain some chemical carcinogens cancer patients should maintain a diet low in fat and calories and high in fresh fruits, grains and legumes, and vegetables, especially yellow vegetables (Friedberg '92: 104-105).

Protein-calorie malnutrition reflected in progressive loss of skeletal muscle, visceral protein and fat tissue is very common in certain forms of advanced cancers. Nutritional deficiencies in the cancer patient result from the effects of cancer on the host as well as from the effects of cancer therapy, including the vegan diet in people who have already metabolized their body fat. The etiology of cancer **cachexia** is complex. Reduced food intake is common in this population and has been reproduced in experimental animals bearing tumors. Some patients develop abnormalities of taste, others complain of early satiety, and may may be depressed. Obstructive lesions of the gastrointestinal tract such as esophageal and gastric tumors can induce pain, nausea and vomiting which understandably decrease nutritional intake. Rarely, gastrointestinal tumors such as diffuse lymphomas or pancreatic cancer will be associated with malabsorption. For the most part, however, cancer patients will lose weight despite apparently appropriate caloric intake. Metabolic abnormalities induced by the presence of the tumor may explain this phenomenon. The common clinical observation that tumor cells grow while host cells atrophy suggests that the cancer cell preferentially uses available energy sources. Much evidence supports the concept of accelerated glucose utilization by the cancer cell and increased levels of gluconogenesis in patients with cancer cachexia. Abnormal lipid metabolism in cancer is manifested by progressive depletion of body fat through persistent mobilization of free fatty acids as the preferential source of metabolic fuel even if exogenous glucose is provided. The Alterations in protein metabolism may be characterized by both decreased synthesis and increased catabolism of protein in cancer patients with weight loss (Bengoa '86: 379).

Oncologic texts are unfortunately devoid of normal nutritional information regarding vegan and vegetarian diets which is normally the mainstay of cancer treatment. This is probably to quickly drive the patients to seek expensive hospital treatments, particularly surgery, recovery from

which seems to benefit greatly from a high protein preoperative diet. In one study 10 days of preoperative parenteral nutrition reduced the postoperative complication rate in patients with gastrointestinal carcinoma from 19% to 11% for wound dehiscence and mortality from 11% to 3% (Bengoa '86: 379, 381). Whereas the text does not label protein an oncologic poison, and many liquid diet formulas contain protein, the word protein in reference to the enteral and parenteral nutrition actually refers to amino acids, which are the building blocks of protein, but are much smaller and more easily absorbed. Generally speaking, protein is the tumor growth factor, and avoidance of complete protein denies neoplastic cells the protein they need to grow and allows the normal human tissues to be well nourished, so that miraculous, or not so miraculous reduction in the acceleration of the cancer growth, can cure or give the patient less pain and more time to find effective medical treatment. When eating a low-calorie vegan or vegetarian diet it is important to consume much larger quantities and/or more frequently to avoid catastrophic weight loss and be well nourished, without having an overly full belly, larger than a fist, to tolerate physical exercise. Liquid diets may be necessary for cancer seriously affecting the digestive tract and this seems to be the entire nutritional concern of oncologists who are not nutritional specialists.

Diet, in the sense of Hippocrates, is a complete regime. Nutrition should be regarded as a remedy, prescribed as to kind and quantity or items to be forbidden. This therapy is based on the concepts (1) that cancer patients have low immune-reactivity and generalized tissue damage, especially of the liver, and (2) that when the cancer is destroyed, toxic degradation products appear in the bloodstream which lead to coma and death from liver failure. The therapy consists of high potassium, low sodium diet, with no fats or oils and minimal animal proteins or gluten (wheat protein). Juices of raw fruits and vegetables provide active oxidizing enzymes which facilitate rehabilitation of the liver. Iodine and niacin supplementation is used. The cancer diet is completely different from normal nutrition. It is limited to fresh juices of fruits, leaves and vegetables; large quantities of raw fruit and vegetables are given in their natural form, or finely grated, salads of fresh leaves, fruits and vegetables, vegetables stewed in their own juice, soups, compotes, stewed fruit, potatoes and oatmeal. Potatoes may be excluded. All must be prepared fresh and without addition of salt. After six to twelve weeks, animal proteins are added in the form of cottage cheese (saltless and creamless) and probiotic yoghurt. Inasmuch as the detoxification of the body is of the greatest importance, especially in the beginning, it is highly recommended to administer frequent **enemas**, about every four hours, day and night, against severe pain, nausea, general nervous tension and depression. Caffeine enemas cause dilation of bile ducts, which facilitates excretion of toxic cancer breakdown products by the liver and dialysis of toxic products from blood across the colonic wall. To make enemas most effective, the patient should lie on their right side, with both legs drawn close to the abdomen, and breathe deeply, in order to suck the greatest amount of the fluid into all parts of the colon. The fluid should be retained 10 to 15 minutes. For cancer patients, even in advanced stages, pain relief was promptly obtained by the use of coffee enemas, given every two hours in some cases (Gerson '90: 139, 191, 397).

This diet forms the basis of medical treatment. It is based on the principle that sodium must be excluded as far as possible and the tissues must be enriched with potassium to the highest possible degree. The diet is digested more easily and quickly than normal nutrition; it burdens the metabolism as little as possible and stimulates the elimination of poisonous substances as well as abnormal intermedial substances of the metabolism. The amount of calories is smaller and the body digests each meal fast; therefore, larger portions and more frequent meals must be served. Patients should eat and drink as much as possible. Tobacco, salt, sharp spices, tea (other than peppermint, chamomile and other effective herbal remedies), coffee, cocoa, chocolate,

alcohol, refined sugar, refined flour, candies, ice cream, cream, cake, berries, nuts, mushrooms, soy beans and soy products, pickles, cucumbers, pineapples and avocados are forbidden. Juices should always be freshly prepared. All vegetables must be cooked slowly, over a low flame. Tomatoes, leeks and onions should be stewed in their own juices, as they contain an abundance of fluid by themselves. Red beets should be cooked like potatoes, in their peel, in water. All vegetables must be carefully washed and cleaned. Peeling or scraping is forbidden, because important mineral salts and vitamins are deposited directly under the skin. The pot (not aluminum) must close tightly, to prevent escape of steam. Cooked foods may be kept in the refrigerator for 48 hours. It may be necessary for the patient to drink freshly prepared vegetable juice every hour. This consists of four glasses of the juice of apple and carrots in equal parts, and also four glasses of green leaf juice. They may lose 60 percent of their active oxidation power within half an hour, and must be consumed immediately after pressing. A good number of patients follow this prescription, are cured and live a normal life after five and more years (Gerson '90: 187-189, 217).

Herbal remedies have been developed for of a number of cancerous diseases. Red sap from bloodroot (*Sanguinaria canadensis*) has been used for the treatment of cancerous disease by the North American Indians living along the shores of Lake Superior. In 1857 a British surgeon concocted a therapy based on a paste of bloodroot extract, zinc chloride, flour and water. The past was smeared on a cloth or cotton and placed on the tumor daily (if healthy tissue covered the tumor, it was eroded with nitric acid. When the tumor became encrusted, incisions were made about one-half inch apart and the paste was inserted into the cuts daily. Generally within 2 to 4 weeks the disease was destroyed, with the mass falling out in 10 to 14 additional days, leaving a flat healthy sore that usually healed rapidly. All cases illustrated remissions, if not cures. 8 of 10 surgical patients returned within 2 years for further treatment, only 3 of 10 returned after using his therapy. North American May apple (*Podophyllum peltatum*) rhizome or underground stem was used by the Penobscot Indians of Maine to treat cancer. Podophyllum resins was used by physicians in Mississippi and Missouri as early as 1897 and by urologists in Louisiana for the treatment of venereal warts (*condyloma acuminate*). Recent clinical reports signify that podophyllin has become the drug of choice in the treatment of human condyloma accuminata. Others report a destructive effect of podophyllin on different cancer cells in animals and in man, but is highly toxic. Seeds of the common apricot (*Prunus armenicaca* or *Armeniaca vulgaris*) native to China, were used there against tumors as early as AD 502. They are as tasty as almonds. Laetrile therapy is based on the theory that once inside the body, the extract from apricot pit breaks down into several components including cyanide. Cyanide is released only when it comes into contact with an enzyme common to tumor cells, β-glucoronidase, at which time cyanide chokes off the tumor cells, leaving the healthy cells surrounding the growth untouched. 10 cases of inoperable cancer, with metastases, regressed, as well as dramatic relief from pain (Elvin-Lewis ’77: 123, 124, 125).

4. Exercise

Abdominal disease is often first noted as **colic** that is intolerably painful with exercise, forcing the patient to curtail their athletic endeavor. Because of the complicated overlapping functions of the abdominal organs, lymphatic, biliary, urinary and digestive system clinical diagnosis begins by pinpointing the part of the abdomen where pain if felt, e.g. upper right quadrant pain (liver, gallbladder), epigastric pain (transverse colon, duodenum, stomach), left upper quadrant pain (pancreas, spleen), or flank pain (kidneys). Exercise is not the cure for gastrointestinal disease. In general, do not exercise, and in particular, do not run, with more than a fist of food in the stomach. Snack frequently. Moderate exercise programs can be continued during pregnancy (Beckmann et al '02: 91, 92). **Regular physical activity** improves chances of living longer and living healthier, helps protect from heart disease, high blood pressure and high cholesterol, helps protect against certain cancers, including colon and breast cancer, helps prevent adult-onset diabetes, helps prevent arthritis, osteoporosis, reduces risk of falling, relieves symptoms of depression and anxiety, improves mood and controls weight. A sedentary life causes muscles to gradually waste away. The less muscle, the less energy the body uses at rest and the easier it is to gain weight. Lost muscle is usually replaced by fat. For a fifty-year-old person who isn't physically active, a ten-pound weight gain over the years may really mean a loss of five pounds of muscle and gain of fifteen pounds of fat. Unlike muscles, fat has very low metabolic activity, meaning it uses very little glucose and burns few calories. Conversely, fat can be turned into muscle in a few minutes of bodybuilding and half-hours of cardiovascular exercise everyday. A person needs to intentionally burn at least two thousand calories a week to begin reaping the benefits of physical activity. Thirty minutes of physical activity is a daily minimum for maintaining health and weight, however most people will benefit from more (Willet '01: 49, 50, 52). This essay on exercise is intended to focus on its relation with the diet.

The documentary *Game Changers* (2018) explains that **plant based diets** do not pollute blood plasma and harden artery endothelium. Plant foods provide more than enough protein. Plant based, vegan diets have been proven by many winning world class athletes to improve performance. Pound for pound, many vegetarian foods are better sources of protein than meat. A hundred-gram portion of meat contains only twenty grams of protein. In comparison, a 100-gram portion of cheese or lentils yields twenty-five grams of protein, while a hundred grams of soybeans yields thirty-four grams of protein. Although meat provides less protein, it costs much more. A spot check in Florida in August 2005 showed sirloin steak costing $7.87 a pound, while staple ingredients for vegetarian meals averaged less than $1.50 a pound. An eight-ounce container of cottage cheese costing $1.59 provides 60 percent of the minimum daily requirement of protein. A study by Dr. Fred State of Harvard and Dr. Mervyn Hording of Loma Linda University made extensive comparisons between the protein intake of vegetarians and that of flesh-eaters. The concluded that “each group exceeded twice its requirement for every essential amino acid and surpassed this amount by a large margins for most of them. For many Americans and Europeans, protein makes up more than 20 percent of their diet, nearly twice the quantity recommended by the WHO. Although inadequate amounts of protein will cause loss of strength, the body cannot use excess protein, rather, it is converted into nitrogenous wastes that burden the kidneys and is eventually passed from the body, taking calcium with it. A number of studies have linked the overeating of protein to the rise in osteoporosis. Although scientists have long known that osteoporosis results from reduced calcium in the bones, they are now coming understand that one of the main causes of calcium deficiency is too much protein in the diet. Carbohydrates are the body's primary source of energy. Only as a last resort does the body use protein to produce energy. Too much protein actually reduces the body's energy capacity. In a series of comparative endurance tests conducted by Dr. Irving Fisher of Yale, vegetarians

performed twice as well as meat-eaters. By reducing the non-vegetarians protein consumption by 20 percent, their efficiency improved by 33 percent. A study by Dr. J. Iotekyo and V. Kipan at Brussels University showed that vegetarians were able to perform physical tests two to three times longer than meat-eaters before exhaustion, and were fully recovered from fatigue in one-fifth the time needed by meat-eaters (Swami '06: 11- 12, 21 - 22).

The American College of Sports Medicine defines **physical fitness** as a set of attributes that people have, or achieve, that relates to the ability to perform physical activity. The fitness components of cardio-respiratory endurance, muscular strength and endurance, flexibility, and body composition are all inherent within a generalized exercise prescription. The Surgeon General's Report, Physical Activity and Health, states: "…significant health benefits can be obtained by including a moderate amount of physical activity (e.g. brisk walking, running, resistance training, recreational sports) on most, if not all, days of the week. Additional health benefits can be gained through greater amounts of physical activity. People who can maintain a regular regimen of activity that is of longer duration, or of more vigorous intensity, are likely to derive greater benefit." The vast majority of physically active adults are not involved in structure, formal exercise programs, nor do they need to be. There is however excellent evidence that good physical fitness reduces all-cause mortality, and coronary artery disease; good evidence that it reduces disease rates of hypertension, obesity, colon cancer, non-insulin dependent diabetes and osteoporosis; some evidence that it reduces disease rates of stroke, breast, prostate and lung cancer; although there is no apparent difference in disease rates across activity categories in peripheral vascular disease, rectal, stomach or pancreatic cancer, or osteoarthritis (Mahler et al '95: 3, 6).

Reduction of body weight is a frequently desired outcome in exercise programs. Obesity may be functionally defined as the percent of body fat at which disease risk increases. Body fat is reduced when a chronic negative caloric balance exists. It is recommended that both an increase in caloric expenditure through exercise and a decrease in caloric intake by used to accomplish this goal, a vegan diet is useful. Exercise increases energy expenditure and slows the rate of fat-free tissue loss that occurs when a person loses weight by severe caloric restriction. Exercise also helps maintain the resting metabolic rate and thus the rate of weight loss. Obese individuals are invariably sedentary and many have had poor experiences with exercise in the past. The initial exercise prescription should be based on low intensity and progressively longer durations of activity. Central obesity, fat deposited primarily in the trunk or abdominal region is particularly problematic. Obesity often carries a negative social stigma and is associated with a reduced physical working capacity. Reduction of body fatness is a need or a goal of many exercise program participants. One pound of fat is equivalent to approximately 3500 kcal of energy (1kg =7700 kcal). In designing the exercise component of a weight loss program, the balance between intensity and duration of exercise should be manipulated to promote a high total caloric expenditure (300 to 500 kcal per session and 1000 to 2000 kcal per week for adults). Obese individuals are at an increased relative risk for orthopedic injury and thus may require that the intensity of exercise be maintained at or below the intensity recommended for improvement of cardiorespiratory endurance. Non-weight-bearing activity and rotation of exercise modalities may be necessary and frequent modification in frequency and duration may also be required (Mahler et al '95: 216-219).

Height Weight Tables for Prior and Non-Prior Service

	Non-Prior Service	Maximum weight by years of	Maximum weight by years of

Height (inches)	Prior Service	age for females (pounds)				age for males (pounds)			
		17-20	21-27	28-39	40 and over	17-20	21-27	28-39	40 and over
58	Non-Prior	112	115	119	122	-	-	-	-
	Prior	109	112	115	119	-	-	-	-
59	Non-Prior	116	119	123	126	-	-	-	-
	Prior	113	116	119	123	-	-	-	-
60	Non-Prior	120	123	127	130	139	141	143	146
	Prior	116	120	123	127	132	136	139	141
61	Non-Prior	124	127	131	135	144	146	148	151
	Prior	120	124	127	131	136	140	144	146
62	Non-Prior	129	132	137	139	148	150	153	156
	Prior	125	129	132	137	141	144	148	150
63	Non-Prior	133	137	141	144	153	155	158	161
	Prior	129	133	137	141	145	149	153	155
64	Non-Prior	137	141	145	148	158	160	163	166
	Prior	133	137	141	145	150	154	158	160
65	Non-Prior	141	145	149	153	163	165	168	171
	Prior	137	141	145	149	155	159	163	165
66	Non-Prior	146	150	154	158	168	170	173	177
	Prior	141	146	150	154	160	163	168	170
67	Non-Prior	149	154	159	162	174	176	179	182
	Prior	145	149	154	159	165	169	174	176
68	Non-Prior	154	159	164	167	179	181	184	187
	Prior	150	154	159	164	170	174	179	181
69	Non-Prior	158	163	168	172	184	186	189	193
	Prior	154	158	163	168	175	179	184	188
70	Non-Prior	163	168	173	177	189	192	195	199
	Prior	159	163	168	173	180	185	189	192
71	Non-Prior	167	172	177	182	194	197	201	204
	Prior	163	167	172	177	185	189	194	197
72	Non-Prior	172	177	183	188	200	203	206	210
	Prior	167	172	177	183	190	195	200	203
73	Non-Prior	177	182	188	193	205	208	212	216
	Prior	172	177	182	188	195	200	205	208
74	Non-Prior	183	189	194	198	211	214	218	222
	Prior	178	183	189	194	201	206	211	214
75	Non-Prior	188	194	200	204	217	220	224	228
	Prior	183	188	194	200	206	212	217	220

76	Non-Prior	194	200	206	209	223	226	230	234
	Prior	189	194	200	206	212	217	223	226
77	Non-Prior	199	205	211	215	229	232	236	240
	Prior	193	199	205	211	218	223	229	232
78	Non-Prior	204	210	216	220	235	238	242	247
	Prior	198	204	210	216	223	229	235	238
79	Non-Prior	209	215	222	226	241	244	248	253
	Prior	203	209	215	222	229	235	241	244
80	Non-Prior	214	220	227	232	247	250	255	259
	Prior	208	214	220	227	234	240	247	250

Height will be measured in stocking feet on a flat surface with the chin parallel to the floor. The body should be straight but not rigid, similar to the position of attention. The measurement will be rounded to the nearest inch with the following guidelines:
If the height fraction is less than 1/2 inch, round down.
If the height fraction is 1/2 inch or greater, round up.
Weight should be measured and recorded to the nearest pound.
All measurements will be taken in the APFT uniform.
Add 6 pounds per inch for males and 5 pounds per inch for females measuring over 80 inches tall.

Source: Army Study Guide

Weight loss diets for fat people, often involve fasting, and always involve expending more calories than consumed. The most important dietary issue for all people, especially, sedentary, overweight and obese people is to get sufficient exercise to digest their sedentary ration and work up an **appetite**. For sedentary workers this means scheduling the time, usually in the early morning, to minimally perform or exceed, a formal athletic training program, on a daily basis e.g. Marine Corp physical fitness test (PFT), 50 crunches, 50 push-ups and three mile run; age adjusted down to 40 crunches and push-ups and three-mile run. The ability to perform more than 100 consecutive crunches and push-ups can be achieved, by performing 250 in 5 sets of 50 in quick succession. For obese and crippled people this means a half an hour or more a day of extra-hard labor walking, due to extra weight, pain and difficulty in mobility. Fatty, adipose tissue is a fine source of nutrition, if a little toxic, and slow to metabolize. Fat quickly turns into large muscles. Sedentary obese people must become body builders and open up to outdoor activities and cardiovascular exercise. With a little practice, overweight people are able to hike and perform physical labor longer without eating than thin people. For those who are merely overweight or recovering from injury, a walk to run strategy reduces the amount of time it takes to digest a sedentary diet, and work up a healthy appetite, from two hours of walking to as little as a three mile run in half an hour, a day, or increase distance to an athletic three to five hour 26.2 mile marathon or superb 24 hour 100 mile ultra-marathon. Do not exercise, particular do not run, with more than a fist-full of food in the stomach, or without some undigested water, carbohydrates, protein and calcium. Do crunches and push-ups to verify if food is sufficiently digested beyond the stomach and duodenum, before running three miles or other main activity, such as swimming a quarter of a mile. The 1.5 mile run of the army is not considered sufficient to prevent atherosclerosis and protect closely quartered troops from preventable communicable diseases, eg. *S. pyogenes,* better than being too fat to join the army.

Exercise is necessary to burn off excess calories and to keep the body fit. Most exercise routines involve strength exercises such as push up and sit ups as well as cardiovascular exercise. Cardiovascular exercise is by far the most important part of an exercise routine. Being physically active is one of the most important steps that Americans of all ages can take to improve their health. The *2008 Physical Activity Guidelines for Americans* provides science-based guidance to help Americans aged 6 and older improve their health through appropriate physical activity. Children and adolescents should do 60 minutes (1 hour) or more of physical activity daily. All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits. For substantial health benefits, adults should do at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 minutes, long enough to break a sweat and increase heart beat and respiration, and, it should be spread throughout the week. For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 minutes (5 hours) a week of moderate intensity, or 150 minutes a week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount. Ideally an adult would exercise for at least an hour, seven days a week, just like children. The Marine Corp Physical Fitness Test (PFT) Requirements for men are three pull-ups, 50 crunches diminishing with age to 40 and 3-mile run in 28:00 minutes diminishing with age to 33:00. For women it is a 15 second flexed arm hang and 50 crunches diminishing to 40 with age and 3-mile run in 31:00 minutes diminishing to 36:00 minutes with age. To enter Marine Corp basic training men have to do 2 pull-ups, 44 sit-ups in two minutes and 1.5 mile run in 13:30 minutes; women do a flexed arm hang for 12 seconds, 44 sit-ups in two minutes and one mile run in 10:30 minutes. The Boston marathon is one of the last marathons in the United States to require qualifying times be run before the race which are 3:05 for men and 3:35 for women between the ages of 18-34, rising five minutes every four year increments to 80+ times of 4:55 for men and 5:25 for women. Cardiologists agree with the Marine Corp on the three mile minimum daily run.

Marine Corp Age Adjusted Physical Fitness Requirements

Age	Push-ups 1 minute	Crunches 3 minutes	Pull-ups	3-Mile Run
Goal	Sets of 50-100	Sets of 50-100	**Sets of 10-20**	25:00
Male 17-26	50	50	3	28:00
27-39	45	45	3	29:00
40-45	45	45	3	30:00
46+	40	40	3	33:00
Females 17-26	50	50	Flexed Armed Hang 15 seconds	31:00
27-39	45	45	15 seconds	32:00
40-45	45	45	15 seconds	33:00
46+	40	40	15 seconds	36:00

Source: Army Study Guide

The **1-1-1 Physical Fitness Assessment**, consists of one minute of push-ups, one minute of sit-ups, and a timed, one-mile run. Soldiers are allowed a minimum of 5 minutes and a maximum of

10 minutes to recover between events. Clients often start out doing push-ups on their knees and work up to 40 to 50 regular push-ups without stopping to rest. The Walk-to-Run Program is for people whose 1-mile time was slower than 8:30 or a female with a 1-mile time slower than 10:30 minutes. During the first four weeks alternate walking and running for 10:30 minutes and repeat the walk-run routine five times in each training session. At week five run continuously for the time period listed on the training schedule. Run at a pace that can be maintained for the entire time or distance without feeling out of breath. The ability to carry on a conversation while running (the talk test), indicates the right pace. Males with 1-mile times 8:30 or faster or a female 10:30 or faster should practice speed running or carry a backpack if they don't increase the distance to the minimal daily distance of 10 km to 10 miles, twice a day, used by most athletes trying to stay healthy and keep the marathon within reach.

The recommended rate of progression in an **exercise conditioning program** has three stages, the initial conditioning stage, improvement stage and maintenance stage. The initial conditioning stage includes light muscular endurance activities and moderate-level cardio respirator endurance activities that produce minimal muscle soreness and control injuries. This stage usually lasts up to four weeks and is dependent upon the individual's adaptation to exercise. The duration of the main activity during the initial stage will begin with approximately fifteen to twenty minutes and may progress to thirty minutes or more. The goal of the improvement stage is to provide a gradual increase in the overall exercise stimulus to allow for more significant improvements in your fitness level. The goal of the maintenance stage is the long-term maintenance of the cardio-respiratory and muscular strength and endurance fitness developed during the weeks spent in the improvement stage. Exercise must be conducted daily at the proper intensity to bring about the desired changes in the body. Missing a whole week of sessions, will probably set the program back a week. If unable to perform certain exercises perform more of those able to do in order to ensure minimal cardiorespiratory exertion. Adequate nutrition, rest and recovery must be studied to optimize health, physical fitness improvement, and control injuries. The military physical training prescription takes approximately 45 minutes per day, and should be done everyday. Training does not require a gym or expensive equipment. It is best to start with just the resistance of the body to develop proper form. Each standardized physical training session expends approximately 300-400 kilocalories found in a ½ cup of cooked rice, cereal, or pasta about the same size of a fist. Exercising with more than a fistful of food in the stomach is likely to cause indigestion and could lead to ulceration.

To make the leap from 50 consecutive push-ups and/or crunches to over 100 it is advised to perform 5 set of 50 push-ups and/or crunches in quick succession, for a total of 250. In the next session, in a few hours or next morning, see how many consecutive push-up and/or crunches can be done without stopping, with 100 as the arbitrary goal, or 10 more than the previous test. Yoga instructors teach to breath through the nose when doing crunches; lightly inhale on the upward crunch and exhale with the help of gravity on the downward crunch to the ground to forcibly clear nostrils. 50 crunches is not enough to prevent or cure pot-belly. Physical education teachers claim it is minimally necessary to do more than 100 consecutive crunches to enjoy wash-board abs. It is not difficult to do more than 100 consecutive crunches, unless the feet are lodged under a bar stressing the quadriceps. It is enough to protect the back from injury with a doubled over hiking mat, or neatly folded blanket. Immobilize the feet and hips with a bar or raise the feet with hands crossed over the chest or allow the hips to rise with hands behind the head. Intensity is increased by moving hands from crossed over the chest for therapeutic crunches, to behind the head for aerobic crunches. On the other hand, it is usually a first experience in body-building, to progress from 50 to 100 push-ups, with 5 sets of 50, or 10 more

than the previous session. Trekking poles help long-distance hikers to keep their push-ups and avoid chest pain from upper body muscle wasting.

Exercise Calorie Expenditure Chart, by Hour, Weight and Activity

Activity	90 lbs.	100 lbs.	110 lbs.	120 lbs.	130 lbs.	140 lbs.	150 lbs.	160 lbs.	170 lbs.	180 lbs.	190 lbs.	200 lbs.	220 lbs.	240 lbs.	260 lbs.	280 lbs.	300 lbs.
Aerobic dancing	104	115	127	138	149	161	172	184	195	207	218	230	253	276	299	322	345
Aerobics, 4" step	131	145	160	174	189	203	218	232	247	261	276	290	319	348	377	406	435
Aerobics, slide	135	150	165	180	195	210	225	240	255	270	285	300	330	360	390	420	450
Badminton	135	150	165	180	195	210	225	240	255	270	285	300	330	360	390	420	450
Basketball (game)	198	220	242	264	286	308	330	352	374	396	418	440	484	528	572	616	660
Basketball (leisurely)	117	130	143	156	169	182	195	208	221	234	247	260	286	312	338	364	390
Bicycling, 10 mph	112	125	138	150	162	175	188	200	213	225	237	250	275	300	325	350	375
Bicycling, 13 mph	180	200	220	240	260	280	300	320	340	360	380	400	440	480	520	560	600
Billiards	41	45	49	54	58	63	68	72	76	81	85	90	99	108	117	126	135
Bowling	50	55	60	66	72	77	82	88	94	99	105	110	121	132	143	154	165
Canoeing, 2.5 mph	63	70	77	84	91	98	105	112	119	126	133	140	154	168	182	196	210
Canoeing, 4.0 mph	122	135	149	162	175	189	202	216	230	243	257	270	297	324	351	378	405
Croquet	54	60	66	72	78	84	90	96	102	108	114	120	132	144	156	168	180
Cross country ski, hard	297	330	363	396	429	462	495	528	561	594	627	660	726	792	858	924	990
Cross country ski, easy	140	155	171	186	202	217	232	248	263	279	294	310	341	372	403	434	465
Cross country ski, med	198	220	242	264	286	308	330	352	374	396	418	440	484	528	572	616	660
Dancing	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300

(noncontact)																	
Dancing (slow)	50	55	60	66	72	77	82	88	94	99	105	110	121	132	143	154	165
Gardening, moderate	81	90	99	108	117	126	135	144	153	162	171	180	198	216	234	252	270
Golfing (walking)	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Golfing (with a cart)	63	70	77	84	91	98	105	112	119	126	133	140	154	168	182	196	210
Handball	207	230	253	276	299	322	345	368	391	414	437	460	506	552	598	644	690
Hiking 10 lb. load	162	180	198	216	234	252	270	288	306	324	342	360	396	432	468	504	540
Hiking 20 lb. load	180	200	220	240	260	280	300	320	340	360	380	400	440	480	520	560	600
Hiking 30 lb. load	211	235	259	282	306	329	352	376	399	423	446	470	517	564	611	658	705
Hiking, no load	140	155	171	186	202	217	232	248	263	279	294	310	341	372	403	434	465
Housework	81	90	99	108	117	126	135	144	153	162	171	180	198	216	234	252	270
Ironing	45	50	55	60	65	70	75	80	85	90	95	100	110	120	130	140	150
Jogging, 5 mph	167	185	203	222	240	259	278	296	315	333	352	370	407	444	481	518	555
Jogging, 6 mph	207	230	253	276	299	322	345	368	391	414	437	460	506	552	598	644	690
Mopping	77	85	94	102	111	119	128	136	144	153	162	170	187	204	221	238	255
Mowing	122	135	149	162	175	189	202	216	230	243	257	270	297	324	351	378	405
Ping Pong	81	90	99	108	117	126	135	144	153	162	171	180	198	216	234	252	270
Raking	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225
Raquetball	185	205	225	246	266	287	308	328	349	369	389	410	451	492	533	574	615
Rowing (leisurely)	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225
Rowing machine	162	180	198	216	234	252	270	288	306	324	342	360	396	432	468	504	540

Running, 08 mph	274	305	336	366	396	427	458	488	518	549	579	610	671	732	793	854	915
Running, 09 mph	297	330	363	396	429	462	495	528	561	594	627	660	726	792	858	924	990
Running, 10 mph	315	350	385	420	455	490	525	560	595	630	665	700	770	840	910	980	1050
Scrubbing the floor	126	140	154	168	182	196	210	224	238	252	266	280	308	336	364	392	420
Scuba diving	171	190	209	228	247	266	285	304	323	342	361	380	418	456	494	532	570
Shopping for groceries	54	60	66	72	78	84	90	96	102	108	114	120	132	144	156	168	180
Skipping rope	257	285	313	342	370	399	428	456	484	513	541	570	627	684	741	798	855
Snow shoveling	176	195	215	234	253	273	292	312	332	351	371	390	429	468	507	546	585
Snow skiing, downhill	117	130	143	156	169	182	195	208	221	234	247	260	286	312	338	364	390
Soccer	176	195	215	234	253	273	292	312	332	351	371	390	429	468	507	546	585
Squash	185	205	225	246	266	287	308	328	349	369	389	410	451	492	533	574	615
Stair climber machine	144	160	176	192	208	224	240	256	272	288	304	320	352	384	416	448	480
Stair climbing	126	140	154	168	182	196	210	224	238	252	266	280	308	336	364	392	420
Swimming (25 yrd/min)	108	120	132	144	156	168	180	192	204	216	228	240	264	288	312	336	360
Swimming (50 yrd/min)	202	225	248	270	292	315	338	360	382	405	428	450	495	540	585	630	675
Table Tennis	81	90	99	108	117	126	135	144	153	162	171	180	198	216	234	252	270
Tennis	144	160	176	192	208	224	240	256	272	288	304	320	352	384	416	448	480
Tennis (doubles)	99	110	121	132	143	154	165	176	187	198	209	220	242	264	286	308	330
Trimming hedges	94	105	115	126	136	147	158	168	178	189	199	210	231	252	273	294	315
Vacuuming	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225
Volleyball (game)	108	120	132	144	156	168	180	192	204	216	228	240	264	288	312	336	360

Volleyball (leisurely)	63	70	77	84	91	98	105	112	119	126	133	140	154	168	182	196	210
Walking, 2 mph	54	60	66	72	78	84	90	96	102	108	114	120	132	144	156	168	180
Walking, 3 mph	72	80	88	96	104	112	120	128	136	144	152	160	176	192	208	224	240
Walking, 4 mph	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Washing the car	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225
Waterskiing	144	160	176	192	208	224	240	256	272	288	304	320	352	384	416	448	480
Waxing the car	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Weeding	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Weights (40 sec. down)	230	255	280	306	332	357	382	408	433	459	484	510	561	612	663	714	765
Weights (60 sec. down)	171	190	209	228	247	266	285	304	323	342	361	380	418	456	494	532	570
Weights (90 sec. down)	112	125	138	150	162	175	188	200	213	225	237	250	275	300	325	350	375
Window cleaning	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225

Source: Nutribase Professional Nutrition and Fitness Software.

A standardized physical training session consists of three essential elements: warm-up, activity, and cool-down. Although any physical activity burns calories and increases a person's caloric needs above the sedentary, it is always advised to warm-up with PFT, to protect the chest and abdomen and verify adequate digestion before running or engaging in the lengthier and more demanding athletic activity. Stretches after running help to eliminate any residual cramps, weariness and woodiness. To count caloric needs, above the sedentary daily recommended allowance, incurred by various forms of exercise the Nutribase Professional Nutrition and Fitness Software estimates of how may calories various forms of physical activity burn every hour for people of different weights. For instance a 150 pound person, hiking with a 30 pound load would burn 352 calories an hour, for 10 hours a day, needs to pack for 3,520 calories plus 2,300 sedentary calories, for a total of 5,820 calories a day, consumed in eight to ten small 500 calories meals of trail mix, jerky, sandwiches, and small portions of cooked food, less with experience. A 150 pound person jogging a marathon at 5 mph to complete a 26.2 mile race would expend 278 calories an hour for 5 hours, 1,390 calories, more than the 2,300 calorie sedentary diet, for a total of 3,690 calories that day. A 150 pound person running to win the same marathon at 10 mph would expend 525 calories over 2 ½ hours for 1,313 extra calories, for a total of 3,613 calories the night before and on race day.

The total **caloric expenditure** of runners completing a marathon, in three to seven hours, is difficult, if not impossible to measure accurately, and in general caloric expenditure from

physical activity requires more scientific study. However, using a treadmill it has been shown that the energy expended running is approximately 1.5kcal/kg/mile. Therefore, if a marathon were held on a motor-driven treadmill, a 50kg runner would expend 1,970 kcal, a 60kg runner 2,360 kcal, a 70 kg runner 2,750 kcal, and 80 kg runner 3,140 kcal, and so on. However marathons are not run on a treadmill, and in actual running conditions, the caloric cost is not independent of running velocity. Most marathon runners require approximately 2,400 kcal to finish the 26.2 miles. A comparison of horizontal running and hill running at the moderate velocity of 8 min/mile has been shown that an athlete running up a 6% incline will expend approximately 35% more energy than on a horizontal track, and on the downhill part of this 6% decline hill, the runner only reduces energy expenditure by 24%. The direct solar heat gain of marathon runners has been determined to be 55 kcal/m^2/hr on a sunny day with an ambient temperature of 22-23°C and relative humidity of 52-58%. For comparison, it has been reported that during desert conditions, the solar heat gain will approach 140 kcal/m^2/hr. For thin runners requiring at least 2 ½ hours to finish a marathon, an additional energy expenditure of at least 250 kcal must be utilized to cool the body. For the larger runner, who may require four hours to finish the marathon, solar heat gain may result in an energy expenditure of 400-500 kcal (Taylor '82: 38, 39).

In a study of **weight control behavior** in female athletes, it was found that about one-fourth of the 182 varsity-level athletes used diet pills routinely, about 15 percent used laxatives, and a small percentage used self-induced vomiting. The percentage of women who restrained their eating, did binge-purge eating, and used self-induced vomiting varied among different sports where leanness is emphasized very often have eating disorders. Ballet dancers and gymnasts have the most, about 70 percent and track runners, about 30 percent. Among athletes who participate in sports where leanness is not emphasized, including tennis, volleyball and swimming, the proportion of women with eating disorders is about 20 percent. A woman should probably not begin intense physical training until she has had her first menstrual period and should monitor the amount and intensity of the exercise to normalize her menstrual cycle, a few menstrual cycles a year (oligomenorrhea) is not enough. When an amenorrheic woman stops training due to an injury or another problem, she usually gains some weight and regains her menstrual periods. With the return of menses she can regain bone mass, but none of the women studies have gained back all the bone mass they lost. Where emphasis on leanness and asexual solitude, is less important, in tennis, volleyball, and swimming, eating disorders, amenorrhea, delayed menarche and stress fractures seem to be less problematic (Lane ’99: 130, 131).

The **age of menarche** (the start of menstruation) is later in athletes compared to non-athletes and swimmers. Breast and pubic hair development are delayed by about a year. This delay occurs more often in activities in which the athletes are thin, such as ballet dancing, gymnastics, running and figure skating. Some dancers and runner do not have their first menstrual period until their 20s. Scoliosis, or curvature of the spine, is also more frequent in ballet dancers with delayed menarche. The end result of delayed menarche is that these women enter menopause with a substantially lower bone mass than normal women. Normal puberty occurs when gonadoptropin-releasing hormone (GNRH) enters the bloodstream and stimulates luteinizing hormone (LH) secretion form the pituitary. In the late-maturing athlete, lack of GNRH suppresses LH secretion. Important information for the physician to obtain includes the athlete’s training intensity, eating habits, history of growth and development, and the blood levels of hormones, including LH, follicle-stimulating hormone (FSD), estradiol, and thyroid hormones. These young athletes should decrease the intensity of their training and improve nutritional intake (Lane ’99: 127, 128).

The rate of bone loss in **amenorrheic women** is similar to that in women who are in early menopause. In general, women tend to lose about 1 percent of their bone mass a year form early in their 30s on, whereas athletes who no longer have menstrual periods appear to lose about 5 percent of their bone mass per year, about the same a post-menopausal woman. Estrogen deficiency, which plays a critical role in the loss of bone mass after menopause, is the main cause of osteopenia in both young women and premenopausal amenorrheic athletes. When these athletes resumed their menstrual cycle the bone mineral density of their lumbar spine increased. The beneficial effects of regular strenuous exercise on heart disease may be reversed by exercise-induced amenorrhea. The estrogen that normally reduces the LDL level is decreased in these women. The increased bone mineral density in weight-bearing bone that is usually seen with exercise is not found in amenorrheic dancers and runners. In fact, amenorrheic athletes lost over 3 percent of their spinal bone mineral density over the 15 months they were followed, despite a regular exercise program, while athletes with a normal menstrual cycle lost no bone mass. The amenorrheic runners who were taking birth control pills had a decreased risk of developing stress fractures, since birth control pills contain both estrogen and progesterone. The young athlete who takes birth control pills appears to be able to prevent some of this bone loss, but she still may not achieve peak bone mass and may never regain the bone mass she has lost (Lane ’99: 129, 130).

There are two major types of **diabetes mellitus**, juvenile onset Insulin dependent diabetes mellitus (IDDM) and maturity onset non-insulin dependent diabetes mellitus (NIDDM). The response to exercise in juvenile onset insulin dependent diabetes (IDDM) varies. If the diabetic is under appropriate control or only slightly hyperglycemic without ketosis, exercise decreases blood glucose concentration and a lower insulin dosage may be required. However, a lack of sufficient insulin prior to exercise may impair glucose transport into the muscles limiting the availability of glucose as an energy substrate leading to ketosis, resulting in greater glucose production further exacerbating the hyperglycemic state. Serum glucose concentrations in the general range of 200 to 400 mg/dL require medical supervision during exercise, while exercise is contraindicated for those with fasting serum values >400 mg/dL pending medical follow-up. Exercise induced hypoglycemia is the most common problem experience by exercising diabetics. Hypoglycemia not only occurs during exercise, but may occur up to 4 to 6 hours following an exercise bout. To counteract this response, the diabetic may need to reduce insulin dosage or increase carbohydrate intake prior to exercising. Proper footwear and good foot hygiene is important. Beta-blockers and other medication may interfere with the ability to discern hypoglycemic symptoms and/or angina. Exercise in excessive heat may cause problems in diabetic with peripheral neuropathy. Patients with advanced retinopathy should not perform activities which cause excessive jarring or marked increases in blood pressure. NIDDM diabetic may benefit from oral hypoglycemic agents rather than injections of insulin, although exogenous insulin is sometimes used. Since insulin facilitate the cellular absorption of glucose a lack of sufficiently circulating insulin usually results in hyperglycemia (Mahler et al '95: 213-215).

Basic military training is not very demanding by athletic standards however many recruits become permanently disabled in boot camp and are discharged due to chronic bone disease before having made a significant contribution, possibly due to shortage of highly safe and effective $1 athlete's foot cream (clotrimazole) rather than $1 antifungal foot powder spray (toftate) that causes diffuse pain and angina. Rheumatism that occurs in conjunction with angina pectoris, usually alternating between angina that gets better with exercise and hip pain that gets worse with exercise, known as rheumatic heart disease, is caused by *Streptococcus pyogenes* 50% of the time, which responds best to penicillin but any antibiotic, with probiotic supplementation during and for two weeks after finishing a course, should eliminate rheumatism,

helping to achieve minimal athletic standards, which heightens the sensitivity to and hastens treatment of new rheumatic infections so that they do not cripple the work-out. **Drug resistance** is only issue for *Staphylococcus aureus* that infects the heart and vertebrae with large lesions 1 cm in diameter and is effectively treated with doxycycline; infectious diarrhea, abdominal and joint infections are always treated with metronidazole (Flagyl ER) whether or not other drugs have been prescribed. Knee pain is rarely can be caused by human influenza, most cheaply treated with Amantadine (Symmetrel) that is also indicated to cure life-threatening extra-pyramidal side-effects of antipsychotic drugs. In general, to avoid injury, before running 3 miles it is necessary to warm up with a minimum of 100 push-ups, sit-ups and some movement drills and after running 3 miles it is necessary to stretch. All organized exercise programs do yoga to help improve flexibility, balance and strength to prevent injury during and after the high intensity endurance activity of the day. A mat or folded blanket is necessary to avoid injuring the back doing crunches. Socks must not make running shoes tight in the winter or the foot bones will be painfully crunched. A ripped pectoral muscle, possibly from doing excessive pull-ups, might lead to an aortic aneurysm and causes pain that is indistinguishable from *angina pectoris*. Do not run so fast that breathing and/or heart beat is anywhere near painful, slow down, one should be able to talk unless a competitive athlete knows they can tolerate the chest pain needed to win.

Make sure exercise clothes are **cardiac glycoside free**. Exceeding 300,000 cases annually, sudden cardiac death (SCD) is the leading cause of death in the U.S. Studies of exercise by apparently healthy adults report an acute event rate of 1 per 187,500 person-hours of exercise and death rate of male joggers of 1 per 396,000 man-hours of jogging. The incidence of cardiac arrest while jogging is approximately 1 episode per year for every 18,000 healthy men, by appears to be lower for men with higher levels of habitual physical activity. While the risk of sudden cardiac death is increased during vigorous exercise, this risk is lower among those habitually active. There are no scientific studies on exercise-related cardiac events in women. The major cause of cardiovascular complications during exercise is coronary artery disease (CAD). During medically supervised cardiac rehabilitation exercise programs , the risk of death in the U.S. is approximately 1 per 60,000 participant hours, maybe one death every four years per program. The risk of SCD in joggers and marathon participants is estimated to 1/15,000 and 1/50,000 respectively. Pre-participation exercise testing should be reserved for men >40-45 years of age and women>50-55 year with moderate to high cardiovascular risk. The probability of an exercise induced cardiac event is greater in athletes with atherosclerotic coronary disease and left ventricular dysfunction and older athletes should be discouraged from participation in high intensity sports if they have left ventricular ejection fraction <50% or evidence of exercise-induced ischemia, ventricular arrhythmia or systolic hypotension.

Exercise is the cure for atherosclerosis, 90% of heart disease. In general, the minimal standards of military basic training must be exceeded to have a fighting chance to perform daily duties when exercise must be reduced to 60% of normal or less due to crippling injury or illness. The essential components of a systematic, individualized **exercise prescription** include the appropriate mode(s), intensity, duration, frequency, and progression of physical activity. These five components apply when developing exercise prescriptions for persons of all ages and functional capacities, regardless of the presence or absence of risk factors and disease. The optimal exercise prescription for an individual is determined from an objective evaluation of that individual's response to exercise, including observations of heart rate (HR), blood pressure (BP), ratings of perceived exertion (RPE), subjective response to exercise, electrocardiogram (ECG) when applicable, and functional capacity measured during a graded exercise test (GXT).

The art of exercise prescription requires modification in accordance with observed individual responses and adaptations because physiological and perceptual responses to acute exercise vary. Improvement of the ability of the body to utilize oxygen efficiently, resulting in improved endurance, is one component of physical fitness. The increase in **maximal oxygen intake** (VO_{2max}) may range from 5 to 30% and is most dramatic in people with low initial levels of fitness, cardiac patients and those exhibiting weight loss. The greatest improvement VO_{2max} occurs when exercise involves the use of large muscle groups over prolonged periods and is rhythmic and aerobic in nature (e.g. walking, hiking, running, stair climbing, swimming, cycling, rowing, dancing, skating, skiing, rope skipping, or endurance game activities). Circuit weight training, which involves 10 to 15 repetitions with 15 to 30 seconds rest between weight stations results in an average improvement of about 5% and is not generally recommended as an activity for improving cardiorespiratory endurance. Intensity and duration of exercise determine the total caloric expenditure during a training session. To reduce the risk of orthopedic injury programs emphasizing low- to moderate-intensity exercise with a longer training duration are recommended for most individuals. The recommended intensity of exercise should be prescribed as 60 to 90% of maximum heart rate, or 50 to 85% of $VO_{2max.}$ However individuals with a very low initial level of fitness respond to a low exercise intensity, for example, 40 to 50% of VO_{2max}. Although improvement in cardiorespiratory endurance have been demonstrated with 5 to 10 minutes of very high intensity (>90% VO_{2max}) exercise, at least 20 to 60 minutes of continuous aerobic activity is recommended.

5. Enzymes

Enzymes are biological catalysts. They increase the rate of chemical reactions taking place within living cells without themselves suffering any overall change. The reactants of enzyme-catalyzed reactions are termed **substrates** and each enzyme is quite specific in character, acting on a particular substrate or substrates to produce a particular product or products, in the biochemical process known as **metabolism**. All enzymes are **proteins** of high molecular weight (10,000 to 2,000,000), made up primarily of chains of amino acids linked together by peptide bonds. However, without the presence of a non-protein component called a **cofacto**r, many enzyme proteins lack catalytic activity. When this is the case, the active component of an enzyme is termed the apoenzyme, and the active enzyme, including cofactor, the holoenzyme. The cofactor may be an organic molecule, when it is known as a coenzyme, or it may be a meta ion. Substances that are able to increase the activity of the enzyme in a non-specific manner are called **activators**. They are part of the activating system and are required before the enzyme can activate its substrate. An activator is not a coenzyme because a coenzyme is a part of the reaction system and plays no role in the activation of the substrate. Many inorganic radicals such as chloride, potassium, calcium, magnesium and phosphates are activators. Any compound which reduces the observed activity of an enzyme is an **inhibitor**. Inhibition of enzyme activity by a compound may be a result of its reaction with apoenzyme, necessary cofactors, activators, intermediates in the pathway, or the essential groups of the enzyme (Naz '02:4).

Amino acids are linked in chains named proteins. Digestive enzymes break down these chains in the small intestine and the gut wall absorbs the amino acids. There are twenty of these amino acids and an infinite variety of ways they can be linked to form proteins. Amino acids are used to build many substances, including the DNA genetic material contained in every new cell produced. The same is true for all living things, plants and animals. That explains why all edible food produced in nature contains protein. However, maintaining a healthy meat-free diet that does not lead to nutritional deficiencies is difficult. Plants construct different proteins than animals, and they often use so little of a given amino aid that the proteins they produce are

known as incomplete. When the body tries to use these to make needed amino acids, it can build the chain only until one of the amino acids runs out. Half-finished proteins are then simply broken down again, and the tiny acids are excreted in the urine or recycled in the body. Beans lack the amino acid methionine; rice and wheat (and it derivative meat substitute, seitan) lack lysine and sweetcorn is deficient in both lysine and tryptophan. Vegetarians and vegans have to be clever at combining their foods to create a complete protein. Beans may be lacking in methionine, but they are packed with lysine. A wheat tortilla with refried beans and rice will provide all the amino acids the body needs for healthy protein production. Vegetarians who eat cheese and eggs can compensate for incomplete proteins that way. People eat meals made of foodstuffs that complement each other, rich and beans, pasta with cheese, pita bread and hummus, or peanut butter on toast. Combining does not need to take place in one meal. It is enough to take in the right combination over the course of the day. Soy, quinoa, amaranth, spirulina, buckwheat and chia seeds contain all the necessary amino acids in the necessary quantities. Tofu has a well-deserved reputation as a meat substitute, although increasing numbers of people are developing allergic reactions to it (Enders '15: 55-57). Enzymes are extremely sensitive to heat, even low to moderate heat, 118°F or above, destroys most enzymes in food, so to obtain enzymes in the diet one needs to eat raw foods (Balch '00: 60). Proteins react to the heat in the hot pan and the acid in our stomach in the same way – they unfold. That means they no longer possess the clever design features that make them soluble in the liquid of the egg white, so they form solid white lumps. In this state, they an be digested far more easily in the stomach and the small intestine. Cooking food saves us the whole first burst of energy required to unfold those proteins, which would otherwise have to be expended by the stomach. By preferring cooked food, the body outsources the first part the digestive process (Enders '15: 40).

The International Union of Biochemistry divides enzymes into **six main classes** on the basis of the total reaction catalyzed. Each enzyme was assigned a code number, consisting of four elements, separated by dots. The first digit shows to which of the main classes the enzyme belong. The second and third digit in the code further describe the kind of reaction being catalyzed. Enzymes catalyzing very similar but non-identical reactions, e.g., the hydrolysis of different carboxylic acid esters, will have the same first three digits on their code. The fourth digit distinguishes between them by defining the actual substrate, e.g. the actual carboxylic acid ester being hydrolyzed. Isoenzymes, different enzymes catalyzing identical reactions, will have the same four digit classification, and its source still must be specified (Naz '02: 4-6). The first general principle of enzymatic nomenclature is that names purporting to be the name of enzymes, those ending in **–ase**, should by used only for single enzymes and not be applied to systems containing more than one enzyme. For example, the system catalyzing the oxidation of succinate by molecular oxygen, consisting of succinate dehydrogenase, cytochrome oxidase, and several intermediate carriers, should not be named succinate oxidase, but may be called the succinate oxidase system. The second general principle is that enzymes are principally classified and named according to **the reaction they catalyse**. A third general principle is that the enzymes are divided into groups on the basis of the type of reaction catalyzed, and this, together with the **name(s) of the substrate(s)** provides a basis for naming individual enzymes. It is also the basis for classification and code numbers (Webb '92: 1992). In 1985 an estimated 1,500 enzymes had been discovered, as of 1992 more than 3,000 enzymes had been discovered and by 2000 it is estimated that the body elaborates upwards of 100,000 different enzymes and isoenzymes.

Enzyme Classification

First Digit	Enzyme Class	Second Digit (First subclass)	Third Digit (Second class)
1	Oxidoreductases	Group oxidized	Group reduced
2	Transferases	Group transferred (further delineated)	Group transferred
3	Hydrolases	Bond hydrolysed: Ester, peptide, etc.	Substrate class: Carboxylic ester, thiol ester, etc.
4	Lyases	Bond cleaved: C-O, C-S, C-N, etc.	Group eliminated: Carboxyl, aldehyde, etc.
5	Isomerases	Type of reaction: Racemization or epimerization	Type of molecule undergoing isomerization
6	Ligases	Type of bond synthesized: C-C, C-O, C-S, C-N, etc.	Substrate, cosubstrate class

Source: Naz '02: Table 1.1, 5, 6

All enzymes are proteins. **Proteins** are macromolecules with molecular weights of at least several thousand. They are found in abundance in living organisms, making up more than half the dry weight of cells. Two distinct types are known: fibrous and globular proteins. Fibrous proteins are insoluble in water and are physically tough, which enables them to play a structural role. Examples include, α-keratin (a component of hair, nails and feathers) and collagen (the main fibrous element of skin, bone and tendon). In contrast, globular proteins are generally soluble in water and may be crystallized from solution. All enzymes are globular proteins. All proteins consist of amino acid units, joined in series. The sequence of amino acids in a protein is specific, being determined by the structure of the genetic material of the cell, and this gives each protein unique properties. An enzyme may be either simple or conjugated protein. Some proteins are composed entirely of these amino acid blocks and are termed simple proteins. Others called conjugated proteins, contain extra material, which is firmly bound to one or more of the amino acid units. Extra components define conjugated proteins, for example, (1) nucleoprotein bond with nucleic acid, (2) lipoprotein with a lipid, (3) glycoprotein with an oligosaccharide, haemoprotein with an iron protoporpyrin, flavoprotein with a flavin nucleotide and metalloprotein with a metal. Amino acids, by definition are organic compounds which contains, within the same molecule, an amino group ($-NH_2$ or >NH) and a carboxyl group (-COOH). Thus catalysts have properties of both bases and acids. The amino group in all of the twenty amino acids commonly found in proteins, is a primary one ($-NH_2$), the exception being proline, which contains a secondary amino group (>NH). Acids can catalyse reactions by temporarily donating a proton, bases can do the same by temporarily accepting a proton. Bases may also increase reaction rate by increasing the nucleophilic character of the attacking groups. (Naz '02: 7, 56).

The pancreas secretes 1.5 to 3 liters per day of an alkaline fluid containing enzymes and proenzymes (zymogen). The regulation of this process involves the hormones secretin and cholecystokinin, produced in the duodenum. The former stimulates water and bicarbonate secretion and the latter enhances the discharge of zymogens by acinar cells. The pancreas also elaborates the enzymes trypsin, chymotrypsin, aminopeptidases, elastase, amylases, lipases, and phospholipases. Trypsin is a key enzyme because it catalyzes activation of the other enzymes.

The islets of Langerhans consist of four major and two minor cell types. The four main types are B (beta), A (alpha), D (delta), and P (pancreatic polypeptide) cells. These make up about 70, 20, 5 to 10 and 1 to 2% of the islet cell population, respectively. The B cell (beta) produces insulin and hyperplasia or neoplasia of these are responsible for hyperinsulinism. A cells (alpha) secrete glucagon which induces hyperglycemia by its blycogenolytic activity in the liver. D cells (delta) contain somatostatin, which suppresses both insulin and glucagon release. PP (pancreatic polypeptide) exert a number of gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes and inhibition of intestinal motility. The two rare cell types are D1 cells and enterochromaffin cells. D1 cells elaborate vasoactive intestinal polypeptide (VIP), that induces glycogenolysis and hyperglycemia and also stimulates gastrointestinal fluid secretion and cases secretory diarrhea. Enterochromaffin cells synthesize serotonin and are the source of pancreatic tumors that induce the carcinoid syndrome (Crawford and Cotran ’94: 898, 908-909).

The level of enzyme is not the same throughout the life cycle of an organism. The enzyme may be essentially absent at an early stage, rise to maximum level and then decrease again. Certain enzymes are present in green fruit but not in ripe and vice versa. Enzymes in fruit are often concentrated near the skin and/or pit with low concentrations of enzymes in the bulk of the tissue. It is worth the effort to use the richest source, the skins and pits. This selection process may lead to several fold (10 to 100) enrichment over that obtained with whole organisms. Cancer patients are specifically cautioned to boil their tubers in their jackets (skins) so as not to discard the richest source of enzymes (Gerson '90). The liver contains different types of cells with different enzyme complements. Enzymes can be normal constituents in food and products in food formulations. Native enzymes do not necessarily show activity. Many milk enzymes, present in constant quantity, do not find enough substrate in their medium. Polyphenol oxidases, which are responsible for enzymatic browning, normally do not occur in fruits and vegetables with intact tissue structure, despite the presence of substrates; enzymes and substrates are often localized in different compartments. Some enzymes may be introduced to a food by various microbial contaminants, or during disease or special physiological conditions that occur in the producing organism. The presence of large quantities of reductases in milk is the indication of a bacterial contamination. The applications of food enzymology include, not only the estimation of the degree of food freshness, but the evaluation of the effectiveness of thermal processing, the study of maturation and the detection of the onset of senescence. **Additive enzymes**, isolated from different source, are introduced voluntarily to various food and food products during the processing to achieve different purposes. The clarification of fruit juices by adding pectin esterases and fungal polygalactuonases is an example. The important industrial food enzymes include hydrolases and oxidoreductases. Enzymes used in food processing can be tailored to increase the efficiency of the process, however so far attempts at bioengineering plants has not improved the functional properties of proteins (Naz '02: 56, 68, 81-86).

Enzymes assist in practically all bodily functions. Digestive enzymes break sown food particles for storage in the liver or muscles. This stored energy is later converted by other enzymes for use by the body when necessary. Iron is concentrated in the blood by the action of enzymes; other enzymes in the blood help the blood to coagulate in order to stop bleeding. Uricolytic enzymes catalyze the conversion of uric acid to urea. Respiratory enzymes aid in eliminating carbon dioxide from the lungs. Enzymes assist the kidneys, liver, lungs, colon and skin in removing wastes and toxins from the body. Enzymes also utilize the nutrients ingested by the body to construct new muscle tissue, nerves cells, bone, skin, and glandular tissue. One enzyme can take dietary phosphorus and convert it into bone. Enzymes prompt the oxidation of glucose, which creates energy for the cells. Enzymes also protect the blood from dangerous waste materials by converting these substances to forms that are easily eliminated from the body. If

proteins are not completely digested, undigested protein particles may make their way into the bloodstream and lymphatic system through the intestinal wall with other nutrients. This phenomenon is known as leaky gut syndrome, and it can result from allergic reaction (Balch '00: 59). Gluten intolerance is the most common allergy associated with leaky gut syndrome. Protein enters the lymphatic system, if you rue the day and put too much flour in the gravy, this is discomforting and causes gluten intolerance until completely digested.

Enzymes are too diverse to name. Enzymes are often divided into two groups: digestive and metabolic enzymes. Digestive enzymes are secreted along the gastrointestinal tract to break down foods, enabling the nutrients to be absorbed into the bloodstream for use in various bodily functions. There are three main categories of digestive enzymes: amylase, protease, and lipase. Amylase, found in saliva and in the pancreatic and intestinal juices, breaks down carbohydrates. It begins to act with chewing. Different types of amylase break down specific types of sugars. Lactase breaks down lactose (milk sugar), maltase breaks down sucrose (cane and beat sugar). Protease, found in the stomach juices and also in the pancreatic and intestinal juices, helps to digest protein. Lipase, found in the stomach and pancreatic juices, and also present in fats in foods, aids in fat digestion. While not technically an enzyme, hydrochloric acid interacts with digestive enzymes. Metabolic enzymes are enzymes that catalyze the various chemical reactions within the cells, such as energy production and detoxification. Enzymes build the body from proteins, carbohydrates and fats. Metabolic enzymes are found doing their specific work in the blood, organs and tissues. Each body tissue has its own specific set of metabolic enzymes. Two particularly important metabolic enzymes are superoxide dismutase (SOD) and its partner, catalase. SOD is an antioxidant that protects the cells by attacking a common free radical, superoxide. Catalase breaks down hydrogen peroxide, a metabolic waste product, and liberates oxygen for the body to use. Of the tens of thousands of enzymes needed, the body uses more of its enzyme producing potential to produce the two dozen enzymes that control the breakdown and utilization of proteins, fats, and carbohydrates, than it uses to create hundreds of metabolic enzymes necessary to maintain the rest of the tissues and organs (Balch '00: 59).

24 Common Digestive Enzymes

Enzyme	Substrate	Enzyme	Substrate	Enzyme	Substrate
Amylase	Carbohydrates	Hyaluronidase	Proteins, adhesions, fibrin	Pectinase	Carbohydrates
Bromelain	Proteins	Invertase	Carbohydrates	Pepsin	Proteins
Cellulase	Fiber	Lactase	Lactose (milk sugar)	Phytase	Carbohydrates
Chymopapain	Protein	Lipase	Fats	Plasmin	Proteins
Diastase	Carbohydrates	Maltase	Carbohydrates	Protease	Proteins
Glucoamylase	Carbohydrates	Pancreatin	Proteins, fats,	Rennin	Proteins

			carbohydrates		
Hemicellulase	Carbohydrates	Papain	Proteins, fats, carbohydrates	Trypsin	Protein

Source: (Balch '00: 60)

Enzymes can be found in many different foods, from both plant and animal sources. Avocados, papayas, pineapples, bananas, and mangos are all high in enzymes. Sprouts are the richest source. Unripe papaya papaya and pineapple are excellent sources of papain and bromelain, proteolytic enzymes which break down protein. Many fat foods supply lipase, which breaks down fats. Fat food exposed only to pancreatic lipase is not as well-digested as fat that is first worked on in the stomach by food lipase Pancreatic lipase digests fat in a highly alkaline environment (the intestines), whereas lipase found in food fats works in a more acidic environment (the stomach). Superoxide dismutase occurs naturally in a variety of food sources, including alfalfa, barley grass, broccoli, Brussels sprouts, cabbage, wheatgrass and most dark green plants. Enzymes do not act alone. Enzymes require adequate amounts of other substances, known as coenzymes, to be fully active. The most important coenzymes are the B-complex vitamins, vitamin C, vitamin E and zinc (Balch '00: 60, 61).

The majority of commercially available enzymes are digestive enzymes extracted from various sources. Most commercial enzyme products are made from animal enzymes, such as pancreatin and pepsin, which help in the digestion of food once it has reached the lower stomach and the intestinal tract. Some companies make their supplement from enzymes extracted from aspergillus, a highly pathogenic fungus. These enzymes begin their pre-digestive work in the upper stomach. All of these products are used primarily to aid in the digestion of foods and absorption of nutrients, especially proteins. Enzyme supplements may not be for everyone. During pregnancy women must be careful with supplements. Nursing mothers must also avoid affecting their milk. People who have hemophilia or who take anticoagulants (blood-thinners) should consult their health care providers before taking large amounts of enzymes. Anyone contemplating surgery where there is a high risk of bleeding should consult a physician before taking any supplement. Enzymes are available over the counter in tablet, capsule, powder and liquid forms. They may be sold in combination with each other or as separate items. Some enzyme products also contain garlic to aid digestion. For maximum benefit, any digestive enzyme supplement should contain all of the major enzyme groups – amylase, protease and lipase. Digestive enzymes should taken after meals, unless eating processed and/or cooked foods, in which case it is best to take them during the meal. Supplemental superoxide dismutase must be enteric coated to protect the SOD to pass intact through the stomach acid to be absorbed in the small intestine. Do not crush or chew these pills. All forms of enzymes must be kept in a reasonably cool and dry place. With age the body's ability to produce enzymes decreases. At the same time malabsorption of nutrients, tissue breakdown, and chronic health conditions increase. Taking supplemental enzymes can help to ensure older people continue to get the full nutritional value of their food (Balch '00: 60, 61).

Recommended enzyme complex products. Absorb Aid from Nature's Sources is made from lat enzymes and includes lipase, amylase and protease from bromelain, as well as cellulase and lactase. It has been shown to significantly improve the absorption of nutrients especially essential fatty acids and zinc. Acid-Ease from Prevail Corporation is a digestive aid from natural plant sources that includes amylase, lipase, and cellulase, as well as the soothing herbs

marshmallow root and slippery elm. All Complete Enzymes from TriMedica, Inc. is a blend of plant enzymes that provide a full range of essential enzymes, plus coenzymes for added efficiency. It is designed to aapt to various body temperatures and pH levels without losing potency. Ingredients include amylase, lipase, bromelain, papain, protease, cellulase, aciophilus, bifidus, and trace minerals. Cardio Enzyme Formula from Prevail Corporation contains a combination of enzymes, herbs and nutrients, including protease 1 and 2, amylase, cellulase and lipase, extracts of hawthorn berry, dan-shen root, arjun bark, passionflower, ginkgo leaf, ginkgo rhizome, and garlic, and magnesium, vitamin B6, vitamin B12, folic acid, vitamin C, taurine, L-carnitine and L-lysine, all in a special blend to support the heart. Digest Sypport from Nytrol is a multi-enzyme formula containing all three classes of digestive enzymes (proteolytic, amyolytic and lipolytic). It also includes A-glactosidase, an enzyme that acts on galactose, a breakdown product of lactose (milk sugar) and fights gas. Elastase from Cardiovascular Research contains elastase a proteolytic enzyme found in pancreatic juices. Infla-Zyme from American Biologics is combination of enzymes and antioxidants for people requiring supplemental digestive enzymes that may be also be helpful for chronic or acute inflammation. Mega-Zyme from Enzymatic Therapy is an extra-strength pancreatic and digestive enzyme tablet. Each tablet contains protease, amylase, lipase, trypsin, papain, bromelain and lysozyme. Mega Zymes from MegaFood is a vegetarian enzyme and herbal formula made from plant-based enzymes, including amylase, cellulase, glucoamylase, invertase, lactase, lipase, and protease, blended with tonic herbs caraway, gentian and ginger, pus acidophilus to support healthy intestinal flora (Balch '61, 62).

Amino acids are the chemical units, the building blocks, that make up protein. They are also the end-products of protein digestion, or hydrolysis. Amino aids contain about 16 percent nitrogen. Chemically it is the nitrogen that distinguishes amino acids from the other two basic nutrients, sugars and fatty acids, which do not contain nitrogen. Proteins are a necessary part of every living cell in the body. Next to water, protein makes up the greatest portion of body weight. Protein substances make up the muscles, ligaments, tendons, organs, glands, nails, hair and many vital body fluids. The enzymes and hormones that catalyze and regulate all bodily processes are proteins. Proteins help to regulate the body's water balance and maintain the proper internal pH. They assist in the exchange of nutrients between the intercellular fluids and the tissues, blood and lymph. A deficiency in protein an upset the body's fluid balance, causing edema. Proteins form the structural basis of chromosomes, through which genetic information is passed from parents to offspring. The genetic code contained in each cell's DNA is actually information for how to make that cell's proteins. Proteins are chains of amino acids linked together by peptide bonds. Each individual type of proteins is composed of a specific group of amino acids in a specific chemical arrangement. It is the particular amino acids present and the way in which they are linked together in sequence that gives the proteins that make up the various tissues their unique functions and characters. Each protein in the body is tailored for a specific need; proteins are not interchangeable (Balch '00: 42).

The **proteins** that make up the human body are not obtained directly from the diet. Rather, dietary protein is broken down into its constituent amino acids, which the body then uses to build the specific proteins it needs. Thus, it is the amino acids rather than protein that are the essential nutrients. In addition to those that combine to form the body's proteins,. There are other amino acids that are important to metabolic function. Some, such as citrulline, glutathione, ornithine, and taurine, can be similar to (or byproducts of) the protein-building amino acids. Some act as neurotransmitters or as precursors of neurotransmitters, the chemicals that carry information from one nerve cell to another. Certain amino acids are thus necessary for the brain to receive and send messages. Unlike many other substances, neuro-transmitters are able to pass through

the blood-brain barrier. The tightly meshed endothelial cells of the capillaries in the brain prevent many substances, especially water-based substances, from diffusing through the capillary walls into brain tissue. Because certain amino acids can pass through this barrier, they can be used by the brain to communicate with nerve cells elsewhere in the body. Amino acids also enable vitamins and minerals to be absorbed and assimilated by the body. For example, low levels of tyrosine may lead to iron deficiency. Deficiency and/or impaired metabolism of the amino acids methionine and taurine has been linked to allergies and autoimmune disorders. Branched-chain amino acids – valine, isoleucine and leucine are amino aids that can be used to provide energy directly to muscle tissue. High does of branched-chain amino acids have been used in hospitals to treat people suffering from trauma and infection. Some people are born with an inability to metabolize branched-chain amino acids. This potentially life-threatening condition, branched-chain ketoaciduria (often referred to as maple syrup urine disease because the keto-acids released into the urine cause it to smell like maple syrup) can result in neurological damage and necessitates a special diet, including a synthetic infant formula that does not contain leucine, isoleucine or valine (Balch '00: 42).

There are **twenty-five** commonly known amino acids that are combined in various ways to create the hundreds of different types of proteins present in all living things. In the human body, the lier produces about 80 percent of the amino acids needed. The remaining 20 percent must be obtained from the diet. These are called essential amino acids. The nine essential amino acids that must enter the body through diet are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. The sixteen non-essential amino acids, which can be manufactured in the body from other amino acids obtained from dietary sources, include alanine, arginine, asparagine, aspartic acid, citrulline, cysteine, cystine, gamma-aminobutyric acid, glutamic acid, glutamine, glycine, ornithine, proline, serine, taurine, and tyrosine. The term non-essential does not mean that they are not necessary, only that they need not be obtained through diet because the body can manufacture them. Nonessential amino acids can become essential under certain conditions. For instance, the nonessential amino acids cysteine and tyrosine are made from the essential amino acids methionine and phenylalanine. If methionine and phenylalanine are not available in sufficient quantities, cysteine and tyrosine then become essential in the diet. The process of assembling amino acids to make proteins, and of breaking down proteins into individual amino acids for the body's use, are continuous ones. When the body needs more enzymes, the body produces more proteins for cells. These different types of proteins are produced as the need arises. Should the body become depleted of its reserves of any of the essential amino acids, it would not be able to produce the proteins that require those amino acids. An inadequate supply of even one essential amino acid can hinder the synthesis, and reduce body levels, of necessary proteins. This can result in a negative nitrogen balance, an unhealthy condition in which the body excretes more nitrogen than it assimilates. Further, all of the essential amino acids must be present simultaneously in the diet in order for the other amino acids to be utilized, otherwise, the body remains in negative nitrogen balance. A lack of vital proteins in the body can cause problems raging from indigestion to depression to stunted growth (Balch '00: 42, 43).

Isoleucine is an essential amino acid, needed for hemoglobin formation and also stabilizes and regulates blood sugar and energy levels. It is metabolized in muscle tissue. It is one of the three branched-chain amino acids. These amino aids are valuable for athletes because they enhance energy, increase endurance and aid in the healing and repair of muscle tissues. Isoleucine has been found to be deficient in people suffering from many different mental and physical disorders. A deficiency of isoleucine can lead to symptoms similar to those of hypoglycemia.

Food sources of isoleucine include almonds, cashews, chicken, chickpeas, eggs, fish, lentils, liver, meat, rye, most seeds and soy protein. It is also available in supplemental form. Supplemental L-isoleucine should always be taken with a correct balance of the other two branched-chain amino acids, L-leucine and L-valine – approximately 2 milligrams of each leucine and valine for each milligram of isoleucine. Combination supplementals that provide all three of the branched chain amino acids are available and may be more convenient to use (Balch '00: 49).

Leucine is an essential amino acid and one of the branched-chain amino acids (the other are isoleucine and valine). These work together to protect muscle and act as fuel. They promote the healing of bones skin and muscle tissue, and are recommended for those recovering from surgery. Leucine also lowers elevated blood sugar levels and aids in increasing growth hormone production. Natural sources of leucine include brown rice, beans, meat, nuts, soy flour and whole wheat. Supplemental L-leucine must be taken in balance with L-isoleucine and L-valine, and it should be taken in moderation, or symptoms of hypoglycemia may result. An excessively high intake of leucine may also contribute to pellagra, and may increase the amount of ammonia in the body (Balch '00: 49).

Valine, is an essential amino acid, it is a branched-chain amino acid, that has a stimulant effect. It is needed for muscle metabolism, tissue repair, and the maintenance of a proper nitrogen balance in the body. Valine is found in high concentrations in muscle tissue. It may be helpful in treating liver and gallbladder disease, and it is good for correcting the type of severe amino acid deficiencies that can be found in drug addiction. An excessively high level of valine may lead to such symptoms as a crawling sensation in the skin and even hallucinations. Dietary sources of valine include dairy products, grains, meat, mushrooms, peanuts, and soy protein. Supplemental L-valine should always be taken in balance with the other branched-chain amino acids, L-isoleucine and L-leucine (Balch '00: 52).

Histidine is an essential amino acid that is significant in the growth and repair of tissues. It is important for the maintenance of the myelin sheaths, which protect nerve cells, and is needed for the production of both red and white blood cells. Histidine also protects the body from radiation damage, helps lower blood pressure, aids in removing heavy metals from the system, and may help in the prevention of AIDS. Histidine levels that are too high may lead to stress and even psychological disorders such as anxiety and schizophrenia. People with schizophrenia have been found to have high levels of histidine in their bodies. Inadequate levels of histidine may contribute to rheumatoid arthritis and may be associated with nerve deafness. Methionine has the ability to lower histidine levels. Histamine, a important immune system chemical, is derived from histidine. Histamine aids in sexual arousal. Because the availability of histidine influences histamine production, taking supplemental histidine – together with vitamins B_2 (niacin) and B_6 (pyridoxine), which are required for the transformation from histidine to histamine – may help improve sexual functioning and pleasure. Because histamines also stimulates the secretion of gastric juices, histidine may be helpful for people with indigestion resulting from a lack of stomach acid. Persons with manic (bipolar) depression should not take supplemental histidine unless a deficiency has been identified. Natural sources of histidine include rice, wheat and rye (Balch '00: 48).

Lysine is an essential amino acid that is a necessary building block for all protein. It is needed for proper growth and bone development in children. It helps calcium absorption and maintains a proper nitrogen balance in adults. This amino acid aids in the production of antibodies, hormones, and enzymes, and helps in collagen formation and tissue repair. Because it helps

build muscle protein, it is good for those recovering from surgery and sports injuries. It also lowers high serum triglyceride levels. Another very useful ability of this amino acid is its capacity for fighting cold sores and herpesviruses. Taking supplemental L-lysine, together with vitamin C with bioflavonoids, can effectively fight and/or prevent herpes outbreaks, especially if foods containing the amino acid arginine are avoided. Supplemental L-lysine also may decrease acute alcohol intoxication. Lysine is an essential amino acid, and so cannot be manufactured in the body. It is therefore vital that adequate amounts are included in the diet. Deficiencies can result in anemia, bloodshot eyes, enzyme disorders, hair loss, an inability to concentrate, irritability, lack of energy, poor appetite, reproductive disorders, retarded growth, and weight loss. Food sources of lysine include cheese, eggs, fish, lima beans, milk, potatoes, red meat, soy products, and yeast (Balch '00: 49).

Methionine is an essential amino acid that assists in the breakdown of fats, thus helping to prevent a buildup of fat in the liver and arteries that might obstruct blood flow to the brain, heart and kidneys. The synthesis of the amino acids cysteine and taurine may depend on the availability of methionine. This amino acid helps the digestive system. Helps to detoxify harmful agents such as lead and other heavy metals. Helps to diminish muscle weakness, prevent brittle hair, and protect against radiation. It is beneficial for people with osteoporosis or chemical allergies. It is useful also I the treatment of rheumatic fever and toxemia of pregnancy. Methionine is a powerful antioxidant. It is a good source of sulfur, which inactivates free radicals and helps to prevent skin and ail problems. It is also good for people with Gilbert's syndrome, an anomaly of liver function, and is required for the synthesis of nucleic acids, collagen and proteins found in every cell of the body. It is beneficial for women who take oral contraceptives because it promotes the excretion of estrogen. It reduces the level of histamine in the body, which can be useful for people with schizophrenia, whose histamine levels are typically higher than normal. As levels of toxic substances in the body increase, the need for methionine increases. The body can convert methionine into the amino acid cysteine, a precursor of glutathione. Methionine thus protects glutathione, it helps to prevent glutathione depletion if the body is overloaded with toxins. Since glutathione is a key neutralizer of toxins in the liver this protects the liver from the damaging effects of toxic compounds. A essential amino acid, methionine is not synthesized in the body and must be obtained from food sources of from dietary supplements. Good food sources of methionine include beans, eggs, fish garlic, lentils, meat, onions, soybeans, seeds, and yogurt. Because the body uses methionine to derive a brain food called choline, it is wise to supplement the diet with choline or lecithin (which is high in choline) to ensure that the supply of methionine is not depleted. **Homocysteine** is an amino acid that is produced in the body in the course of methionine metabolism. This amino acid has been the focus of increasing attention in recent years, because high levels of homocysteine in the blood are associated with an increased risk of cardiovascular disease. Further, it is known that homocysteine has a toxic effect on the cells lining the arteries, makes the blood more prone to clotting, and promotes the oxidation of low-density lipoproteins (LDL, the so-called “bad cholesterol”), which makes it more likely that cholesterol will be deposited as plaque in the blood vessels. Like other amino acids, homocysteine does perform a necessary function in the body. It is then usually broken down quickly into the amino acid cysteine and other important compounds, including adenosine triphosphate (ATP, an important source of cellular energy) and S-adenosylmethionine (SAMe). However, a genetic defect or, more commonly deficiencies of vitamins B_6 and B_{12} and folate (folic acid) can prevent homocysteine form converting rapidly enough. As a result, high levels of the amino acid circulate the body, damaging cell membranes and blood vessels, and increasing the risk of cardiovascular disease, particularly atherosclerosis. Vitamins B_6 and B_{12} and folate work together to facilitate the breakdown of homocysteine and thus help prevent against heart disease (Balch '00: 48, 49).

Phenylalanine is an essential amino acid. Because it ca cross the blood-brain barrier, it can have a direct effect on brain chemistry. Once in the body, phenylalanine can be converted into another amino acid, tyrosine, which in turn is used to synthesize two key neurotransmitters that promote alertness: dopamine and norepinephrine. Because of its relationship to the action of the central nervous system, this amino acid can elevate mood, decrease pain, aids in memory and learning and suppresses the appetite. It can be used to treat arthritis, depression, menstrual cramps, migraines, obesity, Parkinson's disease, and schizophrenia. Phenylalanine is available in three different forms, designated L-, D- and DL-. The L- form is the most common type and is the form in which phenylalanine is incorporated into the body's proteins. The D- type acts as a painkiller. The DL- form is a combination of the D- and the L-. Like the D- form it is effective for controlling pain, especially the pain of arthritis, like the L-form it functions as a building block for proteins, increases mental alertness, suppresses the appetite and helps people with Parkinson's disease. It has been used to alleviate the symptoms of premenstrual syndrome (PMS) and various types of chronic pain. Supplemental phenylalanine, as well as products containing aspartame (an artificial sweetener made from phenylalanine and another amino aid, aspartic aid) should not be taken by pregnant women or by people who suffer from anxiety attacks, diabetes, high blood pressure, phenylketonuria (PKU) or preexisting pigmented melanoma, a type of skin cancer (Balch '00: 50).

Threonine is an essential amino acid that helps to maintain the proper protein balance in the body. It is important for the formation of collagen, elastin, and tooth enamel, and aids liver and lipotropic function when combined with aspartic acid and methionine. A precursor of the amino acids, glycine and serine, threonine is present in the heart, central nervous system, and skeletal muscle, and helps to prevent fatty buildup in the liver. It enhances the immune system by aiding in the production of antibodies, and may be helpful in treating some types of depression. Because the threonine content of grains is low, vegetarians are more likely than other to have deficiencies (Balch '00: 51).

Tryptophan is an essential amino acid that is necessary for the production of vitamin B_3 (niacin). It is used by the brain to produce serotonin, a necessary neurotransmitter that transfers nerve impulses from one cell to another and is responsible for normal sleep. Consequently, tryptophan helps to combat depression aids in insomnia and to stabilize moods. It helps to control hyperactivity in children, alleviates stress, is good for the heart, aids in weight control by reducing appetite, and enhances the release of growth hormone. It is good for migraine headaches and may reduce some of the effects of nicotine. Sufficient amounts of vitamins B6 (pyridoxine) and C, folate and magnesium are necessary for the formation of tryptophan, which in turn, is required for the formation of serotonin. A study reported in the Archives of General Psychiatry found that women with a history of bulimia nervosa, an eating disorder, experienced relapses after they took an amino acid mixture lacking tryptophan. Researchers believe that insufficient tryptophan altered brain serotonin levels and, consequently, the transmission of nerve impulses. A lack of tryptophan and magnesium may contribute to coronary artery spasms. The best dietary sources of tryptophan include brown rice, cottage cheese, meat, peanuts, and soy protein. This amino acid is not available in supplement form in the United States. In November of 1989, the US Centers for Disease Control (CDC) reported evidence linking L-tryptophan supplements to a blood disorder called eosinophiliamyalgia syndrome (EMS). Several hundred cases of the illness – which is characterized by an elevated white blood cell count and can also cause such symptoms as fatigue, muscular pain, respiratory ailments, edema, and rash, were reported. After the CDC established an association between the blood disorder and products containing L-tryptophan in Ne Mexico, the US Food and Drug Administration (FDA) first

warned consumers to stop taking L-tryptophan supplements, then recalled all products in which L-tryptophan was the sole or a major component. Subsequent research showed that it was contaminants in the supplements, not the tryptophan, that was probably responsible for the problem, but tryptophan supplements are still banned from the market in the United States, according to the FDA, at least thirty-eight deaths were attributable to the tryptophan supplements (Balch '00: 51`).

Alanine is a non-essential amino acid. It is involved in the transfer of nitrogen from peripheral tissue to the liver. Aids in the metabolism of glucose into energy. Guards against buildup of toxic substances in muscle cells when muscle cells are broken down to meet energy needs. For people with insulin-dependent diabetes an oral dose of L-alanine can be more effective than a bedtime snack in preventing nighttime hypoglycemia. Epstein-Barr virus and chronic fatigue have been associated with excessive alanine levels and low levels of tyrisone and phylalanine. Beta-alanine is a constituent of pantotheic acid (vitamin B_5) and coenzyme A (Balch '00: 44).

Arginine is a non-essential amino acid. It retards the growth of tumors and cancer by enhancing immune function. Increases size and activity of thymus glands which manufactures T lymphocytes (T cells). Good for liver disorders, such as cirrhosis and fatty liver, neutralizes ammonia. Seminal fluid contains arginine and studies suggest sexual maturity may be delayed by arginine deficiency. Useful in treating sterility. Found in high concentrations in the skin and connective tissues, useful for healing and repair of damaged tissue. Important for muscle metabolism. Helps maintain a proper nitrogen balance by transportation, storage and excretion of excess nitrogen. Reduces nitrogen losses in people who have undergone surgery. Improves the function of lymphatic tissue. Aids in weight loss by increasing muscle mass and decreasing body fat. Aids to stimulate the pancreas to release insulin, in a component of the pituitary hormone vasopressin, and assistance in the releases of hormones. Aids in building new bones and tendon cells. Good for arthritis and connective tissue disorders. Scar tissue that forms during would healing is made up of collagen, that is rich in arginine. Avariety of function including insulin production, glucose tolerance, and liver lipid metabolism, are impaired if the body is deficient in arginine. Arginine is produced in the body; however in newborn infants, production may not occur quickly enough to keep with requirements. It is therefore deemed essential early in life. Foods high in arginine include carob, chocolate, coconut, dairy products, gelatin, meat, oats, peanuts, soybeans, walnuts, white flour, wheat and wheat germ. People with viral infections such as herpes should not take supplemental arginine, and should avoid foods rich in arginine and low it h amino acid lysine, as this appears to promote the growth of certain viruses. L-arginine supplements should be avoided by pregnant and lactating women. Presons with schizophrenia should avoid amounts over 30 milligrams daily. Long-term use, especially of high doses, is not recommended. One study found that several weeks of large doses may result in thickening and coarsening of the skin (Balch '00: 44, 45).

Asparagine is a non-essential amino acid, created form another amino acid, aspartic acid, is needed to maintain balance in the central nervous system; it prevents one from being either overly nervous or calm. As it is converted back into aspartic acid, asparagine releases energy that brain and nervous system cells use for metabolism. It promotes the process by which one amino acid is transformed into another in the liver (Balch '00; 45).

Aspartic acid is a non-essential amino acid that increases stamina, is good for fatigue and depression, and plays a vital role in metabolism. Chronic fatigue may result form low levels of aspartic acid, because this leads to lowered cellular energy. In proper balance, aspartic acid is beneficial for neural and brain disorders; it has been found in increased levels in persons with

epilepsy and in decreased levels in people with some types of depression. It is good for athletes and helps to protect the liver by aiding in the removal of excess ammonia. Aspartic acid combines with other amino acids to form molecules that absorb toxins and remove them from the bloodstream. It helps to move certain minerals across the intestinal lining and into the blood and cells, aids cell function and aids in the function of RNA and DNA, which are the carriers of genetic information. It enhances the production of immunoglobulin and antibodies (immune system proteins). Plant protein, especially that found in sprouting seeds, contains an abundance of aspartic acid. The artificial sweetener aspartame is made from aspartic acid and phenylalanine, another amino acid (Balch '00: 45).

Citrulline is a non-essential amino acid that the body makes from another amino acid, ornithie. Citrulline promotes energy, stimulates the immune system, is metabolized to form L-arginine, and detoxifies ammonia, which damages liver cells. Citrulline is found primarily in the liver. It is helpful in treating fatigue (Balch '00: 46).

Cysteine and **Cystine** are two closely related non-essential amino acids. Each molecule of cystine consists of two molecules of cysteine joined together. Cysteine is very unstable and is easily converted to L-cystine, however, each form is capable of converting into the other as needed. Both are sulfur-containing amino acids that aid I the formation f skin and are important in detoxification. Cysteine is present as alpha-keratin, the chief protein constituent of the fingernails, toenails, skin, and hair. Cysteine aids in the production of collagen and promotes the proper elasticity and texture of the skin. It is also found in a variety of other proteins I the body, including several digestive enzymes. Cysteine helps to detoxify harmful toxins ad protect the body from radiation damage. It is one of the best free radical destroyers and works best when taken with selenium and vitamin E. Cysteine is also precursor to glutathione, a substance that detoxifies the liver by binding with potentially harmful substances there. It helps to protect the liver and brain from damage due to alcohol, drugs, and toxic compounds in cigarette smoke. Cysteine is more readily soluble in the body than cystine, and is usually best for treating most illnesses. This amino acid is formed from L-methionine in the body. Vitamin B_6, Vitamin B_{12}, and folate are necessary for cysteine synthesis, which may not take place as it should in the presence of chronic disease. Therefore people with chronic illnesses may need higher than normal doses of cysteine, as much as 1,000 milligrams three times daily for a month at a time. Supplementation with L-cysteine is recommended in the treatment of rheumatoid arthritis, hardening of the arteries, and mutogenic disorders such as cancer. It promotes healing after surgery and severe burns, chelates heavy metals, and binds with soluble iron, aiding in iron absorption. This amino aid also promotes the burning of fat and the building of muscle. Because of its ability to to break down mucus in the respiratory tract, L-cysteine is often beneficial in the treatment of bronchitis, emphysema, and tuberculosis. It promotes healing from respiratory disorders and plays an important role in the activity of white blood cells, which fight disease. Cystine or the N-acetyl form of cysteine (N-acetylcysteine, or NAC) may be used in place of L-cysteine. NAC aids in preventing side effects from chemotherapy and radiation therapy. Because it increases glultathione levels in the lungs, kidneys, liver and bone marrow, it has an anti-aging effect on the body, reducing the accumulation of age spots. NAC has been shown to be more effective at boosting glutathione levels than supplements of cystine or even of glutathione itself. People who have diabetes should be cautious about taking supplemental cysteine because it is capable of inactivating insulin. Persons with cystinuria, a rare genetic condition that leads to the formation of cystine kidney stones, should not take cysteine (Balch '00: 46).

Gamma-aminobutyric acid (GABA) is a nonessential amino acid that acts as a neurotransmitter in the central nervous system. It is essential for brain metabolism, aiding in proper brain function. GABA is formed in the body from another amino acid, glutamic acid. Its function is to decrease neuron activity and inhibit nerve cells from overfiring. Together with niacinamide and inositol, it prevents anxiety – and stress – related messages from reaching the motor centers of the brain by occupying their receptor sites. GABA can be taken to calm the body in much the same way as diazepam (Valium), chlordiazepoxide (Librium), and other tranquilizers, but without the addiction. GABA has been used in the treatment of epilepsy and hypertension. It is good for depressed sex drive because of its ability as a relaxant. It is also useful for enlarged prostate, probably because it plays a role in the mechanism regulating the release of sex hormones. GABA is effective in treating attention deficit disorder and may reduce cravings for alcohol. It is also though to promote growth hormone secretion. Too much GABA, however, can cause increased anxiety, shortness of breath, numbness around the mouth, and tingling in the extremities. Further, abnormal levels of GABA unbalance the brain's message-delivery system and may cause seizures (Balch '00: 46, 47).

Glutamic acid is a nonessential amino acid that is an excitatory neurotransmitter that increases the firing of neurons in the central nervous system. It is a major excitatory neurotransmitter in the brain and spinal cord. It is converted into either glutamine or GABA. This amino acid is important in the metabolism of sugars and fats, and aids in the transportation of potassium into the spinal fluid and across the blood-brain barrier. Although it does not pass the blood-brain barrier as readily as glutamine does, it is found at high levels I the blood and may infiltrate the brain in small amounts. The brain can use glutamic acid as fuel. Glutamic acid can detoxify ammonia by picking up nitrogen atoms, in the process creating another amino acid, glutamine. The conversion of glutamic acid into glutamine is the only means by which ammonia in the brain can be detoxified. Glutamic acid helps to correct personality disorders and is useful in treating childhood behavioral disorders. It is used I the treatment of epilepsy, mental retardation, muscular dystrophy, ulcers and hypoglycemic coma, a complication of insulin treatment for diabetes. It is a component of folate (folic acid), a B vitamin that helps the body break down amino acids. Because one of its salts is monosodium glutamate (MSG), glutamic acid should be avoided by anyone who is allergic to MSG (Balch '00: 47).

Glutamine is the most abundant free amino acid found in the muscles of the body. Because it can readily pass the blood-brain barrier, it is known as brain fuel. In the brain, glutamine is converted into glutamic acid – which is essential for cerebral function – and vice versa. It also increases the amounts of GABA, which is needed to sustain proper brain function and mental activity. It assists in maintaining the proper acid / alkaline balance in the body, an dis the basis of the building blocks for the synthesis of RNA and DNA. It promotes mental ability and the maintenance of a healthy digestive tract. When an amino acid is broken down, nitrogen is released. The body needs nitrogen, but free nitrogen can form ammonia, which is especially toxic to brain tissues. The liver can convert nitrogen into urea, which is excreted in the urine, or nitrogen may attach itself to glutamic acid. This process forms glutamine. Glutamine is unique among the amino acids in that each molecule contains not one nitrogen atom but two. Thus, its creation helps to clear ammonia from tissues, especially brain tissue, and it can transfer nitrogen from one place to another. Glutamine is found in large amounts in the muscles and is readily available when needed for the synthesis of skeletal muscle proteins. Supplemental glutamine is useful for dieters and bodybuilders. It helps to prevent the muscle-wasting that can accompany prolonged bed rest or diseases such as cancer and AIDS. Stress and injury (including surgical trauma) cause the muscles to release glutamine into the bloodstream. During times of stress, as much as one third of the glutamine present in the muscles may be released. As a result, stress or

illness can lead to loss of skeletal muscle. If enough glutamine is available, however, this can be prevented. Supplemental L-glutamine can be helpful in the treatment of arthritis, autoimmune diseases, fibrosis, intestinal disorders, peptic ulcers, connective tissue diseases such as polymyositis and scleroderma, and tissue damage due to radiation treatment for cancer. L-glutamine can enhance mental functioning and has been used to treat a range of problems, including developmental disabilities, epilepsy, fatigue, impotence, depression, schizophrenia, and senility. It preserves glutathione in the liver and protects that organ from the effects of acetaminophen overdose. It enhances antioxidant protection. L-glutamine decreases sugar cravings and the desire for alcohol, and is useful for recovering alcoholics. Many palnt and animal substances contain glutamine but it is easily destroyed by cooking. If eaten raw, spinach and parsley are good sources. Supplemental glutamine must be kept absolutely dry or the powder will degrade into ammonia and pyroglutamic acid. Glutamine should not be taken by persons with cirrhosis of the liver, kidney problems, Reye's syndrome or any type of disorder that can result in an accumulation of ammonia in the blood. For such individuals, taking supplemental glutamine may only cause further damage to the body. Be aware that although the names sound similar, glutamine, glutamic acid (also sometimes called glutamate), glutathione, gluten and monosodium glutamate are all different substances (Balch '00: 47).

Glycine is a nonessential amino acid that retards muscle degeneration by supplying additional creatinine, a compound that is present in muscle tissue ad is utilized in the construction of DNA and RNA. It improves glycogen storage, thus freeing up glucose for energy needs. Glycine is essential for the synthesis of nucleic acids bile acids, and other nonessential amino acids in the body. It is used in may gastric antacid agents. Because high concentrations of glycine are found in the skin and connective tissues, it is useful for repairing damaged tissues and promoting healing. Glycine is necessary for central nervous system function and a healthy prostate. It functions as an inhibitory neurotransmitter and as such can help prevent epileptic seizures. It has been used in the treatment of mani (bipolar) depression, and can also be effective for hyperactivity. Having too much glycine in the body can cause fatigue, but having the proper amount produces more energy. If necessary, glycine can be converted into the amino acid serine in the body (Balch '00: 48).

Ornithine is a nonessential amino acid hat helps to prompt the release of growth hormone, which promotes the metabolism of excess body fat. This effect is enhanced if ornithine is combined with arginine. Ornithine is is necessary for proper immune-system and liver function. This amino acid also detoxifies ammonia and aids in liver regeneration. High concentrations of ornithine are found in the skin and connective tissue, making it useful for promoting healing and repairing damaged tissues. Ornithine is synthesized in the boy from arginine and in turn serves as the precursor of citrulline, proline and glutamic acid. Supplemental L-ornithie should not be taken by children, pregnant women, nursing mothers, or anyone with a history of schizophrenia, unless they are specifically directed to do so by a physician (Balch '00: 50).

Proline is a nonessential amino acid that improves skin texture by aiding in the production of collagen and reducing the loss of collagen through the aging process. It also helps in the healing of cartilage and the strengthening of joints, tendons, and heart muscle. It works with vitamin C to promote healthy connective tissue. Proline is obtained primarily from meat sources, dairy products, and eggs.

Serine is a nonessential amino aid that is needed for the proper metabolism of fats and fatty acids, the growth of muscle, and the maintenance of a healthy immune system. It is a component of brain protein and the protective myeline sheaths that cover nerve fibers. It is important in RNA and DNA function, cell membrane formation and creatine synthesis. It also aids in the

production of immunoglobulins and antibodies. However, too-high serine levels in the body may have adverse effects on the immune system. Serine an be made from glycine in the body, but this process requires the presence of sufficient amounts of vitamins B_3 and B_6 and folic acid. Food sources of serine include meat and soy foods, as well as many foods that often cause allergic reactions, such as dairy products, wheat gluten, and peanuts. It is included as a natural moisturizing agent in many cosmetics and skin care preparations (Balch '00: 50).

Taurine is a nonessential amino acid that is found in high concentrations in the heart muscle, white blood cells, skeletal muscle, and central nervous system. It is a building block of all the other amino acids, as well as a key component of bile, which is needed for the digestion of fats, the absorption of fat-soluble vitamins, and the control of serum cholesterol levels. Taurine can be useful for people wth atherosclerosis, edema, heart disorders, hypertension or hypoglycemia. It is vital for the proper metabolization of sodium, potassium, calcium and magnesium, and has been shown to play a particular role in sparing the loss of potassium from the heart muscle. This helps to prevent the development of potentially dangerous cardiac arrhythmias. Taurine has a protective effect on the brain, particularly if the brain is dehydrated. It is used to treat anxiety, epilepsy, hyperactivity, poor brain function and seizures. Taurine is found in concentrations up to four times greater in the brains of children than in those of adults. It may be that a deficiency of taurine in the developing brain is involved in seizures. Zinc deficiency also is commonly found in people with epilepsy, and this may play a part in the deficiency of taurine. Taurine is also associated with zinc in maintaining eye function; a deficiency of both may impair vision. Taurine supplementation may benefit children with Down syndrome and muscular dystrophy. This amino acid is also used in some clinics for breast cancer treatment. Excessive losses of taurine through the urine can be caused by many metabolic disorders. Cardiac arrhythmias, disorders of platelet formation, intestinal problems, an overgrowth of candida, physical or emotional stress, a zinc deficiency, and excessive consumption of alcohol are all associated with high urinary losses of taurine. Excessive alcohol consumption also causes the body to lose its ability to utilize taurine properly. Taurine supplementation may reduce symptoms of alcohol withdrawal. Diabetes increases the body's requirements for taurine; conversely supplementation with taurine and cystine may decrease the need for insulin. Taurine is found in eggs, fish, meat and milk, but not in vegetable proteins. It can be synthesized from cysteine in the liver and from methionine elsewhere in the body, as long as sufficient quantities of vitamin B6 are present. For vegetarians, synthesis by the body is crucial. For individuals with genetic or metabolic disorders that prevent the synthesis of taurine, taurine supplementation is required (Balch '00: 50, 51).

Tyrosine is a nonessential amino acid that is important for overall metabolism. It is a precursor of adrenaline and the neurotransmitters norepinephrine and dopamine, which regulate mood and stimulate metabolism and the nervous system. Tyrosine acts as a mood elevator, a lack of adequate amounts of tyrosine leads to a deficiency of norepinephrine in the brain, which in turn can result in depression. It also acts as a mild antioxidant, suppresses the appetite, and helps to reduce body fat. It aids in the production of melanin (the pigment responsible for skin and hair color, and in the functions of the adrenal, thyroid and pituitary glands. It is also involved in the metabolism of the amino acid phenylalanine. Tyrosine attaches to iodine atoms to form active thyroid hormones. Not surprisingly, therefore low plasma levels of tyrosine have been associated with hypothyroidism. Symptoms of tyrosine deficiency can also include low blood pressure, low body temperature (such as cold hands and feet) and restless leg syndrome. Supplemental L-tyrosine has been sued for stress reduction, and research suggests it may be helpful against chronic fatigue and narcolepsy. It has been used to help individuals suffering from anxiety, depression, low sex drive, allergies and headaches, as well as persons undergoing withdrawal from drugs. It may also help people wth Parkinson's disease. Natural sources of

tyrosine include almonds, avocados, bananas, dairy products, lima beans, pumpkin seeds ad sesame seeds. Tyrosine can also be produced from phenylalanine in the body. Supplements of L-tyrosine should be taken at bedtime or with a high-carbohydrate meal so that it does not have to compete for absorption with other amino acids. Persons taking monoamine oxidase (MAO) inhibitors, commonly prescribed for depression, must strictly limit their intake of foods containing tyrosine and should not take any supplements containing L-tyrosine, as it may lead to a sudden and dangerous rise in blood pressure. Anyone who takes prescription medicine for depression should discuss necessary dietary restriction with his or her physician (Balch '00: 51, 52).

Food Sources for Nine Essential Amino Acids

Amino Acid	Source	Amino Acid	Source
Isoleucine	Almonds, cashews, chicken, chickpeas, eggs, fish, lentils, liver, meat, rye, most seeds and soy protein	Methionine	Beans, eggs, fish garlic, lentils, meat, onions, soybeans, seeds, and yogurt
Leucine	Brown rice, beans, meat, nuts, soy flour and whole wheat	Phenylalanine	Aspartame (an artificial sweetener made from phenylalanine and another amino aid, aspartic aid)
Valine	Dairy products, grains, meat, mushrooms, peanuts, and soy protein	Threonine	Low in Grain
Histidine	Rice, wheat and rye	Tryptophan	Brown rice, cottage cheese, meat, peanuts, and soy protein
Lysine	Cheese, eggs, fish, lima beans, milk, potatoes, red meat, soy products, and yeast		

Source: Balch '00: 48 – 52

Many factors can contribute to **deficiencies of essential amino acids**, even if eating well-balanced diet that contains enough protein. Impaired protein absorption, infection, trauma, stress, drug-use, age and imbalances of other nutrients can all effect the availability of essential amino acids in the body. Insufficient intake of vitamins and minerals, especially vitamin C, can interfere with the absorption of amino acids in the lower part of the small intestines. Vitamin B_6 is also needed for the transport of amino acids in the body. If the diet is not properly balanced, if it fails to supply adequate amounts of the essential amino acids, sooner or later, this will become apparent as some type of physical disorder. Eating large amounts of protein is not the answer, in fact, it is unhealthy. Excess protein puts stress on the kidneys and liver, which must process the waste products of protein metabolism. Nearly half of the amino acids in dietary protein are transformed into glucose by the liver and used to provide energy to cells. This process results in

a waste product, ammonia. Ammonia is toxic to the body, so the body protects itself by having the liver turn the ammonia into a much less toxic compound, urea, which is the carried through the bloodstream, filtered out by the kidneys, and excreted in the urine. As long as protein intake is not too great and the liver is working properly, ammonia is neutralized almost as soon as it is produced, so it does no harm. However, if there is too much ammonia for the liver to cope with, as a result of overconsumption of protein, poor digestion, strenuous exercise and/or a defect in liver function, toxic levels may accumulate. This may put a person at risk for serious health problems, including encephalopathy (brain disease) or hepatic coma. Abnormally high levels of urea can also cause problems, including inflamed kidneys and back pain. It is not the quantity by quality of proteins in the diet that is important. It is possible to take supplements containing amino acids, both essential and nonessential. For certain disorders, taking supplements of specific amino acids or amino acid combinations can be very beneficial. They support the metabolic pathway involved in the particular illness. Vegetarians, especially vegans, would be wise to take a formula containing all of the essential amino acids to ensure that their protein requirements are met (Balch '00: 43). Amino acids seem to make obese bodybuilders schizophrenic. Amino acid supplements may be sampled to eliminate deficiencies.

Supplemental amino acids are available in combination with various multivitamin formulas, as protein mixtures, in a wide variety of food supplements, and in a number of amino acid formulas. They can be purchased as capsules, tablets, liquids and powders. Most amino acid supplements are derived from animal protein, yeast protein, or vegetable protein. Crystalline free-form amino acids are generally extracted from a variety of grain products. Brown rice bran is a prime source, although cold-pressed yeast and milk proteins are also used. Free-form means the amino acid is in its purest form. Free-form amino acids need no digestion and are absorbed directly into the bloodstream. These white crystalline amino acids are stable at room temperature and decompose when heated to temperatures of 350°F to 660°F (180°C to 350°C). They are rapidly absorbed and do not come from potentially allergenic food sources. For best results, choose encapsulated powders or powder. When choosing amino acid supplements, look for products containing USP (U.S. Pharmacopeia) pharmaceutical grade L-crystalline amino acids. Most of the amino acids except glycine) can appear in two forms, the chemical structure of one being the mirror image of the other. These are called the D- and L- forms – for example, D-cystine and L-cystine. The "D" stands for for dextro (Latin for 'right') and the "L" for levo (Latin for 'left'); these terms denote the direction of rotation of the spiral that is the chemical structure of the molecule. Proteins in animal and plant tissue are made from the L-forms of amino acids (with the exception of phenylalanine, which is also used in the form of DL-phenylalanine a mixture of the D- add L-forms) (Balch '00: 43, 44).

Each amino acid has specific functions in the body. When taking supplemental amino acids individually or for healing purposes, take them on an empty stomach to avoid making them compete for absorption with other amino acids present in foods. When taking individual amino acids, it is best to take them in the morning or between meals, with small amounts of vitamin B_6 and vitamin C to enhance absorption. When taking an amino acid complex that includes all of the essential amino acids, it is best to take it one-half hour away from a meal, either before or after. If taking individual amino acids, it is wise to also take the full amino acid complex, including both essential and non-essential amino acids, at a different time. This is the best way to assure adequate amounts of all the necessary amino acids. Individual amino acids should not be taken for long periods of time. A good rule to follow is to alternate the individual amino acids that fit needs and back them up with an amino acid complex, taking the supplements for two months and then discontinuing them for two months. Moderation is the key. Some amino acids have potentially toxic effects when taken in high doses (over 6,000 milligrams per day) and may

cause neurological damage. These include aspartic acid, glutamic acid, homocysteine, serine and tryptophan. Cysteine can be toxic if taken in amounts over 1,000 milligrams per day Do not give supplemental amino acids to a child, or take doses of any amino acid in excess of the amount recommended unless specifically directed by a health care provider. Some recommended amino acid products. A/G Pro from Miller Pharmacal Group is a complete amino acid and mineral supplement. Anabolic Amino Balance and Muscle Octane from Anabol Naturals is a complex of twenty-three free-form amino acids. Muscle Octane is a blend of free-form branched-chain amino acids (L-leucine, L-valine and L-isoleucine). Anabol Naturals also produces free-form single amino acids. Amino Blend from Carlson Laboratories, is a complex containing twenty amino acids, both essential and non-essential (Balch '00: 44).

6. Probiotics

The human gut **microbiome** can weigh up to 4 ½ pounds (2 kilos) and contains about 100 trillion bacteria. 1 gram of feces contains more bacteria than there are people on the planet (Enders '15: 148). Humans normally carry around 10^{12} bacteria on the skin and a thousand times more 10^{14} inside the gastrointestinal tract. More than 99 percent of the microbes living in the intestines are bacteria, a very diverse group, with 500 to 1,000 different species. The rest are yeasts or parasites. Bacteria are found not only in people, but in all forms of life - Mammals, birds, fish, insects and plants. Bacteria also live in water and in the earth. Just one teaspoon of rich soil contains over one hundred million bacteria. Some bacteria, such as *Escherichia coli* (better known as *E. coli*) can double their numbers in as little as twenty minutes. In contrast, other bacteria, such as *Bacteroides*, the most numerous bacteria in our intestine, usually estimated at 99% of total gut flora, need a few hours to double their population. Mycobacteria, the cause of tuberculosis, require almost a day. Bacteria can cause disease in both plants and animals. However the great majority of bacteria that live in the soil perform positive and sometimes essential roles. For example, the friendly bacteria in the soil inhibit the growth of bacteria responsible for plant disease. They also decompose plant matter into simpler molecules that plants can use for food or as nutrients. Of the remaining microbes in the intestine the major yeast of the human microflora is *Candida albicans*. If its numbers are kept low by competition with other microbes, it is harmless. But if it proliferates, it can cause various illnesses, including diarrhea, vaginal yeast infection, and thrush, an infection of the mouth, that's common in infants and in people taking antibiotics. The microfloral balance, and thus gastrointestinal health, depends on which microbes succeed.

Microbes compete with each other in several ways. Competition favors microbes that can make use of available nutrients. Probiotic bacteria can be given the edge with a diet high in fiber, a **prebiotic**, because probiotics can digest fiber, whereas many harmful bacteria cannot. On the other hand, sugary foods help certain harmful microbes to thrive. A microbe can survive longer in the gut if it can stick to cells of the intestines. Otherwise, it's likely to be swept out of the body by peristalsis. One of the ways probiotic bacteria help protect us from harmful microbes is by successfully competing with them for access to intestinal cells. Some bacteria produce their own antibiotics. These chemicals don't affect us, but they inhibit the growth of other bacteria. Also, as microbes digest food, their metabolic byproducts may have adverse effects on their competitors. For example, when probiotics use fiber as their nutritional source, some of their metabolic byproducts are acids similar to vinegar – and yeasts don't grow well in the presence of these acids (Huffnagle '07: 28, 29, 30 31).

The **microbial population** of the digestive tract varies from place to place along the tube. Different types of microbes predominate at each site, and they serve different functions.

Probiotics in the intestines, which can actually affect the immune system, are the most important for overall well-being. The balance of microbes in our mouth helps to determine our oral health. The bacterial population in the large intestine outnumbers that of the small intestine by about 100,000 to 1. That's because the small intestine is less hospitable to microbes: its environment is more acidic and has a higher concentration of both digestive enzyme and antimicrobial chemicals. Peristalsis is significantly faster in the small intestine. Different types of bacteria normally live in the small and large intestines. The predominant bacteria in the small intestine are benign species of *Streptococcus* and *Enterococcus*. Though they are are important in maintaining a healthy microflora balance, like many microbes in the gut, they can cause disease if found in high enough numbers in another location. In the large intestine, *Bacteroides* dominates. Probiotics can be found all along the small and large intestines. Their presence is a major force in maintaining a healthy balance among intestinal microbes. The rectum collects wastes and expels them through the anus in the form of feces. Microbes don't actually live in the rectum or anus. However, they pass through in large numbers. One-third of the feces consists of bacteria. Though most of these are harmless, some can make pathogenic. That's why it's vitally important to take measures, from sewage treatment to hand washing, to prevent dangerous expelled microbes from reentering the mouth (Huffnagle '07: 39, 40).

Health Benefits of 13 Highly Studied Probiotic Strains

Genus	Species	Strain	Health Benefits
Bifidobacterium	*animalis*	DN-173 010, (1)	General health, GI health
Bifidobacterium	*lactis*	Bb-12	General health, GI health, viral diarrhea, eczema
Bifidobacterium	*lactis*	HN019, DR10	General health, GI health, viral diarrhea
Lactobacillus	*acidophillus*	NCFM	General health, GI health, viral diarrhea, colds & respiratory virus
Lactobacillus	*casei*	DN-114 001, (2)	General health, GI health, irritable bowel suyndrom, viral diarrhea
Lactobacillus	*casei*	Shirota	General healtg, GI health, inflammatory bowel disease, antibiotic-associated diarrhea, allergy, autoimmunity
Lactobacillus	*fermentum*	RF-14	General health, vaginal yeast infection, urinary tract infection
Lactobacillus	*plantarum*	299v	General health, GI health, viral diarrhea, colds & respiratory

			virus
Lactobacillus	*reuteri*	SD2112, ING1, MM53, ATCC 55739, (3)	General health, GI health, viral diarrhea, colds & respiratory virus
Lactobacillus	*rhamnosus*	GG, LGG, (4)	General health, GI health, inflammatory bowel disease, irritable bowel syndrome, viral diarrhea, antibiotic-associated colitis, C. difficile diarrhea, travelers' diarrhea, eczema, autoimmunity
Lactobacillus	*rhamnosus*	GR-1	General health, vaginal yeast infection, urinary tract infection
Lactobacillus	*rhamnosus*	HN001, DR20	General health, GI health
Saccharomyces	*boulardii*	Iyo	General health, GI health, inflammatory bowel disease, irritable bowel syndrome, Viral diarrhea, Antibiotic-associated diarrhea, C .difficile diarrhea, Traveler's diarrhea

Source: Huffnagle '07: 263

Probiotics counter cavities by keeping *Streptococcus mutans* under control; these are the bacteria that can cause tooth decay, if their numbers are high enough. Other bacteria, such as *Porphyromonoas gingivalis*, may lead to gum disease if not kept in check by competing microbes. The stomach produces acid so strong that it could burn a hole in the living room carpet. Though many microbes can survive passage through the stomach, few are able to live there. The most notable of these is the bacterium *Helicobacter pylori*, which is responsible for ulcers, and functional dyspepsia. *H. pylori* produce chemicals that neutralize acid in their vicinity, allowing them to survive. Certain probiotics including species of *Lactobacillus*, can also live in the stomach. They help prevent ulcers by keeping *H. pylori* numbers low. Food travels from the stomach to the small intestines, where it's broken down into components our body can use for fuel (Huffnagle '07: 35, 37, 38).

During the past forty to fifty years, Americans have made two significant lifestyle modifications, greatly increasing the use of antibiotics and substantially changing the diet. Together, these changes have produced an invisible epidemic of insufficient probiotics. Antibiotics have the most profound impact on a person's microflora. Unless the problem is corrected, the microbial balance after taking antibiotics will be different from what it was before, with likely lingering ill effects on the immune system. In addition to occasional medicinal doses of antibiotics, people

are exposed to them at much lower levels in meat and drinking water. Diet is a major factor in regulating the balance among the various microbes in our microflora. *Bacteroides* are the most numerous bacterium in the gut. It typically outnumbers *E. coli* by over a thousand to one and outnumbers *Candida* by over a million to one. Many companies offer tests that analyze gut flora. The best way to determine if microflora is balanced is to consider the overall state of health. If fortunate enough to feel healthy, energetic and in good spirits chances are the microflora and immune system are in excellent shape. On the other hand those who suffer chronic medical problems, could have a gut-microbe connection. Probiotics and prebiotics in the diet are a necessary corrective force (Huffnagle '07: 40, 41, 42, 44, 45).

Food historians speculate that **yogurt** was first made accidentally, when milk was left inside goatskin bags and fermented by wild bacteria. These days, yogurts are commercially manufactured by a process that's considerably less spontaneous. The milk, which can come from any milk-producing animal, is first pasteurized (ie. Heated sufficiently to kill any harmful bacteria- and then bacterial cultures are added to ferment it. According to FDA regulations, products sold as yogurt in the United States must be fermented with *Lactobacillus bulgaricus* and *Streptococcus thermophiles*, referred to as yogurt starters. The starter bacteria digest lactose (milk sugar) and other carbohydrates int eh milk, producing lactic acid and other acids that give yogurt its characteristic tart taste. The acids also react chemically with milk proteins, causing the milk to thicken. In addition, since harmful bacteria can't grow in an acidic environment, the acids protect the milk from contamination. On top of these useful effects are all the health benefits from probiotic bacteria and from metabiotics, the metabolic products that probiotic bacteria produce. Yogurt also contains lactoferrin, a prebiotic found in milk. After fermentation, fruit, jam, or other flavorings may be added or blended into the yogurt. Some manufacturers add fiber, which boosts the reviotic content. The best way to ensure that yogurt contains probiotics is to select a product with the "live and active cultures" seal from the National Yogurt Association (NYA). This indicates that the yogurt contains 100 million viable bacteria per gram at the time of manufacture, the equivalent of more than **20 billion per 8 ounce serving**. Some yogurts with live bacteria don't carry the NYA seal, instead their lavels may read "contains active yogurt cultures" or "contains living yogurt cultures". But avoid yogurts that simply sya "made with active cultures". Such a yogurt may have been heat-treated after fermentation, in which case the bacteria would no longer by alive. All yogurts with live bacteria contain the straters *Lactobacillus bulgaricus* and *Streptococcus thermohilus*. However, some manfuactuerers add other bacteria to their yogurts, including the probiotics *L. acidophilus, Bifidobacterium animalis, L. casie, L. reuteri*, and others. Check the label All foods fermented by probiotic bacteria contain metabiotics – even foods that have been heated after fermentation, so that the bacteria themselves are no longer alive. Bacteriocins are natural antibiotics that bacteria make to help themselves survive. These antibiotics aren't harmful to the bacteria that make them, but they kill or inhibit other bacteria. The bacteriocins produced by probiotic bacteria help shift the microbial balance in their own favor. Fermented foods, such as yogurt, cheese, sourdough bread, and sauerkraut, contain bacteriocins, thanks to the lactic acid bacteria in them (Huffnagle '07: 210, 211).

Probiotics work to neutralize the dental and gastrointestinal side-effects of such highly effective medicine as antibiotics, vegan diet and NSAIDs. Unlike antibiotics, the supplements have no adverse side effects. An effective oral dose should be at least 25 billion probiotic organisms. A person can consume a trillion without ill effect. Eating tinkers with the microbial balance. Depending on the foods, certain microbes get nutrients while making others go hungry. Prebiotics offer a cornucopia of healthy, delectable options. The chief sources are fruits, vegetables and whole grains. Prebiotics are also found in certain fats, herbs and spices, red wine

and dark chocolate. Dietary fiber is the best-known prebiotic. The body can't digest fiber and turn it into fuel. But probiotic microbes thrive on it. Fiber is a form of carbohydrate, just like sugar and starch. But the human body doesn't produce enzymes that can break it down. When consuming foods containing fiber, the fiber passes right through our digestive tract. It provides no calories, vitamins or minerals. However, that doesn't mean it's useless. Along the way, fiber performs extremely valuable functions. One of the most important is that it serves as prebiotic, selectively supporting probiotic microbes in our gut. Constipation, diarrhea, and heartburn are common side effects of medication. To restore the normal intestinal flora following administration of antibacterial drugs, which often results in diarrhea, lactobacillus cultures (*L. acidophilus, L. bulgaricus*) are available for oral therapy. Prolonged use of any antidiarrheal agent is discouraged (Lewis and Elvin-Lewis '77: 284).

Helping Medication and Probiotics Work Together

Type of Drug	What's the Issue	What to Do
Antibiotic	Kills probiotic bacteria, such as *Lactobacillus and Bifidobacterium*, as well as targeted bacteria. Not: probiotic yeasts, such as *Saccharamuces boulardii*, are not affected by antibiotics	Consume probiotic bacteria at least two hours after taking antibiotics. A probiotic yeast can be taken at the same time as antibiotics.
Systemic oral antifungal medications (e.g. fluconazole, nystatin)	Kills probiotic yeast, such as *Saccharomyces boulardii*, as well as harmful yeasts. Note: probiotic bacteria, such as *Lactobacillus* and *Bifidobacterium* are not affected by antifungal medications.	Take probiotic yeast at least two hours after taking antifungal drugs. Probiotic bacteria can be consumed at the same tiem as antifungals.
Antacids and acid blockers, such as Tagamet	Counters desirable presence of acid in the stomach and the beginning of the small intestine, acid controls growth of harmful bacteria, creating a selective advantage for probiotic bacteria.	If you must take these medications, increase the dose or frequency of probiotics. Gradually work up to double the usual amount of probiotic for as long as the medication is needed.
Nonsteroidal anti-inflamatory drugs, such as aspirin	Can block production of stomach acid, this acid normally gives probiotic bacteria a competitive advantage.	"
Laxatives and any drug that lists diarrhea as a side effect	Speeds emptying of intestinal contents, including probiotic bacteria.	"
Muscle relaxants or any drug that lists constipation as a side effect	Decreases peristalsis, which slows emptying of intestinal contents, allowing competing bacteria to proliferate.	"

Source: Huffnagle ’07: 326

Acidophilus supplementation proves beneficial in irritable bowel sufferers at decreasing diarrhea and reestablishing proper flora balance. A different probiotic *Faecalibacterium prausnitzii* was studied in France for the Treatment of Crohn’s disease and proved beneficial in reducing inflammation in the colon. *Sachharomyces boulardi* is a very important probiotic to use in times of excess yeast of chronic fungal infections. Many specialized tests can be used to check for unwanted fungi and yeasts are found using saccharomyces can help by settling into the areas within the gastrointestinal tract that are normally inhabited by yeast and fungus species. Same with the use of the bacterial probiotic crowding out pathogenic bacteria, probiotic yeast can move into and compete for survival within the GI tract with pathogenic or overpopulated yeasts and fungi. If yeast infections or fungi overgrowth are strong only supplementing with saccharomyces may not be effective (Black ’10: 150, 151).

Age-related changes in the microflora make us more susceptible to *Clostridium difficile*, which causes diarrhea. This bacterium is normally present in the GI tract, but its numbers are kept in check by friendly bacteria. Probiotics such as *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* Iyo have proven very effective at treating diarrhea caused by *C. difficile*. As women go through menopause, their vaginal microflora changes. The population of *E. coli* increases, while the probiotic *Lactobacilli* decline and women become more vulnerable to vaginal infections after menopause. Aging has the potential to tip the microfloral balance away from probiotics, and consequently the balance of regulatory versus helper T cells. As a result, the immune system will regulate itself less effectively, leading to increased inflammation in the body. Research suggests that probiotics can help counter the physically damaging effects of stress, including effects on the gut and immune system. In a study of 68 infants whose bouts of crying lasted for three or more hours daily, three or more days per week, over a period of more than than three weeks. Half of the babies received drops containing the probiotic *Lactobacillus reuteri*, the rest received simethicone, the standard treatment for cholic. After four weeks the conventionally treated infants were still crying for an average of 2 hours and 27 minutes per day and those who received *L. reuteri* drops were down to an average of just 17 minutes of crying per day, which is well within the range of normal. Over the years, the composition of gut microflora changes. In midlife there is a decrease in the members of the probiotic *Bifidobacterium* genus and an increase in *E. coli* and *Clostridia*. *E. coli* can perform useful functions in the gut, they help compete against harmful microbes, they make certain vitamins that we absorb. On the other hand, if they leave the GI tract, they can cause disease. Many species of *Clostridia* are bad news. If their numbers get out of hand, they can cause serious illnesses. Members of the *Clostridium* genus are responsible for tetanus, botulism, and gangrene, as well as antibiotic-associated colitis (Huffnagle ’07: 94, 102, 104, 105).

7. Supplements

There are so many natural food supplements (Balch '00: 63) and multivitamins on the market , use of the term supplements is limited in this article to the fortification of grains and most commonly dispensed vitamin and mineral supplementation through the life-stages prescribed by the WHO *Essential Nutrition Actions: Mainstreaming Nutrition Through the Life-Course* (2019) with extra calcium supplementation for postmenopausal women (WHO '19: 103). **Micronutrient malnutrition** remains a significant public health challenge – approximately one third of the world’s population (32.9%) suffers from anemia, as of 2010. The population groups most vulnerable to anemia, as of 2016, include children under 5 years of age (41.7% with anemia), particularly infants and children under 2 years of age; non-pregnant women (15–49 years; 32.5%

with anemia); and pregnant women (40.1% with anemia). This equates to roughly 800 million women and children with anemia globally. **Iron deficiency**, a primary cause of anemia in many settings, is estimated to affect an even larger number of people – 2 billion – and, independently of the negative effects caused by anemia, is associated with delayed cognitive and behavioral development in children, as well as reduced productivity in adults and impaired cognitive functioning in women. Industrialized nation multivitamins are encouraged to include iron; iron and phosphorus for vegans. Other prevalent micronutrient deficiencies include vitamin A and zinc. **Vitamin A deficiency** increases the risk of infectious morbidity and mortality from diarrhea or measles, and can cause visual impairment in children and pregnant women, as well as anemia. **Zinc deficiency** is also associated with increased risk of infectious morbidity and can impair growth. Still other nutrient deficiencies, notably of calcium and folic acid, place pregnant women at risk of pregnancy complications and poor birth outcomes (WHO '19: 7, 8).

Fortification of condiments and staple foods with micronutrients is recommended for all population groups. Universal salt iodization is appropriate for all countries and all settings, whereas the fortification of maize flour, corn meal, rice and wheat flour with vitamins and minerals is only applicable, where the food is a staple food. There is documented evidence from several countries that fortification of other staple foods with zinc, vitamin A, folic acid, vitamin D and calcium is associated with significant reductions in the incidence of deficiency-related outcomes, and improvements in the health status of populations. Food fortification should be guided by national standards, with quality assurance and quality control systems to ensure quality fortification. Continuous program monitoring should be in place, as part of a process to ensure high-quality implementation. Monitoring of consumption patterns and evaluation of micronutrient status in the population can inform adjustment of fortification levels over time (WHO '19: 11, 19-20, 29).

All food-grade salt, used in household and food processing, should be fortified with iodine. **Iodized salt** has a large effect on reducing the risk of goiter, cretinism, low cognitive function, and iodine inadequacy, as indicated by low urinary iodine excretion. In some contexts, iodization of salt at the population level may cause a transient increase in the population incidence of hyperthyroidism, but not hypothyroidism. However, the beneficial effects of iodization of salt far outweigh the potential adverse effects. Monitoring of sodium (salt) intake and iodine intake at country level is needed to adjust salt iodization over time as necessary, depending on observed salt intake in the population, to ensure that individuals consume sufficient iodine despite reduction of salt intake. Iodized salt should reach, and be used by, all members of the population after 1 year of age. Infants and young children are assumed to be covered via breast milk, or iodine-enriched infant formula milk when this is prescribed. Addition of salt to products consumed by young children may need regulation, to avoid insufficient or excessive consumption of either sodium (salt) or iodine. Pregnant women have a daily iodine requirement of 250 μg/day, other interventions such as iodine supplementation could be considered if iodine inadequacy is found. Fortification of salt with iodine should be appropriately regulated by governments and harmonized with other local or country programs, to ensure that fortified food-grade salt is delivered safely within the acceptable dosage range. Legislation should cover not only proper iodization of salt, but also the salt content of industrialized food products. Policies for salt iodization and reduction of salt to below 5 g/day are compatible, cost effective and of great public health benefit. Although salt is an appropriate vehicle for iodine fortification, iodization of salt should not justify promotion of salt intake to the public (WHO '19: 27-28).

Fortification of maize flour and corn meal with iron is recommended to prevent iron deficiency in populations, particularly vulnerable groups such as children and women. Fortification of maize our and corn meal with folic acid is recommended to reduce the risk of occurrence of births with neural tube defects. Evidence on fortification of maize flour with folic acid or iron shows a positive effect on health outcomes in the general population. Fortification of maize flour with iron, in combination with other micronutrients, reduces the risk of iron deficiency but has no effect on anaemia in children. Addition of folic acid to wheat and maize flour in the United States of America (USA) and other countries has had a significant impact on multiple measures, including folate intake, blood folate concentrations and the prevalence of neural tube defects. The choice of iron compound is a compromise between cost, bioavailability, micronutrient interactions and the acceptance of texture, taste, smell and/or color. Nixtamalized flour (lime treated), commonly used in the Americas, is more reactive to ferrous compounds. The use of electrolytic iron does not appear to be effective in fortification of nixtamalized maize flour. Since some of the B-complex vitamins naturally present in the maize grain are removed during milling and degerming, the restoration of niacin, riboflavin and thiamine in maize flour should remain a regular practice in fortification, especially niacin for non-nixtamalized maize flour. This strategy has contributed to the virtual elimination of beriberi and pellagra in many countries. The addition of vitamin C and the removal of phytates in maize flour and corn meal could increase the bioavailability of iron (WHO '19: 29-30).

Fortification of rice with iron is recommended as a public health strategy to improve the iron status of populations, in settings where rice is a staple food. Fortification of rice with vitamin A may be used as a public health strategy to improve the iron status and vitamin A nutrition of populations. Fortification of rice with folic acid may be used as a public health strategy to improve the folate nutritional status of populations. Provision of rice fortified with vitamins and minerals including iron, when compared with unfortified rice, probably improves iron status by reducing the risk of iron deficiency by 35% and increasing the average concentration of hemoglobin by almost 2 g/L, but may not make a difference to the risk of anaemia in the general population of those aged over 2 years. When the fortification of rice includes vitamin A, it may reduce both iron deficiency and vitamin A deficiency. When fortification includes folic acid, fortified rice may slightly increase serum folate concentrations. Rice milling results in the loss of a significant proportion of B vitamins and minerals that are found predominately in the outer germ and bran layers. Nutrient losses during milling can be minimized by a process called parboiling, in which raw rice is soaked in water and partially steamed before drying and milling, resulting in some of the B vitamins migrating further into the grain. Since some of the fat- and micronutrient-rich bran layers are removed during rice milling, the restoration of thiamine, niacin, riboflavin and vitamin B_6 (pyridoxine) in the fortification profile should remain a regular practice in fortification. The prevalence of depletion and deficiency of vitamin B_{12} (cobalamin) is high in all age groups, reaching 50% in some countries. The inclusion of vitamin B_{12} is recommended when staples are fortified with folic acid, to avoid the masking effect of folic acid on vitamin B_{12} deficiency. Fortification of rice with iron has been a challenge, since most of the bioavailable iron powders used in food fortification are colored, which produces changes in the aspect of fortified kernels compared to unfortified ones. Rice fortification on a national scale requires a large, cost-effective and sustainable supply of fortified kernels. In malaria-endemic areas, the provision of iron through rice fortification, as a public health strategy, should be done in conjunction with public health measures to prevent, diagnose and treat malaria (WHO '19: 30-31).

Fortification of wheat flour is a preventive food-based approach to improve the micronutrient status of populations over time, which can be integrated with other interventions in efforts to

reduce vitamin and mineral deficiencies when these are identified as public health problems. Fortification of wheat our with folic acid increases the intake of folate by women and can reduce the risk of neural tube and other birth defects. Addition of folic acid to wheat flour in various countries has had a significant impact on multiple measures, including folate intake, blood folate concentrations and the prevalence of neural tube defects. The selection of the type and quantity of vitamins and minerals to add to flour, either as a voluntary standard or a mandatory requirement, lies with national decision-makers in each country and therefore the choice of compounds as well as quantities should be viewed in the context of each country's situation. Flour-fortification programs should include appropriate quality assurance and quality control programs at mills, as well as regulatory and public health monitoring of the nutrient content of fortified foods and assessment of the nutritional/health impacts of the fortification strategies. Some pleasant flours are fortified with iron (WHO '19: 31-32).

It can be challenging to meet the requirements for key nutrients like iron and vitamin A in young children through plant-based diets alone. In many settings, the cost of animal-source foods is prohibitive and mass-fortified products may not be available or may not meet nutrient needs. Daily iron supplementation for children aged 6–23 months decreases the risk of anemia, iron deficiency and iron deficiency anaemia. MNPs – powders that contain multiple micronutrients that can be mixed into complementary foods – have been shown to reduce iron deficiency and anaemia and increase hemoglobin concentrations. **Anemia** is frequently caused by iron deficiency, but other factors may contribute to anaemia, including other micronutrient deficiencies (e.g. folic acid, zinc, vitamins A and B12), malaria, soil- transmitted helminths, other infections, and blood disorders (e.g. thalassemia, sickle cell). Iron deficiency is thought to be the primary nutritional cause of anemia and is associated with diarrhea, impaired cognitive development and school performance. In populations where anemia is a public health problem, where the prevalence of anemia in children aged under 2 years or under 5 years is 20% or higher, point-of-use fortification of complementary foods with iron-containing micronutrient powders (MNPs) is recommended, to improve iron status and reduce anemia among infants and young children aged 6–23 months. Daily iron supplementation is recommended as a public health intervention for infants and young children aged 6–23 months, living in settings where the prevalence of anaemia is 40% or higher in this age group, for preventing iron deficiency and anemia. Iron: 10–12.5 mg of elemental iron, 12.5 mg of elemental iron equals 37.5 mg of ferrous fumarate or 62.5 mg of ferrous sulfate heptahydrate or equivalent amounts in other iron compounds. If sodium iron EDTA (NaFeEDTA) is selected as a source of iron, the dose of elemental iron should be reduced by 3–6 mg due to its higher bioavailability. Vitamin A: 300 μg of retinol. Zinc: 5 mg of elemental zinc. With or without other micronutrients to achieve 100% of the recommended nutrient intake. 90 sachets/doses over a 6-month period (WHO '19: 66-70).

Approximately 600 million preschool and school-age children have anaemia and roughly half of anaemia cases are estimated to be due to iron deficiency. **Iron deficiency anaemia** in children has been linked to increased children morbidity and impaired cognitive development and school performance. Children are particularly vulnerable to iron deficiency anaemia because of their increased iron requirements in the periods of rapid growth, especially in the first 5 years of life. Daily iron supplementation for children aged 24–59 months is associated with increased ferritin (an indicator of iron stores) and hemoglobin levels, and lower risk of anaemia, iron deficiency and iron deficiency anaemia in children aged 5–12 years. Daily iron supplementation is recommended as a public health intervention for preschool children (24–59 months) and school-age children (5–12 years), living in settings where the prevalence of anaemia in these age groups is 40% or higher, for increasing hemoglobin concentrations, improving iron status and preventing iron deficiency and anaemia. Preschool-age children (24–59 months) should receive

30 mg of elemental iron. School-age children (5–12 years) should receive 30–60 mg of elemental iron. 30–60 mg of elemental iron equals 150–300 mg of ferrous sulfate heptahydrate, 90–180 mg of ferrous fumarate, or 250–500 mg of ferrous gluconate. In settings where the prevalence of anaemia in preschool (24–59 months) or school-age (5–12 years) children is 20% or higher, intermittent iron supplementation is recommended as a public health intervention for preschool and school-age children, to improve iron status and reduce the risk of anaemia. Preschool-age children (24–59 months) should receive 25 mg of elemental iron, 25 mg of elemental iron equals 75 mg of ferrous fumarate, 125 mg of ferrous sulfate heptahydrate or 210 mg of ferrous gluconate. School-age children (5–12 years) should receive 45 mg of elemental iron 45 mg of elemental iron equals 135 mg of ferrous fumarate, 225 mg of ferrous sulfate heptahydrate or 375 mg of ferrous gluconate. Where infection with hookworm is endemic (prevalence 20% or greater), it may be more effective to combine iron supplementation with anthelminthic treatment in children aged over 5 years. Universal anthelminthic treatment, irrespective of infection status, is recommended at least annually in these areas (WHO '19: 71-74).

More than one third of non-pregnant women have **anemia** and roughly half of these cases are estimated to be due to iron deficiency. Because of their iron losses due to menstruation and typically low iron content of their diets, menstruating non-pregnant adolescent girls are at particular risk of iron deficiency and anaemia. Intermittent supplementation with iron and folic acid (i.e. once, twice or three times a week) has been shown to be effective, safe and more acceptable than daily supplementation for improving hemoglobin concentrations in menstruating adolescent girls and lowering their risk of anaemia. Daily iron supplementation is recommended as a public health intervention for menstruating non-pregnant adolescent girls where anaemia is highly prevalent (40% or higher anaemia prevalence), for the prevention of anaemia and iron deficiency. 30–60 mg of elemental iron equals 90–180 mg of ferrous fumarate, 150–300 mg of ferrous sulfate heptahydrate or 250–500 mg of ferrous gluconate. Daily oral iron supplementation should be considered in the context of other interventions containing iron (fortified foods, multiple micronutrient powders, lipid-based nutrient supplements). In populations where the prevalence of anaemia among non-pregnant women is 20% or higher, intermittent iron and folic acid supplementation is recommended as a public health intervention for menstruating non- pregnant adolescent girls, to improve their hemoglobin concentrations and iron status and reduce the risk of anaemia. Iron: 60 mg of elemental iron, equals 300 mg of ferrous sulfate heptahydrate, 180 mg of ferrous fumarate or 500 mg of ferrous gluconate. Folic acid: 2800 μg (2.8 mg). One tablet per week. 3 months of supplementation followed by 3 months of no supplementation, after which the provision of supplements should restart. If an adolescent girl is diagnosed as having anemia in a clinical setting, she should be treated with daily iron (120 mg of elemental iron) and folic acid (400 μg or 0.4 mg) supplementation until her hemoglobin concentration rises to normal. In malaria-endemic areas, the provision of iron and folic acid supplements should be implemented in conjunction with adequate measures to prevent, diagnose and treat malaria. Where infection with hookworm is endemic (prevalence 20% or greater), it may be more effective to combine iron supplementation with anthelminthic treatment (WHO '19: 80- 83).

Vitamin A deficiency during infants and children can lead to visual impairment, and increased illness and mortality from children infections, including diarrhea and measles. Vitamin A deficiency alone is responsible for 6% of deaths in children aged under 5 years in Africa and 8% in South-East Asia. Vitamin A supplementation for children aged 6–59 months is associated with a reduced risk of all- cause mortality and a reduced incidence of diarrhea. In settings where vitamin A deficiency is a public health problem (where the prevalence of night-blindness is 1%

or higher in children aged 24–59 months, or where the prevalence of vitamin A deficiency [serum retinol 0.70 μmol/L or lower] is 20% or higher in infants and children aged 6–59 months), high-dose vitamin A supplementation is recommended for infants and children aged 6–59 months. An oil-based vitamin A solution can be delivered using soft gelatin capsules, as a single-dose dispenser or a graduated spoon. Consensus among manufacturers to use consistent color coding for the different doses in soft gelatin capsules, namely red for the 200 000 IU capsules and blue for the 100 000 IU capsules, has led to much improved training and operational efficiencies in the field. Infants aged 6–11 months (including HIV-positive infants) should receive 100 000 IU (30 mg RE) vitamin A once. Children aged 12–59 months (including HIV-positive children) should receive 200 000 IU (60 mg RE) vitamin A Every 4–6 months (WHO '19: 75-76).

Iodine is essential for healthy brain development in the fetus and young child. Countries, or areas within countries, in which less than 20% of the households have access to iodized salt should assess the current situation of their salt-iodization program, to identify national or subnational problems and to update their strategies and action plans. Children aged 6–23 months should be given either a supplement or complementary food fortified with iodine until the salt-iodization program is scaled up. Infants and young children aged under 2 years should receive a daily dose of iodine equal to 90 (μg/day) or single annual dose of iodized oil supplement 200 (mg/year). For infants aged 0–5 months, iodine supplementation should be given through breast milk. This implies that the infant is exclusively breastfed and that the lactating mother received iodine supplementation. Evidence suggests that in settings where universal salt iodization is not fully implemented, pregnant and lactating women and children under 2 years of age may not be receiving adequate amounts of iodized salt and thus are getting insufficient iodine for their needs (WHO '19: 77-78).

Mothers, other caregivers and health workers should provide children with diarrhea with 20 mg per day of **zinc** supplementation (10 mg/day for children <6 months of age) for 10–14 days. Diarrhea remains a leading cause of death among infants and young children in low- and middle-income countries. Oral rehydration salts are a proven life-saving treatment for children with diarrhea. Use of zinc supplements with oral rehydration salts has been shown to reduce diarrheal mortality by 23%, reduce the duration and severity of diarrhea, and prevent subsequent diarrheal episodes. Zinc is thought to affect immune function or intestinal structure or function, as well as the epithelial recovery process during diarrhea (WHO '19 : 79).

In undernourished populations (20% or more low BMI among women), nutrition education on increasing daily energy and **protein intake** is recommended for pregnant women to reduce the risk of low-birth- weight neonates. Good nutrition and a healthy diet during pregnancy are critical for a mother's health, as well as that of her child. A healthy diet contains adequate energy, protein, vitamins and minerals, obtained from a variety of foods, including green and orange vegetables, meat, fish, beans, nuts, whole grains and fruit. Evidence suggests that nutrition education and counseling may support optimal gestational weight gain, reduce the risk of anemia in late pregnancy, increase birth weight, and lower the risk of preterm delivery. This strategy aims to increase the diversity and amount of foods consumed; promote adequate weight gain through sufficient and balanced protein and energy intake; and promote consistent and continued use of micronutrient supplements, food supplements or fortified foods. In undernourished populations (20% or more low BMI among women), balanced energy and protein dietary supplementation is recommended for pregnant women, to reduce the risk of stillbirths and small- for-gestational age neonates. Providing balanced protein–energy supplementation (i.e. supplements in which protein provides less than 25% of the total energy

content) to undernourished pregnant women has been shown to promote gestational weight gain, improve fetal growth, and reduce the risk of stillbirth, low-birth-weight infants and small-for-gestational age infants. High-protein supplementation during pregnancy does not appear to be beneficial and may be harmful to the fetus. In the first and third trimesters, the hemoglobin threshold for diagnosing anemia is 110 g/L; in the second trimester, it is 105 g/L. The above guidelines are a preventive strategy for anaemia. If a woman is diagnosed with anaemia during pregnancy, her daily elemental iron should be increased to 120 mg until her hemoglobin concentration rises to normal (110 g/L or higher). Thereafter, she can resume the standard daily antenatal iron dose to prevent recurrence of anemia. Intermittent iron and folic acid supplements could be given to women planning pregnancy, to improve their iron stores. All women, from the moment they begin trying to conceive until 12 weeks of gestation, should take a folic acid supplement. Daily oral iron and folic acid supplementation should be part of routine antenatal care, started as early as possible and continued throughout pregnancy. Where the prevalence of anaemia in pregnant women is high (40% or more), supplementation should continue for 3 months in the postpartum period. On confirmation of pregnancy, women should receive standard antenatal care, including daily or intermittent iron and folic acid supplementation, depending on their anemia status (WHO '19: 84 – 89).

Vitamin A is important for vision, immune function and fetal growth and development. Vitamin A deficiency can cause visual impairment in the form of night-blindness and also increase susceptibility to illness. Vitamin A supplementation is only recommended for pregnant women in areas where vitamin A deficiency is a severe public health problem,a to prevent night-blindness. In such settings, vitamin A can be given daily or weekly. Existing WHO guidance suggests a dose of up to 10 000 IU vitamin A per day, or a weekly dose of up to 25 000 IU. Vitamin A deficiency is a severe public health problem if >5% of women in a population have a history of night blindness in their most recent pregnancy in the previous 3–5 years that ended in a live birth, or if >20% of pregnant women have a serum retinol level <0.70 μmol/L. Pregnant women are susceptible to vitamin A deficiency throughout gestation, but are at most risk during the third trimester of pregnancy, owing to accelerated fetal development and the physiological increase in blood volume during this period. Some evidence indicates that low doses of vitamin A supplements given daily or weekly to pregnant women, starting in the second or third trimester, can reduce the severity of decline in maternal serum retinol levels during late pregnancy and the symptoms of night-blindness. Vitamin A supplements provided to pregnant women who are vitamin A deficient probably reduce maternal anaemia. However, current evidence indicates that vitamin A supplementation during pregnancy does not reduce the risk of illness or death in mothers or their infants. Vitamin A supplementation for pregnant women is only recommended in settings where vitamin A deficiency is severe, and is not recommended to improve maternal and perinatal outcomes. A single dose of a vitamin A supplement greater than 25 000 IU is not recommended, as its safety is uncertain. Furthermore, a single dose of a vitamin A supplement greater than 25 000 IU might be teratogenic if consumed between day 15 and day 60 from conception. There is no demonstrated benefit from taking vitamin A supplements in populations where habitual daily vitamin A intakes exceed 8000 IU or 2400 μg, and the potential risk of adverse events increases with higher intakes (above 10 000 IU) if supplements are routinely taken by people in these populations (WHO '19: 89 - 90)

In populations with low dietary calcium intake, a daily **calcium supplementation** (1.5–2.0 g elemental calcium) is recommended for pregnant women, to reduce the risk of pre-eclampsia. The target group for this recommendation comprises populations with observed low dietary calcium intake or those living in geographical areas where calcium-rich foods are not commonly available or consumed. In some studies, low dietary calcium intake has been determined as less

than 900 mg per day. Hypertensive disorders such as pre-eclampsia and eclampsia are among the main causes of maternal deaths and preterm births, especially in low-income countries. Preterm births are the leading cause of early neonatal deaths and infant mortality, and survivors are at higher risk of respiratory disease and long-term neurological morbidity. Obesity, diabetes, twin or teenage pregnancies and low calcium consumption increase the risk of developing pre-eclampsia. Calcium supplementation improves calcium intake and consequently reduces the risk of hypertensive disorders during pregnancy. Pregnant women should be given information on rich dietary sources of calcium and the importance of adhering to supplementation schemes. Women should be counseled to avoid taking iron and calcium supplements concomitantly, owing to negative interactions between the two nutrients on absorption; supplements should ideally be taken several hours apart. The acceptability of supplements may be improved if the total daily dose is divided into three doses, preferably taken at mealtimes (WHO '19: 91 - 92).

Routine use of multiple micronutrient powders during pregnancy is not recommended as an alternative to standard iron and folic acid supplementation. Multiple micronutrient supplements that contain iron and folic acid may be considered for maternal health. There is insufficient evidence on the benefits and harms, if any, of routine vitamin B6 supplementation in pregnancy. Combined vitamin C and E supplements have been evaluated mainly in the context of preventing pre- eclampsia (on which they appear to have little or no effect). Vitamin C alone may prevent pre-labor rupture of membranes, and future research should consider vitamin C supplements apart from vitamin E. Owing to the limited evidence currently available to directly assess the benefits and harms of the use of vitamin D supplementation alone in pregnancy for improving maternal and infant health outcomes, the use of this intervention during pregnancy as part of routine antenatal care is not recommended. The moderate-certainty evidence showing that adding vitamin D to calcium supplementation probably increases the incidence of preterm birth is of concern and this potential harm needs further investigation. Pregnant women should be advised that sunlight is the most important source of vitamin D. They should also be encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy, balanced diet. It is unclear from the available evidence, what dose or timing of zinc supplementation, if any, might lead to a possible reduction in preterm birth. There is also little to no evidence of the side-effects of zinc supplementation, nor is it clear how zinc may compete with iron and calcium for absorption. Vitamin A supplementation for postpartum women is not recommended for the prevention of maternal and infant morbidity and mortality (WHO '19: 92- 95).

Undernutrition increases the risk of **TB infection** progressing to active disease, by weakening the immune system. Undernourished patients with TB have an increased risk of death and relapse. In turn, TB infection increases the risk of undernutrition, by reducing food intake from loss of appetite, nausea and abdominal pain; increasing nutrient losses from diarrhea and vomiting; and causing metabolic alterations. An adequate diet, containing all essential macro- and micronutrients, is necessary for the well-being and health of all people, including those with TB infection or TB disease. When undernutrition is identified at the time of TB diagnosis, TB is considered a key causal factor that needs to be addressed. All pregnant women with active TB should receive multiple micronutrient supplements that contain iron and folic acid and other vitamins and minerals. Children aged under 5 years with active TB and moderate acute malnutrition (weight-for-height between 2 and 3 z-scores below the WHO child growth standards median without edema) should be managed as any other children with moderate undernutrition. This includes provision of locally available nutrient-rich or fortified supplementary foods, in order to restore appropriate weight-for-height. Persons with active TB and moderate undernutrition who fail to regain normal BMI after 2 months' treatment for TB, as well as those who are losing weight during TB treatment, should be evaluated for adherence and

comorbid conditions. TB is commonly accompanied by comorbidities such as HIV, diabetes mellitus, smoking and alcohol or substance abuse, which have their own nutritional implications, and these should be fully considered during nutritional screening, assessment and counseling. They should also receive nutrition assessment and counseling and, if indicated, be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status. A daily multiple micronutrient supplement at 1× recommended nutrient intake should be provided, where fortified or supplementary foods are unavailable. All infants should be fed according to normal infant feeding guidelines. They should start breastfeeding within one hour after birth, be exclusively breastfed for 6 months, and continue to breastfeed up to 2 years of age or beyond, with the addition of adequate complementary foods from about 6 months of age. Infants at risk of TB infection from their mothers should be given preventive chemotherapy (isoniazid 5 mg/kg once daily orally) for 6 months. The infant should then be immunized with Bacillus Calmette– Guérin (BCG) vaccine when preventive chemotherapy is completed. The best way to prevent TB infection in infants of mothers infected with TB is timely and properly administered chemotherapy for the mother (WHO '19: 110 - 117).

Schistosome and soil-transmitted helminth (roundworms, hookworms and whipworms) infections are among the most common infections in developing countries and can cause internal bleeding, leading to anaemia. They can also cause malabsorption of nutrients, diarrhoea and vomiting, and loss of appetite, further damaging nutritional status. Children infected with soil-transmitted helminths benefit significantly from anthelminthic treatment, in terms of reduction of worm burden and weight and height gain. Preventive chemotherapy (deworming), using annual or biannual single-dose albendazole (400 mg)b or mebendazole (500 mg), is recommended as a public health intervention for all young children (12–23 months of age), preschool (24–59 months of age), school-age children (5–12 years) and non-pregnant women (15-49) living in areas where the baseline prevalence of any soil-transmitted infection is 20% or more among children, in order to reduce the worm burden of soil-transmitted helminths. Albendazole and mebendazole are well tolerated among children over 12 months of age, at appropriate doses, with only minor and transient side-effects reported. The most cost-effective approach to reach infected individuals is to treat the entire group at risk without individual diagnosis. Deliver deworming together with promotion of health and hygiene, to reduce transmission by encouraging healthy behaviours, such as hand-washing, use of footwear and proper disposal of feces. Take extra care and precaution in ensuring that women receiving anthelminthic medicines are not pregnant. Albendazole and mebendazole are well tolerated, with no adverse events in pregnant women and their fetuses when given after the first trimester of pregnancy. Anthelminthic medicines must not be given during the first trimester. Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for pregnant women, after the first trimester, living in areas where both: (i) the baseline prevalence of hookworm and/or *T. trichiura* infection is 20% or higher among pregnant women, and (ii) anaemia is a severe public health problem, in order to reduce the worm burden of soil-transmitted helminths (WHO '19: 117 – 121).

Ebola and Marburg viruses have been found in breast milk. Given the potential risk of transmission through breast milk and close physical contact during breastfeeding and general infant care, a woman who has been admitted as an Ebola, Marburg, Lassa fever or Crimean-Congo hemorrhagic fever patient may have already infected her breastfed infant. If the lactating woman and child are both positive for infection and replacement feeding with ready- to-use infant formula (RUIF) is acceptable, feasible, and provision is guaranteed: it is recommended to suspend breastfeeding until breast-milk tests are negative. If the lactating woman positive (or suspected awaiting results) and the child is negative (or contact- asymptomatic) for infection

suspend breastfeeding if already initiated. Lactating women who are discharged cured (after two consecutive negative blood polymerase chain reaction [PCR] tests) and have an infant or young child who is Ebola-negative or non-suspected (asymptomatic), should not resume breastfeeding until after they have had two negative breast-milk PCR tests. Safe, sustainable feeding with an appropriate breast-milk substitute will be necessary for neonates and some other infants but is challenging and, in many contexts, may expose infants to immediate risks of malnutrition and infectious disease. These infants require special attention and support. There may be cultural stigma associated with use of breast-milk substitute. Where possible, provide liquid ready-to-use infant formula milk, which is a less risky option than powdered infant formula milk, since it does not require reconstitution with water. When artificial feeding is possible, provide RUIF for infants less than 6 months of age or RUIF or ultra-high temperature (UHT) full-cream (or whole) cow's milk and complementary feeding (with the addition of multiple micronutrient powders if the nutrient contents of the complementary foods is expected to be inadequate). A mother who abruptly stops breastfeeding will need help to express her breast milk, to alleviate pain and engorgement and prevent inflammation, especially within the first month after delivery. Her breast milk is a contaminated product and should be treated as per infection-control protocols (WHO '19: 122- 124).

Signs and symptoms that affect nutritional care in patients with **Ebola virus disease** include a lack of appetite, nausea, sore throat, difficulty swallowing and breathing difficulties. Vomiting also interferes with nutritional care and, along with diarrhea, causes additional nutritional stress through rapid loss of electrolytes, protein, other essential nutrients and fluid. In feeding protocols for adults and children older than 6 months with Ebola virus disease the foremost considerations in the selection of food commodities includes the low osmolarity and renal solute load of the diet, along with the texture of food commodities. In the rehydration phase when exhibiting severe dehydration nutritional management is with Oral Rehydration Salts (ORS) and, if needed, IV fluids. In the maintenance phase where the patient is not severely dehydrated, has little or no appetite, and may or may not have eating difficulties, Milk-based fortified diets (F-75), for adults: “sip feeds” (low renal solute load, low-osmolarity options). In the transition phase the patient is not severely dehydrated and has some appetite, No eating difficulties: Any one or combination of any of the following: Ready-to-use fortified nutrient-rich biscuits/bars (can also be offered as a porridge or paste). MNP: multiple micronutrient powder. 1–2 porridges per day of fortified cereal legume blends with added sugar (adults) and added sugar and milk (children) common family meal (plus MNP, if no fortified food is given), preferably offer LNS in addition to common family food; LNS must be eaten separately. LNS refers generically to a range of fortified, lipid-based spreads, including products like ready-to-use therapeutic food (RUTF), used to treat severe acute malnutrition; ready-to-use supplementary food (RUSF), sometimes used as supplementary food to treat moderate acute malnutrition; and others that are used for “point-of-use” fortification to improve diets and aiming to prevent malnutrition. Eating difficulties: as for those with no eating difficulties, except that: common family meal should be offered as mashed food or as soups. LNS are not suitable for patients with swallowing difficulties, ready-to-use fortified nutrient-rich biscuits/bars should be offered as porridge. In addition, the following commodities are also suitable: milk-based fortified diets (F-100) for adults: “sip feeds” (low renal solute load, low-osmolarity options) (WHO '19: 126 – 130).

In critically ill patients with **severe dehydration**, nutritional support should not interfere with strategies for volume and electrolyte repletion, as nutritional requirements will temporarily be of a lower priority. Even in critically ill patients without severe dehydration who have no appetite, excess energy or protein is not needed and an excess could further compromise liver and kidney

function. As soon as appetite starts to return, patients need sufficient energy (kcal) and essential nutrients, in addition to fluid electrolytes. Patients with Ebola virus disease should be provided with a minimum of the recommended daily allowance for each nutrient. Excess use of any micronutrient is currently not recommended. For patients who receive adequate quantities of fortified ready-to-use food, multivitamins are not required. The food that is offered to the patient should ideally be palatable and attractive; be nutrient dense; be liquid, semi-solid or solid (depending on the patient's condition); be easy to ingest and require minimal assistance from health-care staff when the patient eats; carry limited risk of bacterial contamination when kept at the bedside for 2–3 hours; and not require eating utensils, as these can be a source of contamination. The intake of highly nutrient-dense foods (e.g. ready-to-use therapeutic food and ready-to-use supplementary food) may be important in patients in the boost feeding phase and for patients in the transition feeding phase with no feeding difficulties. Owing to the high osmolarity of sugary carbonated beverages and fruit juices, it is important that they are not given to patients with diarrhea, as they may exacerbate diarrhea. In addition, sugary carbonated beverages are low in electrolytes and nearly all essential nutrients. If patients request these commodities, they should only be offered during the boost feeding phase. It is recommended that recovered patients receive a discharge food ration. A nutritional assessment of recovered patients should be taken at discharge, as the presence or absence of malnutrition will determine the appropriate food ration and follow-up care (WHO '19: 130 - 131).

Zika virus is a mosquito-borne virus transmitted by Aedes mosquitoes; the same mosquito also transmits other vector-borne diseases – dengue, chikungunya and yellow fever. Currently, there is no treatment or vaccine to protect specifically against Zika virus infection. Breastfeeding has significant benefits for mothers and children in low-, middle- and high-income countries, including, among children, lower infectious morbidity and mortality, fewer dental malocclusions and higher intelligence scores; and for mothers, preventing breast cancer, improving birth spacing, and potentially reducing a woman's risk of diabetes and ovarian cancer. Though Zika virus RNA has been detected in breast milk and thus breast milk may be considered as potentially infectious, there are currently no documented reports of Zika virus being transmitted to infants through breastfeeding. In light of the evidence available, the benefits of breastfeeding for the infant and mother outweigh any potential risk of transmission of Zika virus through breast milk. Infants born to mothers with suspected, probable or con rmed Zika virus infection, or who reside in or have travelled to areas of ongoing Zika virus transmission, should be fed according to normal infant feeding guidelines. They should start breastfeeding within one hour after birth, be exclusively breastfed for 6 months and have timely introduction of adequate, safe and properly fed complementary foods, while continuing breastfeeding up to 2 years of age or beyond (WHO '19: 132 – 133).

There is no evidence that breastfeeding from a mother who is infected with **hepatitis B virus** poses an additional risk to her infant of hepatitis B virus infection, even without immunization. Thus, even where infection with hepatitis B virus is highly endemic and immunization against hepatitis B is not available, breastfeeding remains the recommended method of infant feeding. Immunization for hepatitis B will substantially reduce perinatal transmission, and virtually eliminate any risk of transmission through breastfeeding or breast-milk feeding. Immunization of infants will also prevent infection from all other modes of transmission of hepatitis B virus. one hour after birth, be exclusively breastfed for 6 months and continue to breastfeed up to 2 years of age or beyond, with the addition of adequate complementary foods from about 6 months of age. All infants worldwide should receive hepatitis B vaccine as part of routine children immunization. Where feasible, the first dose should be given within 48 hours after birth, or as

soon as possible thereafter. Hepatitis B vaccination is recommended for all children worldwide. Reaching all children with at least three doses of hepatitis B vaccine should be the standard for all national immunization programs. Importantly, all national programs should include a dose of monovalent hepatitis B vaccine at birth (WHO '19: 134 - 135).

There is a considerable risk of morbidity and mortality among infants who are not breastfed. Infants who are not breastfed are more vulnerable to infectious diseases, including severe respiratory tract infection. All infants should be fed according to normal infant feeding guidelines. They should start breastfeeding within one hour after birth, be exclusively breastfed for 6 months, and continue to breastfeed up to 2 years of age or beyond, with the addition of adequate complementary foods from about 6 months of age, including during periods of pandemic influenza A (H1N1) circulation. If the mother is ill with influenza, she should follow measures to prevent transmission. These include covering coughs and sneezes when caring for and breastfeeding the baby, as well as performing frequent hand hygiene. Do not separate the baby from the mother. Institute rooming-in. Keep newborn infants close to their mothers. In general, this closeness promotes infant survival from various threats. Anyone with respiratory symptoms should not provide care for a pregnant woman or a mother and newborn baby. The mother can continue breastfeeding, even if she is ill and on antiviral medicines. She should take additional fluids, especially if she has fever. If severe maternal illness prevents the mother from feeding the infant at her breast, she should be helped to express her breast milk and feed it to the infant by cup or cup and spoon (WHO '19: 136 -137).

Vitamin A deficiency affects the body's immune system and the cells that protect the lining of the lungs and gut, limiting the body's ability to control and prevent infections. Vitamin A deficiency is linked with a higher rate of measles infection, as well as increased mortality from measles. Children with vitamin A deficiency and measles infection have increased risk of mortality, delayed recovery and post-measles complications. Measles infection may precipitate acute vitamin A deficiency and xerophthalmia and is a primary contributor to preventable children blindness. Vitamin A is recommended for all children with measles. Children should be provided with one dose of vitamin A immediately on diagnosis. In areas where the case-fatality for measles is likely to be more than 1%, or in areas of known vitamin A deficiency, a second dose should be provided the following day. In cases in which any eye signs of vitamin A deficiency are present, a third dose is to be provided, at least 2 weeks after the second dose. Infants aged under 6 months should be given 50,000 IU immediately on diagnosis, 50,000 IU the next day and 50,000 IU 2-4 weeks later if eye signs. Infants aged 6-11 months should receive 100,000 IU immediately on diagnosis, 100,000 IU the next day and 100,000 IU 2-4 weeks later (if eye signs). Children agd 12 months or over should receive 200,000 IU immediately on diagnosis, 200,000 the next day and 200,000 2-4 weeks later (if eye signs) (WHO '19:`38 -139).

In emergency settings, **breast milk** plays a particularly critical role for feeding and protecting possibly malnourished children in the unhygienic conditions that often prevail. Breast milk provides adequate nutrition and also protection from infections, especially diarrhea, which is particularly problematic during emergencies. In emergency settings, where unsafe water, inadequate sanitation and lack of cooking fuel are common, artificial feeding carries increased risk of infection and mortality. In emergencies, it is important to protect, promote and support exclusive breastfeeding in infants under 6 months of age and continued breastfeeding in children aged 6 months to 2 years or beyond. Every effort should be made to identify alternative ways to breastfeed infants whose biological mothers are unavailable (e.g. relactation or wet-nursing if culturally acceptable). The aim should be to create and sustain an environment that encourages frequent breastfeeding for children up to the age of 2 years and beyond. The quantity,

distribution and use of breast-milk substitutes at emergency sites should be strictly controlled. A nutritionally adequate breast-milk substitute should be available, and fed by cup, only to those infants who have to be fed on breast-milk substitutes. There should be no general distribution of breast-milk substitutes. Those responsible for feeding a breast-milk substitute should be adequately informed and equipped to ensure its safe preparation and use. The use of infant-feeding bottles and artificial teats during emergencies should be actively discouraged. Non-breastfed infants in emergency settings are a group that is particularly at risk of infection and malnutrition and should be provided special attention. Nutritional status should be continually monitored to identify malnourished children, so that their condition can be assessed and treated, and prevented from deteriorating further. The underlying causes of malnutrition should be investigated and corrected. Promoting optimal feeding for infants and young children in emergencies requires a flexible approach based on continual careful monitoring. Any support of artificial feeding in an emergency should be based on a needs assessment by skilled technical staff, including a risk analysis (WHO '19: 140 - 141).

In emergency situations infants from 6 months of age onwards and older children need hygienically prepared, and easy-to-eat and digest foods that nutritionally complement breast milk. This should occur in an environment that encourages frequent breastfeeding for children up to 2 years and beyond. The health and vigor of infants and children should be protected so that they are able to suckle frequently and well, and maintain their appetite for complementary foods. Caregivers need secure uninterrupted access to appropriate ingredients with which to prepare and feed nutrient-dense foods to older infants and young children. For children aged 6–59 months, multiple micronutrient supplements may be necessary to meet their nutrition requirements where fortified foods are not being provided. Recommended composition of a **multi-micronutrient supplement for infants and children in emergency settings** Vitamin A 400.0 µg, Vitamin D 5.0 µg, Vitamin E 5.0 mg, Vitamin C 30.0 mg, Thiamine (vitamin B1) 0.5 mg, Riboflavin (vitamin B2) 0.5 mg, Niacin (vitamin B3) 6.0 mg, Vitamin B6 0.5 mg, Vitamin B12 0.9 µg, Folic acid 150.0 µg, Iron 10.0 mg, Zinc 4.1 mg, Copper 0.56 mg, Selenium 17.0 µg, Iodine 90.0 µg (WHO '19: 142 - 144)

Pregnant and lactating women are one of the groups that are most vulnerable to nutritional deficiencies because of their relatively greater nutrient needs – for water, energy, protein and micronutrients – to support their growth and development, as well as that of the fetus, during pregnancy. For a lactating mother, her micronutrient status determines the health and development of her breast-fed infant, especially during the first 6 months of life. Pregnant and lactating women should be ensured access to sufficient drinking water (extra 1 L of clean water per day). Pregnant and lactating women in emergency settings should be provided with fortified blended food commodities, in addition to the basic general ration, that are designed to provide 10–12% (up to 15%) of energy from protein and 20–25% of energy from fat. The fortified blended food should be fortified to meet two thirds of the daily requirements for all micronutrients. In malaria-endemic areas, pregnant women can be administered sulfadoxine–pyrimethamine through clinics at the beginning of the second and third trimesters. Pregnant women should be encouraged to use an insecticide-treated bed-net during pregnancy. Women should be advised to seek immediate medical attention for episodes of fever. Pregnant and lactating women in emergency settings should receive a multiple micronutrient supplement that provides one recommended nutrient intake (RNI) daily, throughout the duration of the emergency, regardless of whether they receive fortified rations or not. Recommended micronutrient formula for pregnant and lactating women in emergency settings: Vitamin A 800.0 µg, Vitamin D 5.0 µg, Vitamin E 15.0 mg, Vitamin C 55.0 mg, Thiamine (vitamin B1) 1.4 mg, Riboflavin (vitamin B2) 1.4 mg, Niacin (vitamin B3) 18.0 mg, Vitamin B6 1.9 mg, Vitamin B12

2.6 µg, Folic acid 600.0 µg, Iron 27.0 mg, Zinc 10.0 mg, Copper 1.15 mg, Selenium 30.0 µg, Iodine 250.0 µg (WHO '19: 145 – 146).

Older adults with undernutrition are defined with (BMI lower than 18.5 kg/m2). Increasing age coincides with many physiological changes that increase the risk of undernutrition and subsequent physical and cognitive impairments. Undernutrition is a major problem among older adults, affecting up to 22%. Undernutrition in the elderly leads to reduced bone and muscle mass, increased frailty, diminished cognitive function and ability to care for oneself, and thus a higher risk of becoming dependent on care. Aging is accompanied by physiological changes that can have a negative impact on nutritional status and, consequently, intrinsic capacity. Sensory impairments (a decreased sense of taste and smell, for example), poor oral health, isolation, loneliness and depression – individually or in combination – all increase the risk of undernutrition in older age. Aging is associated with changes in body composition; after the age of 60 years, there is a progressive decrease in body weight that results mainly from a decrease in fat-free mass and lean mass, and an increase in fat mass. Stable body weight overall masks such age-related changes in body composition. Protein absorption decreases with age, and thus standard protein intakes may not be sufficient for older adults. Older people who do not consume enough protein are at increased risk of developing sarcopenia, osteoporosis and impaired immune response. Evidence indicates that oral supplemental nutrition for older adults with undernutrition can significantly reduce mortality and improve weight gain. Consider specially formulated supplementary foods, such as those that are in ready-to-eat form, to help meet the nutritional requirements of older adults. Consider social dining (eating with others) or family-style meals to help manage undernutrition, particular among those who are living alone or are socially isolated. Refer older people with evidence of potentially serious underlying physical illness (gross cachexia, rapid weight loss, obstruction or difficulty swallowing, vomiting, chronic diarrhea, abdominal pain or swelling) for medical review by a physician or specialist (WHO '19: 103-104).

The recommended daily allowance (RDA) of calcium is 1200 to 1500 milligrams for a postmenopausal woman. **Osteoporosis** is a skeletal disease, marked by low bone mass and microarchitectural deterioration that leads to an increased susceptibility to fracture, most often as a symptom of menopause. Worldwide, the disease causes nearly 2 million hip fractures each year. Osteoporotic fractures can become life-threatening; nearly 24 percent of elderly people who suffer a hip fracture die within the first year of the fracture, and many others can never live independently again. Osteoporosis currently affects about 25 million people in the United States. 20 percent of women and 5 percent of men aged 50 and above in the United States have osteoporosis. An estimated 250,000 hip fractures occur annually in the United States. Osteoporosis can be diagnosed easily by measuring bone mineral density at the spine or hip with dual energy x-ray absorptiometry (DXA) or at the forearm or heel with single energy x-ray absorptiometry (SXA) or peripheral-DXA. The techniques are readily available and are covered by Medicare and most insurance companies. About 40 percent of bone mass must be lost before it can be seen on an X-ray. According to the National Osteoporosis Foundation, the World Health Organization (WHO) and the European Foundation for Osteoporosis and Bone Disease there are four diagnostic categories for osteoporosis. (1) Normal. A value for bone mineral density or bone mineral content not more than 1 standard deviation below average for young adults, or about 10 percent below the young adult average or higher. (2) Low bone mass (osteopenia), a value for bone mineral density or bone mineral content more than 2 standard deviation below the young adult average, but not more than 2.5 standard deviations below the young adult average or 10 to 25 percent below this average. (3) Osteoporosis, a value for bone mineral density or bone mineral content more than 2.5 standard deviations below the young adult

average value, or 25 percent below this average or less. (4) Severe osteoporosis (established osteoporosis), a value for bone mineral density of bone mineral content more than 2.5 standard deviations below the young adult average value, or 25 percent or more below this average and the presence of one of more osteoporotic fractures. For each standard deviation of below-peak bone mass, the fracture risk nearly doubles (Lane '99: 39, 40, 56).

The recommended daily allowance (RDA) of calcium is 1200 to 1500 milligrams for a postmenopausal woman. At menopause, calcium absorption is reduced due to estrogen deficiency. In the early 1980s researchers found that a high proportion of older American women took in less than 500 milligrams of calcium a day. Less than a third of the RDA. Women whose diets are high in calcium and who take high doses of calcium supplements appear to have decreased risk of hip fractures. Most children and adults only consume about 700 to 800 milligrams a day. A supplement of about 200 to 400 mg a day for most adults, would provide all the calcium they need. **Calcium carbonate** is the preferred calcium supplement for young and old alike. Tums® is the trademark one of them. It has about 40 percent per milligram of calcium, and tablets come in 500 to 650 milligram doses. Usually women take 400 to 2000 milligrams of calcium a day in divided doses. To help absorption, the supplement should be taken with food. To help absorption, the supplement should be taken with food. Another good supplement is calcium citrate, but this has only about 21 percent calcium in each tablet, but may be easier to absorb for people who don't have much stomach acid, it is more expensive and comes in 950 and 1500 milligram tablets. Another supplement, **calcium gluconate**, has only 9 percent calcium and is generally supplied in tablets containing 500 to 600 milligrams. **Calcium phosphate dibasic**, is 23 percent calcium, and available in 486 milligram tablets. **Tricalcium phosphate** is 39 percent calcium and comes in 300 and 600 milligram tablets. Some calcium preparations are combined with vitamin D, for example Oscal®, containing calcium carbonate and 200 IU of vitamin D for calcium absorption. Most of the time calcium supplements cause no problem are very safe, but some side effects do occur, including bloating, flatulence or constipation, but these are uncommon. Too much calcium is excreted in the urine and over time painful calcium kidney stones may develop. To protect against this possibility a doctor should do a test after taking a calcium supplement for 2 to 3 weeks. Also some women a have a disease called sarcoid or take large amounts of vitamin D, which can lead to large concentrations of calcium in the urine (Lane '99: , 87, 88, 91, 92).

Calcium + vitamin D + phosphorus = **Apatite**. Bones and teeth contain 99 percent of all the body's calcium and phosphorus, that is where the body gets it (Fishman '06: 95, 96). For osteoporosis therapeutic and preventive measures should emphasize adequate intake of calcium (1500 mg/day), vitamin D (400-800 IU/day) and 1,000-1,250 mg/day of phosphorus. **Calcium** is found in milk and milk products, fish, shellfish, bone meal, dark green, leafy vegetables, whole grains, broccoli, almonds, nuts, legumes, egg yolk, tofu, navy and soy beans. In conjunction with phosphorus Calcium builds bones and teeth and aids in blood clotting. Calcium is necessary for nerve transmission, heart function, muscle contraction and relaxation, and cell wall permeability. There is an increased risk for fractures and decreased bone strength with a deficit. **Vitamin D**, that can be derived from ½ exposure to sunlight or fortified milk, is essential for absorption of calcium from the large intestine and assimilation into bone. **Phosphorus** is found in great quantities in milk and milk products, meats, seafood, and egg yolk, and is difficult to obtain from vegetable sources such as mushrooms, mung and soy beans. Phosphorus aids in formation of nucleic acids and works with vitamin D and calcium to build and maintain healthy bones teeth and cell membranes. Deficit results in weakness, malaise, anorexia, bone loss, and pain (Muscari '01: 301, 302).

8. Additives

There are 1,450 **food additives**, listed in the the Joint FAO/WHO Expert Committee on Food Additives (JECFA), all of which are designed to do a specific job in making food safer or more appealing, as of October 2019. WHO, together with FAO, groups 1,450 food additives into 3 broad categories based on their function – Flavoring agents, enzyme preparations and other additives for preservation, coloring and sweetening. Substances that are added to food to maintain or improve the safety, freshness, taste, texture, or appearance of food are known as food additives. Some food additives have been in use for centuries for preservation – such as salt (in meats such as bacon or dried fish), sugar (in marmalade), or sulfur dioxide (in wine). Many different food additives have been developed over time to meet the needs of food production, as making food on a large scale is very different from making them on a small scale at home. Additives are needed to ensure processed food remains safe and in good condition throughout its journey from factories or industrial kitchens, during transportation to warehouses and shops, and finally to consumers. The use of food additives is only justified when their use has a technological need, does not mislead consumers, and serves a well-defined technological function, such as to preserve the nutritional quality of the food or enhance the stability of the food. Food additives can be derived from plants, animals, or minerals, or they can be synthetic. They are added intentionally to food to perform certain technological purposes which consumers often take for granted.

Flavoring agents – which are added to food to improve aroma or taste – make up the greatest number of additives used in foods. There are hundreds of varieties of flavorings used in a wide variety of foods, from confectionery and soft drinks to cereal, cake, and yoghurt. Natural flavoring agents include nut, fruit and spice blends, as well as those derived from vegetables and wine. In addition, there are flavorings that imitate natural flavors. **Enzyme preparations** are a type of additive that may or may not end up in the final food product. Enzymes are naturally-occurring proteins that boost biochemical reactions by breaking down larger molecules into their smaller building blocks. They can be obtained by extraction from plants or animal products or from micro-organisms such as bacteria and are used as alternatives to chemical-based technology. They are mainly used in baking (to improve the dough), for manufacturing fruit juices (to increase yields), in wine making and brewing (to improve fermentation), as well as in cheese manufacturing (to improve curd formation). **Other food additives** are used for a variety of reasons, such as preservation, coloring, and sweetening. They are added when food is prepared, packaged, transported, or stored, and they eventually become a component of the food. **Preservatives** can slow decomposition caused by mould, air, bacteria, or yeast. In addition to maintaining the quality of the food, preservatives help control contamination that can cause food-borne illness, including life-threatening botulism. **Coloring** is added to food to replace colors lost during preparation, or to make food look more attractive. Non-sugar **sweeteners** are often used as an alternative to sugar because they contribute fewer or no calories when added to food. WHO, in cooperation with the Food and Agriculture Organization of the United Nations (FAO), is responsible for assessing the risks to human health from food additives. Risk assessment of food additives are conducted by an independent, international expert scientific group – the Joint FAO/WHO Expert Committee on Food Additives (JECFA). *Codex Alimentarius* Commission identifies all additives world-wide by number. The United States Food and Drug Administration (FDA) lists these items as "generally recognized as safe" (GRAS); they are listed under both their Chemical Abstracts Service number and FDA regulation under the United States Code of Federal Regulations.

With the increasing use of **processed foods** since the 19th century, food additives are more widely used. Many countries regulate their use. For example, boric acid was widely used as a food preservative from the 1870s to the 1920s, but was banned after World War I due to its toxicity, as demonstrated in animal and human studies. During World War II, the urgent need for cheap, available food preservatives led to it being used again, but it was finally banned in the 1950s. Such cases led to a general mistrust of food additives, and an application of the precautionary principle led to the conclusion that only additives that are known to be safe should be used in foods. In the United States, this led to the adoption of the Delaney clause, an amendment to the Federal Food, Drug, and Cosmetic Act of 1938, stating that no carcinogenic substances may be used as food additives. However, after the banning of cyclamates in the United States and Britain in 1969, saccharin, the only remaining legal artificial sweetener at the time, was found to cause cancer in rats. Widespread public outcry in the United States, partly communicated to Congress by postage-paid postcards supplied in the packaging of sweetened soft drinks, led to the retention of saccharin, despite its violation of the Delaney clause. However, in 2000, saccharin was found to be carcinogenic in rats due only to their unique urine chemistry

Monosodium glutamate, or MSG, is a common food additive used to intensify and enhance the flavor of savory dishes. MSG is used to enhance the flavor of many processed foods. Some people may have a sensitivity to MSG, but it's safe for most people when used in moderation. Ramen noodles without added MSG are much less toxic. **Artificial food coloring** is used to brighten and improve the appearance of everything from candies to condiments. In recent years, though, there have been many concerns about potential health effects. Specific food dyes like Blue 1, Red 40, Yellow 5 and Yellow 6 have been associated with allergic reactions in some people. Artificial food coloring may promote hyperactivity in sensitive children and can cause allergic reactions. Red 3 has also been shown to increase the risk of thyroid tumors in animal studies. **Sodium nitrite** is a common ingredient in processed meats that can be converted into a harmful compound called nitrosamine. A higher intake of nitrites and processed meats may be linked to a higher risk of several types of cancer. **Guar gum** is a long-chain carbohydrate used to thicken and bind foods. It has been associated with better digestive health, lower levels of blood sugar and cholesterol, as well as increased feelings of fullness. High-fructose corn syrup is associated with weight gain, diabetes and inflammation. It's also high in empty calories and contributes nothing but calories to your diet. **Artificial sweeteners** may help promote weight loss and blood sugar control. Certain types may cause mild side effects like headaches, but they are generally considered safe in moderation. Derived from red seaweed, **carrageenan** acts as a thickener, emulsifier and preservative in many different food products. Test-tube and animal studies have found that carrageenan may cause high blood sugar and could cause intestinal ulcers and growths. One study also found that carrageenan contributed to an earlier relapse of ulcerative colitis. **Sodium benzoate** is a preservative often added to carbonated drinks and acidic foods like salad dressings, pickles, fruit juices and condiments. Sodium benzoate may be associated with increased hyperactivity. If combined with vitamin C, it may also form benzene, a compound that may be associated with cancer development. **Trans fats** are a type of unsaturated fat that have undergone hydrogenation, which increases shelf life and improves the consistency of products. Eating trans fats has been associated with many negative effects on health, including inflammation, heart disease and diabetes, and they have been ordered to be removed from consumer products. **Xanthan gum** is a common additive that's used to thicken and stabilize many types of food such as salad dressings, soups, syrups and sauces. Xanthan gum may help reduce levels of blood sugar and cholesterol. In large amounts, it may cause digestive issues like gas and soft stools. **Artificial flavors** are chemicals designed to mimic the taste of other ingredients. Some animal studies have found that artificial flavoring may be toxic to bone

marrow cells. More research is needed to evaluate the effects in humans. **Yeast extract**, also called autolyzed yeast extract or hydrolyzed yeast extract, is added to certain savory foods like cheese, soy sauce and salty snacks to boost the flavor. Yeast extract is high in sodium and contains glutamate, which may trigger symptoms in some people, bug is unlikely to cause problems for most people in the doses added to consumer food products (Link '18).

Food additives can be divided into several groups, although there is some overlap because some additives exert more than one effect. For example, salt is both a preservative as well as a flavor. **Acidulents** confer sour or acid taste. Common acidulents include vinegar, citric acid, tartaric acid, malic acid, fumaric acid, and lactic acid. **Acidity regulators** are used for controlling the pH of foods for stability or to affect activity of enzymes. **Anticaking agents** keep powders such as milk powder from caking or sticking. **Antifoaming agents** reduce or prevent foaming in foods. Foaming agents do the reverse. **Antioxidants** such as vitamin C are preservatives by inhibiting the degradation of food by oxygen. **Bulking agents** such as starch are additives that increase the bulk of a food without affecting its taste. **Colorings** are added to food to replace colors lost during preparation or to make food look more attractive. **Fortifying agents** such as vitamins, minerals, and dietary supplements to increase the nutritional value.
Color retention agents are used to preserve a food's existing color. **Emulsifiers** allow water and oils to remain mixed together in an emulsion, as in mayonnaise, ice cream, and homogenized milk. **Flavors** are additives that give food a particular taste or smell, and may be derived from natural ingredients or created artificially. **Flavor enhancers** enhance a food's existing flavors. A popular example is monosodium glutamate. Some flavor enhancers have their own flavors that are independent of the food. **Flour treatment agents** are added to flour to improve its color or its use in baking. Glazing agents provide a shiny appearance or protective coating to foods. **Humectants** prevent foods from drying out. **Tracer gas** allow for package integrity testing to prevent foods from being exposed to atmosphere, thus guaranteeing shelf life. Preservatives prevent or inhibit spoilage of food due to fungi, bacteria and other microorganisms. **Stabilizers**, thickeners and gelling agents, like agar or pectin (used in jam for example) give foods a firmer texture. While they are not true emulsifiers, they help to stabilize emulsions. **Sweeteners** are added to foods for flavoring. Sweeteners other than sugar are added to keep the food energy (calories) low, or because they have beneficial effects regarding diabetes mellitus, tooth decay, or diarrhea. **Thickening agents** are substances which, when added to the mixture, increase its viscosity without substantially modifying its other properties. **Packaging**, bisphenols, phthalates, and perfluoroalkyl chemicals (PFCs) are indirect additives used in manufacturing or packaging. In July 2018 the American Academy of Pediatrics called for more careful study of those three substances, along with nitrates and food coloring, as they might harm children during development (Lück '02).

Sodium nitrate and sodium nitrite, chemicals used as preservative to slow putrefecation in cured meat and meat products including ham, bacon, bologna, salami, frankfurters and fish endanger health. These chemicals give meat its bright red appearance by reacting with pigments in the blood and muscle. Without them, the natural gray-brown color of dead meat would turn away many prospective customers. Unfortunately, these chemicals do not distinguish with the blood of a corpse and the blood of a living human, and many persons accidentally subjected to excessive amounts have died of poisoning. Only a small margin of safety exists between the amount of nitrate that is safe and that which may be dangerous. Even smaller quantities can prove hazardous especially for young children or babies. The UN joint FAO/WHO Expert Committee on Food Additives has warned, “Nitrates, should on no account be added to baby food”. Nitrosamines are shocking. Nitrosamines are formed when secondary amines, prevalent in beer, wine, tea and tobacco, for example, react with chemical preservatives in the meat. The

Food and Drug Administration labeled nitrosamines, “one of the most formidable and versatile groups of carcinogens yet discovered, and their role in the etiology of human cancer has caused growing apprehension among experts.” Dr. William Lijinsky of Oak Ridge National Laboratory conducted experiments in which nitrosamines were fed to test animals. Within six months he found malignant tumors in 100 percent of animals. The cancers, he said, “are all over the place; in the brain, lungs, pancreas, stomach, liver adrenals and intestines.”. (Swami '06: 8, 4-5).

There are many environmental factors that can contribute to cancer. The list includes exposure to radiation, pesticides, and exoestrogens (synthetic chemicals which mimic or block estrogen in the human body) and many others. Much of the damage is caused by “persistent organic pollutants” (POPs) a group of highly toxic, long-lived, bio-accumulative chemicals. Many of these chemicals cause irreversible damage in people and animals at levels the experts called inconsequential a decade ago. People receive about 90 percent of their total intake of these compounds from foods of animal origin. Dioxin is an extraordinarily carcinogenic and perilous threat to health and the environment. Yet the EPA says that up to 95 percent of human dioxin exposure comes from red meat, fish, and dairy products. Dioxin may be responsible for 12 percent of human cancers in industrialized societies. More than 90 percent of US beef cattle receive hormone injections and in the larger feedlots the figure is 100 percent. The European Union refuses to import US hormone-treated beef. After the European Union banned the sale of hormone-treated meat within European Union countries, the United States complained to the World Trade Organization (WTO) where a three-lawyer panel ruled that the European Union was required to pay the US $150 million a year as compensation for lost profit although scientists called such hormones as so carcinogenic as to cause cancer by themselves. In 1999 the EU found that 12 percent of the US hormone free cattle had in fact been treated with sex hormones (Robbins '01: 42 143, 144).

Numerous potentially hazardous chemicals of which consumers are generally unaware, are present in meat and meat products. **Recombinant Bovine Growth Hormone** (rBGH/BST, a synthetic growth hormone designed to replace dethylstilbestrol in the US., which was shown to be carcinogenic. RBGH/BST is used to increase milk production, despite the fact that the US has a milk surplus Aside from the fat that rBGH/BST treated mili has been banned as a serious health hazard by the members of the European Union and Canada, it has been linked with two hazards for meat-eaters. The first is that cows treated with rGBH/BST tend to develop inflamed udders much more frequently than other cows. To counteract this problem, farmers pump their cows full of antibiotics, detectable residue of which remain in the cow fatty tissues, including the fats in milk. This process is causing the growth of antibiotic resistant bacteria, making antibiotics used to treat humans less effective. The FDA estimates that penicillin and tetracycline save the meat industry $1.9 billion a year, giving them sufficient reason to overlook the potential health hazards to humans. The second health hazard is the elevation of Insulin Growth Fact (IGF-$_1$) found in hormone treated milk. IGF-$_1$ takes the same for in humans as it does in cows, and in both, controls the way the body's cells respond to growth hormones. An increase in IGF-1 in humans can cause a number of diseases, not least of which are colorectal, thyroid, bone, epidermal and breast cancer (Swami '06: 5-6).

For some time bovine growth hormone (BGH) has been used to stimulate milk production in cows. The hormone was too expensive for widespread use until Monsanto came up with a genetically altered hormone called rBGH (recombinant bovine growth hormone), sold under the brand name Posilac. This genetically engineered hormone is now injected into about a quarter of the cows in US dairies. rBGH increases milk production, that is sure. But since 1950 US dairy farmers have been producing vastly more milk than Americans can consume. In 1986-87 the

federal government paid farmers to kill their cows and stop dairy farming for five years. More than 1.5 million milk cows were slaughtered. Another issue, milk from cows that have been injected with Monsantos genetically engineered rBGH contains 2 to 10 times as much IGF-1 (**insulin-like growth factor**) as normal cow's milk. This pushed prostate cancer risk for men over 60 years of age with high IGF-1 8 times greater than men with low levels, and the risk of pre-menopausal breast cancer was 7 times greater. IGF-1 is not destroyed in pasteurization. Cows treated with rBGH have a 25 percent increase in udder infections (mastitis) and a 50 percent increase in lameness. To counter the health problems among cows injected with rBGH more antibiotics are used. American consumers overwhelmingly support the labeling of milk products produced with rBGH. But the FDA has said such labeling would unfairly stigmatize rBGH milk as less healthy. The FDA official was a partner in the law firm representing Monsanto when it applied for FDA approval for rBGH (Robbins '03, 335, 336, 343).

Formally known as bovine spongiform encephalopathy (BSE), **Mad Cow disease** has caused fear across the world. Scientists say it belongs to a family of brain-wasting diseases – other forms exist in sheep, mink, deer, elk, cats, and humans. Mad Cow Disease was proven to transmitted by cannibalism, as was the case with the human form of the disease – and could jump species, say, from infected beef to human. Modern farmers around the world raise livestock in feedlots and feed them grain instead of grass. Grain is an expensive protein to grow, and farmers decided to take advantage of a cheaper source. Farm animals that die of disease, all anial parts not used in the meat-packing and leather industries (up to one-half of an animal's weight), road kill, euthanized pets, and animal control kills are part of a $2.4 billion dollar rendering industry. In Los Angeles alone 200 tons of euthanized pets are sent every month to the renderers. The number is almost the same in the UK. All these animals and animal parts are steam-cooked until they separate into fats and protein solids. The fats are used for cosmetics, lubricants, soaps and candles and the protein solids are dried, pulverized, and sold as "protein concentrates" to feedlots. There, they are added to the animal's feed. Cows, sheep, chickens and pigs are being forced to cannibalize their own kind. In 1988 over 2,000 cases of BSE were reported in Great Britain. Despite a ban on feeding ruminant proteins to ruminants, 35,000 new cases of BSE were confirmed in 1992. In 1993, two British dairy farmers died of Creutzfeldt-Jakob disease (CJD), the human form of BSE. Two things became clear: BSE is transmitted from cow to calf through the milk, and other species can contract it by eating infected meat. Americans cows have had BSE, and American people have suffered from CJD. In April of 1996 eight cases of CJD were diagnosed in the northeastern corner of Texas alone. The normal rate of infection prior to BSE jumping species is one death per million population. While both the US and UK have restricted farmers from feeding their livestock ruminant proteins, farmers have not given up on trying to provide herbivorous animals with animal protein: spray dried blood products, which have undergone little processing to remove infectivity, are increasingly used in feed. In 2006 new cases of BSE continued to break out in the US, England, Scotland, Sweden, Canada and Japan (Swami '06: 7-8).

USDA **meat inspections** are based on the Meat Inspection Act of 1907, which instructs inspectors to rely on sight, smell and touch, the "poke and sniff" method – to check for contaminations. The problem is, however, that the "poke and sniff" method cannot detect such deadly contaminants as E. coli 0157:H7 or salmonella. In 1996, the USDA changed its inspection policy, allowing meat-packing companies to perform more of their own food inspections. The US General Accounting Office cited the USDA for failure to correct various violations by slaughterhouses. Carcasses contaminated with rodent feces, cockroaches, and rust were found in meat-packing companies such as Swift, Armour and Carnation. Federal inspectors check paperwork, not food, and are prohibited from removing feces and other contaminants

before products are stamped with the purple USDA seal of approval. Some 206 meat inspectors who responded to a 2004 survey said that "there were weekly or monthly instances when they did not take direct action against animals feces, vomit, metal shards, or other contamination because of the new rules." It has also become common knowledge that seafood is contaminated by high levels of polychlorinated biphenyls (PCBs) caused by industrial waste run-off and dumping in our water systems. Some PCBs have dioxin-like properties (dioxin is one of the most toxic man-made chemicals), some act like hormones and others function as nerve poisons. They cause cancer, liver disease, birth defects and other serious diseases (Swami '06: 9 -10).

In 2000 the Centers for Disease Control and Prevention (CDC) and the Animal Health Institute estimated that 50 million pounds of **antibiotics** were produced annually in the United States. Of that 18 million pounds, 36 percent were antibiotics used in livestock feed. In 2001, a study appeared in the New England Journal of Medicine reporting that antibiotic-resistant bacteria had been found in supermarket samples of ground chicken, beef, turkey, and pork. Two additional studies found antibiotic-resistant bacteria in chicken and pork. Meanwhile, European scientists were finding high levels of antibiotics in streams and drinking water. They traced this discovery to the use of antibiotics in agriculture. These findings have prompted leading infectious disease specialists to urge a ban on routine use of low-dose antibiotics simply to aid animal growth. They argue that public health could be compromised if the practice leads to new disease-causing bacteria that no existing antibiotic can treat. Sweden adopted such a ban in 1986, Denmark followed in 2000. The entire European Union agreed to ban the routine use of antibiotics in animal feed starting in 2006. Individual companies have cut or eliminated use of antibiotics to promote animal growth. For example, in 2005 McDonald's announced that their poultry suppliers worldwide could no longer promote growth with antibiotics used in human medicine. Several leading American chicken growers have almost completely ended antibiotic use. And the U.S. Food and Drug Administration is considering new regulations to reduce antibiotic use in livestock feed (Huffnagle '07: 58, 59, 56, 57). After many years of concern, in 2012 the FDA declared an end to the non-medicinal use of antibiotics in livestock feed. Antibiotics in livestock feed has been known to increase a 200 lb. hog's weight by 30 lbs., but the meat and dairy industries have produced more than the market can bear since the 1960s. However antibiotics have been found to contaminate meat and water and this increases the hazards of antibiotic resistance for humans. The use of antibiotics in livestock must be limited to the treatment of a bacterial infection individually diagnosed, as by a veterinarian. The animals must be withheld from the market, for the specified time it takes for the antibiotic to be fully excreted. Farm Animal Medicine and Surgery: For Small Animal Veterinarians, published in print and online in pdf, by Dr. Graham Donaldson in the United Kingdom in 2013, provides a readily accessible comprehensive resource for the diagnosis and treatment of diseases withholding livestock from the market.

Chemical farms are in production on about 930 million acres in the United States and 3.8 billion acres globally – the vast majority of all agricultural land in the world – while organic farming practices are in use on approximately 4 million acres in the United States and 30.4 million acres globally (Rodale '10' 47, 138). There has been a six-fold increase in the amount of synthetic fertilizer used since 1945 (synthetic fertilizers are now an 8 billion dollar industry), and the seventeen-fold increase in the use of pesticides for the same period (Schwenke '91: 4). World pesticide expenditures totaled more than $35.8 billion in 2006 and more than $39.4 billion in 2007. Pesticides accounted for 3.1 percent, $7.3 billion of $237.8 billion total expenditure in US agriculture in 2006 and 2.8 percent, $7.95 billion of $283.5 in 2007 (Grube *et al* '11). Chemical weed-killers cost $15 or more an acre, slug killer and insect pesticides cost another $10 an acre (Logsdon '94: 155). Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and

the Federal Food, Drug, and Cosmetic Act (FFDCA), the U.S. Environmental Protection Agency (EPA), in cooperation with states and other agencies, such as the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA), are responsible for regulating the production and use of pesticides in the US (Grube *et al* '11).

Chemically grown vegetables may be eaten for food, but they cannot be used as medicine (Fukuoka '77.100). In 1997 a panel of international cancer experts evaluated over 70 sites and concluded it was not aware of any definitive evidence to suggest that synthetic pesticides contribute significantly to overall cancer mortality. Other potential environmental causes of cancer being investigated include infectious agents, maternal diet during pregnancy, ultraviolet and ionizing radiation, certain medications, food additives, tobacco, alcohol, heavy metals and air pollution. Federal and state governments regulate pesticides. These regulations require that compounds go through over 120 separate tests before they can be registered for use. A panel of cancer experts including members of the American Cancer Society concluded in 1997 that a diet rich in fruits and vegetables is important in the reduction of cancer risk. The Agricultural Health Study that appears in the May 1, 2003 issue of the American Journal of Epidemiology found that only a few pesticides showed evidence of a possible association with prostate cancer. Methyl bromide was linked to the risk of prostate cancer, while exposure to six other pesticides was associated with an increased risk of prostate cancer only among men with a family history of the disease – chlorphyrifos, coumaphos, fonofos, phorate, permetrhin and butylate. Risks were two to four times higher than among men who were not exposed to methyl bromide. The most consistent risk factors associated with prostate cancer are age, family history and African-American ethnicity. Hormonal factors and high levels of animal fat and red meat in the diet are also suspected risk factors. Several previous occupational studies have linked farming to prostate cancer risk, however, the variety of environmental exposures in the farming community such as pesticides, engine exhausts, solvents, dusts, animal viruses, fertilizers, fuels and specific microbes have made it difficult for researchers (Mooney '07: 29-40).

Since 1998, when "Roundup Ready" GMO seeds were first introduced 91 percent of all soybeans, 85 percent of all corn, and 88 percent of all cotton in the United States are grown from GMO seeds. These plants are exposed to heavy applications of the herbicide and survive. Before Roundup Ready soybeans were on the market the tolerance for Roundup was 3 ppm. Soybean seeds were meeting that requirement. By the time Roundup Ready soybeans showed up at the marketplace, they had concentrations up to 20 ppm, indicating that farmers upped the application rate since it wouldn't kill the plants. So Monsanto went to the EPA and asked to have the tolerance raised. The tolerance was raised not only in the US but in Australia and other countries where substantial amounts of Roundup Ready soybeans were being grown, but not in the European Union, which has still banned GMOs. GMO products do not need to be labeled as containing GMOs and should be assumed to be in everything not labeled organic or non-GMO (Rodale '10: 33).

For countless centuries plant breeders have sought to alter the characteristics of plants in order to create desired effects. But they have been limited to working with characteristics that were already present in the species. In genetic engineering genes are usually taken from one species and then inserted into another species in an attempt to transfer a desired trait. The first large scale commercial plantings of genetically engineered crops tool place in 1996 after they were approved by the FDA in 1993. The five top five biotech companies - Monsanto, Astra-Zeneca, DuPont, Novartis and Aventis, account for nearly 100 percent of the market in genetically engineered seeds. They also account for 60 percent of the world pesticide market. And, thanks to a flurry of recent acquisitions, they now own 23 percent of the commercial seed market.

Almost 80 percent of the world's GMO crops have been modified to tolerate large quantities of herbicide, namely Roundup, The other 20 percent have been engineered to produce pesticides in every cell of the plants throughout their entire life cycle. Not too long ago a species of potato was developed that required no pesticides of any sort to protect it from insects, but this potato was so loaded with poisons it could have killed a full-grown adult if eaten in normal quantities; hence, it was withdrawn from the market. In a similar vein a strain of celery was produced that was highly insect resistant. This celery contained more than ten times the level of a well-known carcinogen present in "normal" strains caused skin irritation and many of the people who handled the celery developed skin rashes (Friedberg '92: 55-57).

The Roundup patent expired in 2000 but farmers who grow Monsanto's Roundup Ready crops are required to sign a contract that requires them to buy only Monsanto's brand of herbicide. The FDA has tripled the residue that can remain on the crop. The global area of GM food grew nearly 25-fold in the three years after 1996, the first year of large-scale commercialization. Yet this enormous growth took place almost entirely in only three countries who by 1999 accounted for 99 percent of the world's genetically modified crops - the United States by itself accounted for 72 percent of the global area. Argentina was responsible for another 17 percent and Canada weighed in with another 10 percent. By 1999 nearly 100 million acres of GM crops were planted worldwide, more than 70 million of them in the US. Two thirds of foods for sale in US grocery stores contain GM ingredients. Soy and corn are so widely disseminated in processed foods. (Soy oil accounts for 80 percent of all vegetable oil consumed in the US, and various forms of corn syrup are the most widely used sweeteners). Genetically altered foods are not labeled in the US so consumers have been eating increasing amounts of GMO ingredients without even knowing it. By 2000, more than half of the American soybean and cotton crops and one-third of the corn crop were GM. Much of the Canadian canola (rapeseed) crop was also GM. For this rapid change to have occurred with a minimum of resistance from consumers, the FDA had to insist that GM foods not be labeled. Polls have consistently found that 80 to 95 percent of the American public wants genetically engineered food to be labeled (Robbins '01: 306, 307, 309, 311-313, 315, 358, 343). It should not be difficult for people who do not want to consume GM products to identify GM products.

To date no insurance company has been willing to insure the biotech industry. In our society insurance is the litmus test for safety. If the insurance industry isn't willing to bet its money on the safety of a product or technology, the risks are too high for them to take the gamble. There is today no insurance whatsoever against the kinds of catastrophic losses and tragedies that could ensure form introducing transgenic organisms into the environment and into the human food chain. In 1999 the EU announced its governments had drawn up a five-point Emergency Response Plan to cope if GM plants result in widespread illness or the death of wildlife. In France a band of 120 farmers broke into a storage facility of the biotech company Novartis and destroyed 30 tons of GM corn. In the US, Germany and the Netherlands GM crops have been destroyed by angry citizens. In 1999 the seven largest grocery chains in six European countries, Tesco, Safeway, Sainsbury's Iceland, Marks & Spencer, the Co-op and Waitrose, made a public commitment to go GMO free. In December 1999 a statement was posted to the cafeteria of the Monsanto Corporations United Kingdom headquarters in High Wycombe, England – In response to concerns raised by our customers…we have decided to remove, as far as is practicable, genetically modified soy and maize from all food products served in our restaurant. We will continue to work with our suppliers to replace GM (genetically modified) soy and maize with non-GM ingredients… We have taken the above steps to ensure that you, the consumer, can feel confident in the food we serve. African Civil Society groups, from more than 45 African countries, participating in the World Summit on Sustainable Development in 2002, joined hands

with the Zambian and Zimbabwean governments and their people in rejecting GM contaminated food for our starving brothers and sisters.

The American Academy of Environmental Medicine has called for an immediate "moratorium on genetically modified food" citing serious health risks associated with GM food consumption including infertility, immune dysregulation, accelerated aging, dysregulation of genes associated with cholesterol synthesis, insulin regulation, cell signaling, and protein formation, and changes in the liver. GM foods not only poison consumer by fostering negligent overuse of pesticides by farmers but some GM crops are designed to produce pesticides of their own. In 2000 insect resistant crops made up roughly a quarter of the nearly 100 million acres planted in transgenic worldwide, the other three-quarters of worldwide transgenic acreage were planted in herbicide resistant, mostly Roundup Ready varieties. Insect resistant crops contain a gene from a naturally occurring soil organism, *Bacillus thuringiensis* (commonly known as Bt). By transferring the gene responsible for making Bt, a natural pesticide that kills many kinds of leaf-eating caterpillars – into corn and cotton – engineers have produced crops that are toxic to the European corn borer and the cotton bollworm. Every cell of the plant contains the Bt gene and produces the Bt toxin. Caterpillars that nibble, die. Ladybugs who fed on aphids who had been eating potatoes genetically engineered to be insect-resistant by incorporating the Bt gene, laid fewer eggs and lived only half as long. Monarch butterflies that fed on milkweed leaves that had been contaminated with pollen from Bt corn died. People who are eating Bt crops are exposed to unprecedented doses of the Bt toxin, that may have decimated honey bee populations.

Seeds of today are not like the seeds farmers have used for thousands of years. Billions of dollars were spent to develop these seeds, yet the government required absolutely no health and safety testing before the seeds were planted. When farmers purchased GMO seed, they sign contracts prohibiting them from saving seeds produced by this year's crop to pant next year. The seeds are protected by a patent which requires farmers to buy new seeds (at higher prices). GMO-seed companies also charge more for their seeds than standard hybrid ones. They are referred to as "improved" or "better" seeds by farmers and, even more enthusiastically, by investors. By choosing this expense, farmers commit to paying more for seeds each year. All creatures are programmed from birth to reproduce, and reproduction happens with sex, even in plants. GMOs are like a giant pandemic of sexually transmitted disease. Pollen from these plants drift on the wind into non-GMO fields and do what comes naturally - procreate. A perfectly good organic field becomes contaminated. Chemical companies – Monsanto is renowned for this – have claimed that farmers who saved seeds from GMO crops stole their "intellectual property" and sued them for damages, in some cases even when the farmer swore he never planted them in the first place. In recent years, Monsanto has filed at least 100 lawsuits around the country related to this "theft". "Terminator seed" technology is prohibited. Terminator seeds were GMOs that become infertile after 1 year. Loss of sex is almost always followed by swift extinction. Gardeners want watermelons with seeds and plant breeders who don't try to patent God's creation and have more idealistic objectives of plant breeding than Roundup resistance, such as yield, flavor and nutrition. Taking into consideration corn produced for ethanol it is easy to imagine how these airborne genetic material from GM, or other inferior crop species, could ruin food quality for everyone.

Biotechnology is regulated **Convention on Biological Diversity** (CBD). Whether or not the United States is party to the CBD US exports may be rejected because they have been contaminated by transgenic organisms crops. Essentially the monopolistic tendencies of the North American biotechnology industry has encountered persistent legal opposition from the CBD of 1992 and its protocols of 2000 and the protocol of 2010 aims to share the benefits of

biotechnology equitably. Art. 8(g) of the Convention on Biological Diversity (CBD) of 1992 aims to regulate the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health: Art. 19 of the CBD tires of waiting for the benefits of biotechnology to be shared and calls for a protocol to provide for the safe transfer, handling and use of any living modified organisms resulting from biotechnology that may have adverse affect on the sustainable use of biological diversity. Art. 24(2) of the Cartagena Protocol on Biosafety to the CBD of 2000 encourages non-Parties contribute appropriate information to the Biosafety Clearing-House on living modified organisms released in, or moved into or out of, areas within their national jurisdictions. Art. 25 allows Parties to penalize the illegal transboundary movement of living modified organisms; the cost of repatriation or destruction is paid by the country of origin. The Nagoyo Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising form the Their Utilization to the CBD of 2010. The objective of this Protocol is the fair and equitable sharing of the benefits arising from the utilization of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding, thereby contributing to the conservation of biological diversity and the sustainable use of its components. Art. 6(2)(e) and Art. 17(2) provide, evidence of the decision to grant prior informed consent be made available to the Access and Benefit-sharing Clearing-House and shall constitute an internationally recognized certificate of compliance, equal to non-parties under Art. 24.

III. Anatomy and Physiology

A. Digestive Tract

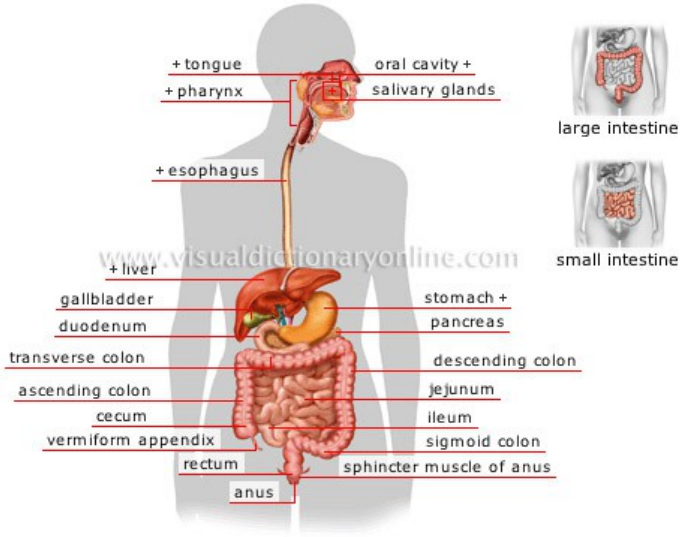
There are four stages of food processing in the body: ingestion, digestion, absorption, and elimination. **Digestion** includes six activities: ingestion, propulsion, mechanical or physical digestion, chemical digestion, absorption, and defecation. Digestion is important for breaking down food into nutrients, which the body uses for energy, growth, and cell repair. Food and drink must be changed into smaller molecules of nutrients before the blood absorbs them and carries them to cells throughout the body. Digestion involves breaking down large food molecules into water-soluble molecules that can be passed into the blood and transported to the body's organs. For instance, carbohydrates are broken down into glucose, proteins into amino acids, and fats into fatty acids and glycerol (Enders '15). A typical adult human in the United States imbibes 2 liters of fluid per day, to which is added 1 liter of saliva; 2 liters of gastric juice; 1 liter of bile; 2 liters of pancreatic juice; and 1 liter of intestinal secretions. About one liter of urine is excreted from the bloodstream autonomously by the kidney and urinary tract daily (Tanagho '88: 3-5). The 35 million glands lining the walls of the stomach secrete up to 80fl oz (3.5l) of gastric juice (mainly hydrochloric acid) per day in order to prepare food for entry into the duodenum – the first part of the small intestine. Of the 9 liters of fluid presented to the intestine, less than 200 gm of stool are excreted per day, of which 65 to 85% is water. Jejunal absorption of water amounts to 3 to 5 liters/ day, ileal absorption 2 to 4 liters/day. 75% of bile salts are reabsorbed in the ileum. The colon normally absorbs 1 to 2 liters/day but is capable of absorbing almost 6 liters/day (Crawford ’94: 790).

Smooth muscle is not under conscious control. Under the microscope it looks very different from the striated muscles over which we have conscious control. The microscopic structure of smooth muscles resembles an organic network, and it moves in mellifluous waves. Blood

vessels and digestive organs are surrounded by smooth muscle tissue. Smooth muscle tissue slackens in response to emotions such as embarrassment causing the blood capillaries in the skin of the face to dilate. In many people, stress has the opposite effect, causing the muscles surrounding the blood vessels to contract, restricting the flow of blood. This can lead to high blood pressure. The gut is covered by no fewer than three coats of smooth muscle tissue. This is incredibly supple. The enteric nervous system controls all processes that take place in the digestive system, and it is extraordinarily autonomous. If the connection between the enteric nervous system and the brain is severed, the digestive tract carries blithely on as if nothing has happened. This property is unique to the enteric nervous system, and is found nowhere else in the human body (Enders '15: 79-80). Higher animals develop from three tubes. The first tube runs right through with a knot in the middle, this is the cardiovascular system. The second tube develops more or less parallel to the first, forms a bubble that floats to the top, this is the nervous system. The third tube runs from end to end, this is our intestinal tube. It grows buds that that bulge out farther and farther into the right and left. These buds will later develop into lungs. A little bit lower down, the intestinal tube bulges again and the liber begins to develop. It also forms the gall bladder and pancreas. The tube itself beings to grow increasingly clever. It is involved in the complex construction of the mouth, creates the esophagus, with its ability to move and develops a little stomach pouch to store food for a couple of hours. And, last but not least, the intestinal tube completes the eponymous intestine or gut (Enders '15: 10).

Digestive Tract

Credit: Wikipedia



The **digestive system** comprises the mouth, esophagus, stomach, pancreas, liver, gallbladder, small intestine, large intestine and rectum. The digestive system involves "hollow" organs and "solid" organs. Food travels through the hollow organs — mouth, esophagus, stomach, small intestine, large intestine, and anus. The solid organs — pancreas, liver, and gallbladder — add various products into the mix. The gastrointestinal tract (also called the alimentary canal) is around 8 meters (26 feet) long. The bolus takes five to ten seconds to reach the esophagus from the mouth. On the arrival of the bolus the esophagus widens to let it pass, closing again behind it. It is known as propulsive peristalsis. The top third of the esophagus is surrounded by striated muscle. The unconscious smooth muscles begin at the level of the small hollow at the top the breastbone. The esophagus is sealed at the bottom end by a ring-shaped sphincter muscle.

Taking its cue from the peristaltic motion above, that muscle relaxes for eight seconds, allowing the bolus to plop unhindered into the stomach. The muscle then closes again, and normal breathing service resumes up in the pharynx. The first part of the intestinal tract is the small intestine made up of the duodenum, about 10 in (25 cm) long, the jejunum, about 8 ft (2.4 m) long and the ileum, about 12 ft (3.6 m) long. Next is the large intestine, which although wider than the small intestine, is considerably shorter – only about 5ft (1.5 m) long in total. The large intestine is divided into the ascending, transverse, descending and sigmoid colons. Any material that the intestines cannot process, such as dead bacteria, lubricating mucus, and rough, fibrous material that cannot be absorbed, is passed through the anus and out of the body (Gillanders '95: 42). The liver is the largest organ in the body and in an adult weighs between 2.6 and 4 lb (1.2 and 1.8 kg) and is profused with 25% of the body's blood supply. It lies in the right side of the upper abdomen, and stores bile in the gallbladder. The pancreas is about 6 in (15 cm) long and lies behind the stomach and in front of the spine. It performs two important functions: it produces blood sugar, which is fuel for the cells, and it produces insulin, which regulates the level of blood sugar in the body (Gillanders '95: 42).

Digestion begins even before the food enters the mouth. The smell, or even the thought of food, starts the production of saliva by the salivary glands. Once the food is inside the mouth, it is moistened by saliva, and the teeth and tongue begin the process of mechanical digestion. Saliva contains an enzyme called salivary amylase, which breaks down starch. Saliva also contains mucus that helps ease the passage of food through the digestive system. Once chewing (mastication) and amylase digestion are complete, the food will have become a small round blob, which is known as a **bolus**. After swallowing, the bolus enters the esophagus and is moved down to the stomach through a process called peristalsis. **Peristalsis** is the slow contraction of smooth muscles around the pipes of the digestive system. Slow waves of contraction run along the gut, pushing the bolus along in the right direction — away from the mouth and toward the anus. The bolus enters the stomach through a muscular valve at the top called the cardiac sphincter. This sphincter controls how much food enters the stomach and when. The stomach contains gastric juice, which contains mostly, Hydrochloric acid — an acid that is strong enough to dissolve razor blades and Pepsin — an enzyme that breaks down proteins. Both of these chemicals could potentially harm the lining of the stomach, so it produces a slimy layer to protect itself from damage. In the stomach, peristalsis continues, which helps to mix the food with the gastric juices. Not many compounds are absorbed into the blood from the stomach; exceptions to this include water, alcohol, and non-steroidal anti-inflammatory drugs (NSAIDs). After 1–2 hours in the stomach, the food is a thick paste, referred to as chyme. It leaves the stomach through the pyloric sphincter at the bottom of the stomach.

The duodenum is the first section of the small intestine. Here, the chyme mixes with enzymes from the pancreas, bile from the liver, and intestinal juice: Bile — produced by the liver, it helps break down fats and is stored in the gallbladder. Pancreatic juice — contains a cocktail of enzymes, including trypsinogen, elastase, and amylase. Intestinal juice — this fluid activates some of the enzymes in the pancreatic juice. It also contains other enzymes, mucus, and hormones. The food continues its journey through the remaining parts of the small intestine — the jejunum and ileum — being gradually digested as it goes. Once it is fully broken down, it is absorbed into the blood. In humans, the vast majority of nutrients are absorbed in the small intestine. Tiny finger-like projections called villi stick out from the walls of the duodenum and increase its surface area. **Villi** maximize the amount of nutrients that can be absorbed. The surface area is further increased by microvilli, which are even smaller projections that come from the cells of the intestine's epithelium (lining).

Also called the colon and large bowel, the **large intestine** is 1.5 meters (5 feet) in length. Although it is shorter than the small intestine, it is thicker in diameter. In the large intestine, water and minerals are absorbed into the blood. Food travels through this region much slower to allow fermentation by gut bacteria. The large intestine absorbs any products produced by bacterial activity, such as vitamin K, vitamin B12, thiamine, and riboflavin. The large intestine is split into sections: The **ascending colon** — this includes the cecum (a pouch that joins onto the ileum) and the appendix (another small pouch. Its function is unclear, but it may play a role in maintaining gut bacteria). The **transverse colon** — this section crosse the abdomen. **The descending colon** – this section has a dense population of gut bacteria and is used to store feces. The **sigmoid** (S-shaped) **colon** – has muscular walls that help push feces into the rectum. Any waste left over that the body cannot use is moved to the rectum and excreted through the **anus** during **defecation**. This may occur multiple times in a single day, or once every few days. Stretch receptors in the wall of the rectum detect when the chamber is full and stimulate the desire to defecate. If defecation is delayed, the feces can be moved back into the colon where water is absorbed back into the body. If defecation is postponed for an extended period, more water is removed, the stool becomes hard, and the individual may become constipated.

Different components of the diet are broken down in various ways: Protein — digested by three enzymes called pepsin (in the stomach), trypsin, and chymotrypsin (in the duodenum, secreted by the pancreas). Fat — lingual lipase begins fat digestion in the mouth. However, most fat is broken down in the small intestine by pancreatic lipase. Bile also helps in the process of breaking down fats. Carbohydrate — salivary and pancreatic amylase break down starches into individual glucose units. Lactase breaks down lactose, the sugar in milk. Sucrase breaks down sucrose (table sugar or cane sugar). DNA and RNA — broken down by deoxyribonuclease (DNase) and ribonuclease (RNase) produced by the pancreas. Certain essential, complex molecules would be ruined if they mixed with digestive juices in the stomach. For instance, vitamin B12 is very sensitive to acid and, if it was broken down into its parts, it could not fulfill its role in the body. In these cases, non-destructive digestion takes place. For vitamin B12, a chemical in saliva called haptocorrin binds to and protects the molecule. In the duodenum, the bond is split, and B12 attaches to intrinsic factor. Then, once in the ileum, special receptors carry the two bound molecules into the blood.

Digestion is a complex process that requires different organs to make moves at the right time. For instance, the right enzymes need to be squirted into the right place at the right time and in the right amounts. To help organize this system, a range of hormones are involved, these include: **Gastrin** — released in the stomach, this hormone stimulates the production of hydrochloric acid and pepsinogen (an inactive form of pepsin). Gastrin is produced in response to the arrival of food in the stomach. Acidic pH levels reduce the levels of gastrin. **Secretin** — stimulates bicarbonate secretion to neutralize acid in the duodenum. **Cholecystokinin (CCK)** — also found in the duodenum, this hormone stimulates the pancreas to release enzymes and the gallbladder to release bile. **Gastric inhibitory peptide** — decreases the churning of the stomach and reduces the speed that food empties from the stomach. It also triggers the secretion of insulin. **Motilin** — stimulates the production of pepsin and speeds up peristalsis.

Feces are three-quarters water. Around 3 ½ ounces (100 milliliters) of fluid are lost everyday. During a passage though the digestive system, some 10 quarts (9.8 liters) are reabsorbed. Whatever fluid is left in the feces belongs there. This optimal water content makes feces soft enough to ensure metabolic waste products an be transported out of the body safely. A third of the solid components are bacteria, that have died or otherwise are exiting the digestive system. Another third is made up of indigestible vegetable fiber. The more fruit and vegetables eaten,

the more feces excreted per bowel movement. Increasing the proportion of that food group can raise the weight of a bowel movement from the average 3 ½ to 7 ounces (100 to 200 grams) to as much as 178 or 18 ounces (500 grams) per day. The remaining third is made up of substances the body wants to get rid of, such as the remains of medicines, food coloring or cholesterol (Enders '15: 70, 71). Depending on the individual and the type of food they have eaten, digestion — from mouth to bathroom — takes 24–72 hours. Poop or **feces i**s the remains of food that could not be absorbed by the small intestine that has been rotted down by bacteria in the large intestine. It contains bacteria, and some small amounts of metabolic waste products, such as bile and bilirubin (from the breakdown of blood). Feces can vary in color widely and can be different consistencies, from watery to solid (Newman '18). Constipation is discomforting but is not considered life-threatening and is easily treated with enema; diarrhea on the other hand can be deadly, cholera untreated with Oral Rehydration Salts (ORS) has a 50% fatality rate. Diarrhea is perceived as the body's production of more than 4/5 cups (0.2 L) of stool a day. Low-volume, painful, bloody diarrhea is known as dysentery (Crawford '94: 790).

The **natural color** of human feces ranges from brown to yellowish-brown, even when not eating anything of these colors. The same is true of urine, it always tends towards yellow. This is due to freshly manufactured blood. The body creates about 2.4 million new blood corpuscles a day. But the same number are broken down every day too. In that process, the red pigment they contain is first turned green, then yellow. The same process occurs during the various stages of bruise on the skin. A small portion of this yellow pigment is excreted in the urine. Most of it, though, passes through the liver and into the gut. There, bacteria change its color once again – this time turning it brown. Light brown to yellow feces can be the result of a harmless disorder, affecting about 8 percent of the world's population, called Gilbert's syndrome (or Gilbert-Meulengracht syndrome). In this condition, of the enzymes involved in the breakdown of blood works at only 30 percent of its normal efficiency. This means less pigment finds its way to the gut. This enzyme defect is not harmful. The only effect is a reduced tolerance for acetaminophen, that should be avoided. Anther possible cause of yellowish feces is problems with bacteria in the gut. If they are not working as they should, the familiar brown pigment will not be produced. Antibiotics or diarrhea can cause such an alteration in fecal color. Light brown to gray feces can result if the connection between the liver and the gut is blocked by a kink in the tubes or by pressure (usually behind the gall bladder), no blood pigment an make it into the feces. Blocked connections are never good, and those who notice a gray tint to their fees should consult their doctor. Black or red feces is caused by black congealed blood or red fresh blood. The color is not caused by the pigment, but by the presence of entire blood corpuscles. For those with hemorrhoids, a small amount of bright red blood in the stool is not reason to worry. However, anything darker in color than fresh, bright red blood should be checked by a doctor, unless the reddish color is caused by eating a large amount of beetroot (Enders '15: 71-73).

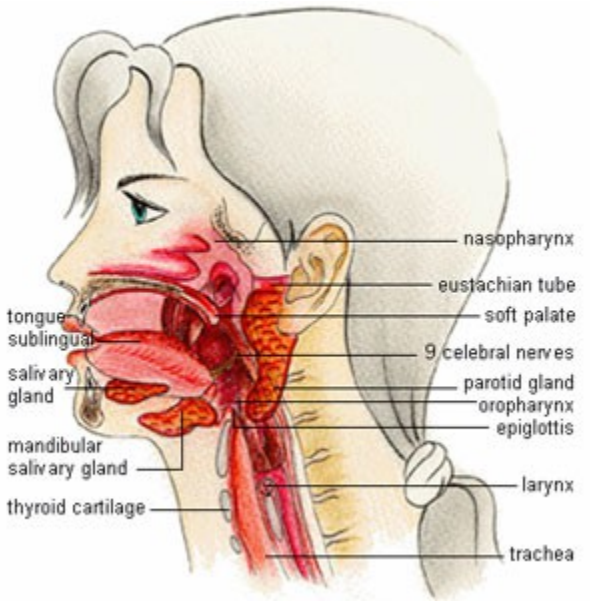
The **Bristol stool scale** was first published in 1997 by Dr. Ken Heaton at the University of Bristol in the United Kingdom. The scale classifies the consistency of feces into seven groups. A healthy digestive system, producing fees with the optimum water content, will produce types 3 or 4. The other types are less than ideal. Type 1 separate hard lumps, like nuts (hard to pass. Type 2 sausage shaped, but lumpy. Type 3 Like a sausage but with cracks on its surface. Type 4 like a sausage or snake, smooth and soft. Type 5 Soft blobs with clear-cut edges (passed easily). Type 6 fluffy pieces with ragged edges, a mushy stool. Type 7 watery, no solid pieces, entirely liquid. The type a person's feces belong to can be an indication of how long indigestible particles take to pass through their gut. Type 1 digestive remains take around one hundred ours t pass through the system (constipation). In Type 7 they pass through in just ten hours (diarrhea). Type 4 is considered ideal, because it has the optimum ratio between fluid and solid content.

Those who find types 3 or 4 may also want to observe how quickly their feces sink in water. Ideally, they should not plummet straight to the bottom, as this would indicate the possibility that they still contain nutrients that have not been digested properly. Feces that sink slowly contain bubbles of gas that keep them afloat in water. These gas bubbles are produced by gut bacteria that mostly perform useful services, so this is a good sign, as long as it is not accompanied by flatulence (Enders '15: 73-75).

1. Mouth

Like most other mammals, humans have **two sets of teeth**, the primary and the permanent. Humans have twenty baby (primary) teeth and thirty-two adult (permanent) teeth. The first set of teeth are acquired during the first year of life, and begin to lose them, prior to replacement with the permanent set, from 6 years of age onward (Lewis & Elvin-Lewis '77: 226). **Tooth eruption** in humans is a process in tooth development in which the teeth enter the mouth and become visible. There are 20 primary teeth, 10 in each jaw. By the age of 13, most children have 28 of their permanent teeth (4 central and 4 lateral incisors, 8 premolars, 4 canines and 8 molars. The last teeth to appear are the third molars or "wisdom teeth" at around the ages 16 to 21 years. Between the ages of 12 and 18 years and before orthodontic treatment, the third molars, which usually emerge during the late teen years, should be evaluated by radiographs (Smith '97: 13, 153). By age 21, all 32 of the permanent teeth have usually appeared (Jerome '00: 369, 374) (Sanders '12 : 8).

Diagram of Oral Cavity and Salivary Glands



Credit: ConMedia

The **oral cavity** contains the teeth and its supporting structures, the gums (gingiva), surrounded by the periodontium and alveolar bone of the jaw. The roof of the mouth is known as the hard palate and posterior to this the soft palate; these and the inner tissues of the cheek are lines with oral mucosa. The tongue (having taste buds on its surface) is a muscle that aids in talking, tasting and swallowing (Lewis & Elvin-Lewis '77: 226). There are three pairs of major **salivary glands**: the parotid, submandibular, and the sublingual. The parotid glands are largest. They are located in front of and below each ear and are the ones involved in the viral disease infectious

parotitis, commonly referred to as mumps. Their main duct opens into the mouth on the wall of either cheek opposite the upper second molars. The submandibular glands are the size of walnuts. They are situated beneath the back of the tongue. The almond sized sublingual glands are in the mucosa of the floor of the mouth. The spurts of saliva that sometimes erupt from the openings underneath the tongue and on the cheek near the upper molars can help you locate the glands. These glands secret about 3 pints of liquid a day (Smith '97: 10).

The **teeth** and the structures that support and supply nutrients to them (the gingival tissues, the dentogingival junction, periodontal ligament, and the alveolar bone) are composed of different types of tissues. The soft pink-red lining that covers everything but the teeth in your mouth is oral mucosa. *Alveolar mucosa* covers the part of the jaw into which the teeth sink. *Gingival mucosa* covers the roots of the teeth. In most persons the gingival tissues are well keratinized, this makes them resistant to bacteria, chemicals, heat and injuries. Teeth are composed of four dental tissues – cementum, dentin, and enamel are hard or calcified. Pulp is soft or non-calcified. The visible part of the tooth is the crown. It is covered with enamel, the hardest substance the body produces. Because it contains no living cells, enamel can neither repair nor replenish itself. At the core of the tooth are the dentin and the pulp. **Dentin** (ivory) is a bonelike tissue that makes up the largest portion of the tooth. It is pale yellow and highly calcified. It is harder than cementum but not as durable or brittle as enamel. Dentin surround the pulp, except at the apical foramen, the opening at the root canals of the tooth, where blood vessels and nerves enter. Dentin is formed in the dental pulp by the odontoblast cells. Dentin is manufactured continually throughout the life of the tooth. The root is the part of the tooth beneath the gums that is not visible. A tooth may have one or multiple roots, which are firmly anchored into sockets in the alveolar process. The roots are covered with cementum, a thin, pale-yellow layer of calcified connective tissue similar to bone but without the blood vessels and nerves. It forms slowly throughout life, and is attached to collagen fibers of the periodontal ligament, a tendonlike tissue surround the root. The mandible, the lower jaw, is the largest and strongest of the facial bones (Smith '97: 4, 5, 6, 7, 8, 9). Calcium phosphate **apatite** are inorganic compounds encountered in many different mineralized tissues, around the body in concentrations of 1.5% for calcium and 1.2% for phosphorus (Drouet '13).

There are four **salivary glands** in the mouth that produce about 2 – 3 pints (1 – 1.5 liters) of saliva a day. The parotid papillae, are two little nubs that are found in the same place in everyone's mouth, on the inside of the cheeks, opposite the upper molars, more or less in the middle. The other two points, the sublingual papillae, are beneath the tongue, just to the right and left of the lingual frenulum, the fold of skin connecting the tongue to the floor of the mouth. The papillae in the cheeks secrete saliva whenever it's needed right away, for example, when eating. The sublingual papillae are constant suppliers of saliva. Saliva is basically filtered blood. The salivary glands sieve the blood, keeping back the red blood cells, which are needed in our arteries, not in our mouth. But calcium, hormones, and some produces of the immune system enter the saliva from the blood. Saliva contains a pain-killer that is stronger than morphine, it is called opiorphin and was discovered in 2006. When chewing, saliva is produced, and with it more analgesic substances. Saliva protects the oral cavity not only from too much pain but also from too many bad bacteria. Mucins are proteins that form the main constituent of mucus. They are shot out of salivary glands to envelop teeth and gums in a protective mucin net. When bad bacteria are caught in the net antibacterial substances in saliva kill them off. When sleeping very little saliva is produced.(Enders '15: 21-24).

A ring of immune tissue encircles the entire throat, known as **Waldeyer's tonsillar ring**, it includes those lingual tonsils at the bottom of the circle; the palatine tonsils, at either side, and at

the top of the ring, where the ear, nose and throat areas meet, there is more such tissue. The entire collection of tissue in Waldeyer's ring makes up the tonsils. This who believe their tonsils have been entirely removed are not correct. The tonsils, that are often removed, rather than forming bumps, tend to form deep grooves, to increase surface area, known as crypts. Sometimes, too much foreign material gets caught in the crypts, leading to frequent infections. This is a side-effect of over-inquisitive tonsils. Lingual tonsils are nodules that investigate everything swallowed. They pick up tiny particles of anything eaten or drunken, or inhaled and draw them into the nodule. Inside, immune cells waits to receive training in how to deal with foreign substances. When swollen and infected, especially in children, this is known as adenoids. Before the age of seven the tonsils are still an important training camp for immune cells and removing them may lead to obesity. If the tongue and teeth have been excluded as a cause of bad breath, the next place to check is the tonsils. Sometimes, little white stones can be found hiding in the crypts, and these stones smell terrible. The little stones will eventually work their way out of their hiding places, with no permanent harm done. But with a little practice, they can also be squeezed out, that done, bad breath disappears instantaneously. Run a finger or a cotton bud over the tonsils and then sniff it, if it smells unpleasant, it is time to go hunting for tonsil stones. Ear, nose and throat doctors can also remove them. For more than thirty years, doctors have described cases of psoriasis patients whose skin condition improved or cleared up entirely following a tonsillectomy. In 2012 researchers from Iceland and the United States investigated the phenomenon. Twenty-nine psoriasis patients who also suffered sore throats were split into two groups. One group had their tonsils surgically removed, the other didn't. Thirteen of the fifteen detonsilized patients reported a signifiant long-term improvement in their skin, the other didn't. (Enders '15: 27-30).

In humans the **thyroid gland** adheres to, and is situated just in front of the trachea (and behind the larynx). The thyroid is a bilobed structure connected by an isthmus that extends across the ventral surface of the trachea below the larynx. In goiters, blood flow can increase markedly and this increased flow can produce an audible bruit over the gland. The thyroid-hormone producing cells, which are arranged in groups of follicles, have a powerful mechanism for concentrating iodine which is used for the synthesis of the thyroid hormone. The circulating hormones are thyroxine (T_4) 90%, tri-iodothyronine (T_3) 9% and reverse T_3 (rT_3). In the target tissues, T_3 is the active metabolite of T_4. The parafollicular cells are also in the thyroid, scattered between the thyroid follicles. They produce calcitonin. Hormones Secreted by the Thyroid Gland: Triiodothyronine (T3) is secreted by Thyroid epithelial cell is a more potent form of thyroid hormone that stimulates body oxygen and energy consumption, thereby increasing the basal metabolic rate, it stimulates RNA polymerase I and II, thereby promoting protein synthesis. Thyroxine (tetraiodothyronine)(T4) is secreted by Thyroid epithelial cells and is a less active form of thyroid hormone) that acts as a prohormone to triiodothyronine to stimulates body oxygen and energy consumption, thereby increasing the basal metabolic rate, it stimulates RNA polymerase I and II, thereby promoting protein synthesis. Calcitonin is secreted by the Parafollicular cell*s* to stimulate osteoblasts and thus bone construction. Inhibits Ca^{2+} release from bone, thereby reducing blood Ca^{2+}. The **parathyroid glands**, which are embedded in the thyroid, produce parathyroid hormone (parathormone; PTH). PTH plays an important part in the control of levels of calcium and phosphate in the blood. Parathyroid hormone (PTH) is secreted by the Parathyroid chief cell to produce calcium by stimulating Ca^{2+} release from bone, thereby increasing blood Ca^{2+}. Stimulates osteoclasts, thus breaking down bone. Stimulates Ca^{2+} reabsorption in kidney. Stimulates activated vitamin D production in kidney. Phosphate: Stimulates PO^{3-}_4 release from bones, thereby increasing blood PO^{3-}_4. Inhibits PO^{3-}_4 reabsorption in kidney, so more PO^{3-}_4 is excreted. Overall, small net drop in serum PO^{3-}_4. (Greenstein '94: 8).

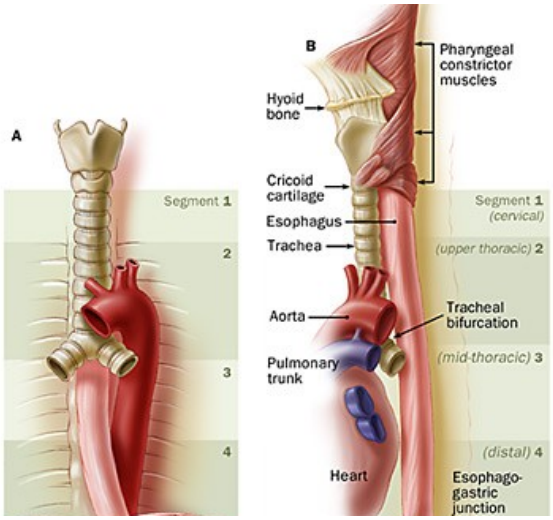
The most powerful muscles in the body are the **jaw** muscles and the most flexible striated muscle is the tongue. Working together they are incredible crunchers and nimble manipulators. Tooth enamel is the hardest substance produced in the body . It needs to be, whereas, the jaw can exert a pressure of up to 180 pounds (80 kilos) on each molar. The tongue lays an important part in mastication. When the food is sufficiently mushy it is ready for swallowing. The tongue rounds up about half an ounce (20 milliliters) of mush and presses it against the palate, the stage curtain of the esophagus. When the tongue presses against the esophagus, the swallowing reflex starts automatically. The ball of mush, known as the bolus, makes it way toward the pharyngeal area (Enders '15: 82-83). The velum (or soft palate) and the superior pharyngeal constrictor muscle are two formations responsible for closing the connections to the nose. The vocal chords are silenced and have to be closed. The epiglottis rises majestically, the entire base of the mouth is lowered, and a powerful wave pushes the bolus into the esophagus, washed down by copious amounts of saliva (Enders '15: 84).

2. Esophagus

The bolus takes five to ten seconds to reach the esophagus. On the arrival of the **bolus** the esophagus widens to let it pass, closing again behind it. This prevents anything from slipping back up the wrong way. This process is known as propulsive peristalsis. The top third of the esophagus is surrounded by striated muscle. The unconscious smooth muscles begin at the level of the small hollow at the top the breastbone. The esophagus is sealed at the bottom end by a ring-shaped sphincter muscle. Taking its cue from the peristaltic motion above, that muscle relaxes for eight seconds, allowing the bolus to plop unhindered into the stomach. The muscle then closes again, and normal breathing service resumes up in the pharynx. Unborn babies swallow up to one pint (half a liter) of amniotic fluid a day, if something goes wrong at this stage, no harm is done, since the fetus is completely surrounded by liquid and the lungs are full of it, the baby is unable to choke in the normal sense. Adults swallow somewhere between six hundred and two thousand times a day. Each act of swallowing involves more than twenty pairs of muscles. Despite this frequency and complexity things rarely go wrong. In older age there is a propensity for choking. The muscles that coordinate the process may no longer work quite so precisely. The superior pharyngeal constrictor muscle might not be quite the strict timekeeper it was in its youth (Enders ';15: 84-86).

Beyond the mouth, a 1-inch (2 centimeter) wide esophagus, or gullet, leads down from the throat, misses the top of the stomach, and passes into it somewhere at the side. The right-hand side of the stomach is much shorter than the left, which is why it curls up into a crescent-shaped, lopsided pouch. The reason for the **terminolateral connection** between the esophagus and stomach is that when walking normally abdominal muscles are tenses, doubling the pressure in the abdomen with every step. When laughing and coughing, the pressure increases by several times. Since the abdomen presses against the stomach from below it would be bad for the esophagus to dock directly onto the top end of the stomach. Connected as it is at the side, it has to deal with only a fraction of the pressure. Walking is possible after a heavy meal without having to burp every step. While a fit of laughter might result in losing a little control over the outer sphincter, few people have been known to vomit from laughing. A side-effect of this lateral connection is the so-called gastric bubble. This small bubble of air at the top of the stomach can be seen clearly on X-rays. Air rises vertically, after all, and does not search out a side exit. This bubble is the reason many people find they have to swallow a little air in order to burp. This swallowing motion moves the opening of the esophagus a little closer to the bubble and a burp escapes. Some muscle fibers run around the esophagus in a spiral pattern. They are the reason for its elasticity. It these fibers are extended lengthways, they constrict spirally, like a

telephone receiver cable. Bundles of fibers connect the esophagus to the spinal column. Sitting up straight and looking upwards stretches the esophagus along its length. This causes it to narrow, in turn allowing it to close more efficiently at each end, helping to prevent heartburn after a large meal (Enders '15: 33-34).



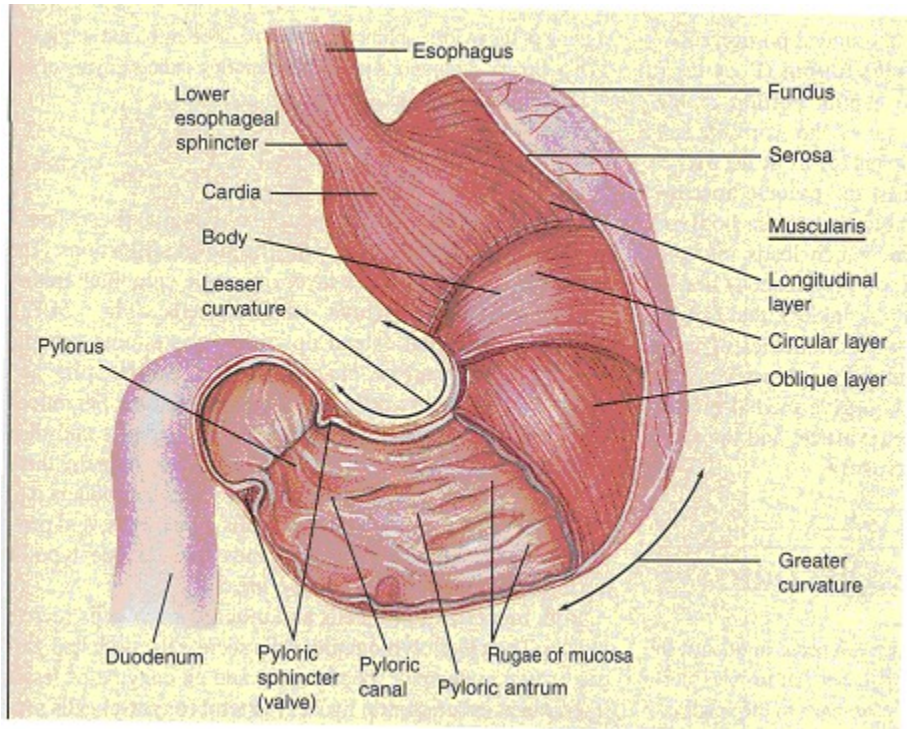
The **esophagus** is a muscular tube between the mouth and the stomach. The esophagus has a sphincter at either end. The esophageal sphincters are normally in a contracted state and relax when necessary. Most other muscles are relaxed normally and contract when necessary. The sphincters are designed to allow passage of esophageal contents in only one direction, from top to bottom (Newman ’11: 17). The esophagus is a hollow, highly distensible muscular tube that extends from the mouth at the pharynx, at about the level of the C-6 vertebra. Keeping with the structural organization of the gastrointestinal tract, the wall of the esophagus consists of mucosa, submucosa, mulcularis propria and an adventitia. The **mucosa** is comprised of a nonkeratinizing stratitifed squamous epithelial layer that overlies a lamina propria (submucosa). A small number of specialized cell types, such as melanocytes, endocrine cells and Langerhans’ cells are present in the deeper portion of the epithelial layer. Finger-like extensions of the lamina propria, termed “papillae” extend into the epithelial layer. The **muscularis mucosa** is a delicate layer of longitudinally oriented smooth muscle bundles. The **submucosa** consists of loose connective tissue containing blood vessels, a rich network of lymphatics, a sprinking of inflammatory cells, occasional lymphoid follicles, nerve fibers (including the ganglia of Meissner’s plexus) and submucosal glands. The **submucosal glands** are considered to be continuation of the minor salivary glands or the oropharynx and are scattered along the entire esophagus. The **muscularis mucosa**, similar to other portions of the gastrointestinal tract, consists of an inner circular and an outer longitudinal coat of smooth muscle with an intervening, well-developed myenteric plexus (Auerbach’s plexus). In sharp contrast to the rest of the gastrointestinal tract the esophagus is mostly devoid of a serosal coat (Crawford ’94: 755-756).

The functions of the esophagus is to conduct food and fluids from the pharynx to the stomach and to prevent reflux of gastric contents in to the esophagus. These functions require coordinated motor activity, a wave of peristaltic contraction in response to swallowing or to esophageal distention, relaxation of the LES in anticipation of the peristaltic wave, and closure of the LES after the swallowing reflex. The mechanisms governing this motor function are strikingly complex. Although many chemical agents (e.g. gastrin, acetylcholine, serotonin, prostaglandin $F_{2\alpha}$ motilin substance P, histamine, and pancreatic polypeptide) increase LES tone, their role in normal physiological function is uncertain. Coordinated motor function is critical to proper function of the esophagus; gravity alone is not sufficient to move food from the pharynx to the stomach (Crawford ’94: 761, 762).

3. Stomach

Swallowed food all ends up in the **stomach**, where it is mixed together with stomach acid – dilute hydrochloric acid – and some digestive enzymes. The 35 million glands lining the walls of the stomach secrete up to 80fl oz (3.5l) of gastric juice (mainly hydrochloric acid) per day in order to prepare food for entry into the duodenum – the first part of the small intestine. In the normal state, the stomach empties itself of most of a meal within 90 minutes (Newman '11: 18). The stomach sits much higher in the abdomen that thought. It begins just below the left nipple and ends below the bottom of the ribcage on the right. The heart and lungs sit on top of the stomach. Roemheld syndrome is when so much gas collects in the stomach that it presses up against the heart and the nerves in the gut, causing symptoms ranging from dizziness and discomfort, to anxiety, difficulty breathing and severe chest pain that feels like a heart attack. In the long term it is best that patients avoid food and alcohol, that leaves them bloated or flatulent. The stomach has a strange shape. One side is much longer than the other and so the entire organ has to bend double. That creates large folds inside it. When taking a drink of water, the liquid can flow straight down the shorter, right-hand side of the stomach to end up at the entrance of the small intestine. Food, on the other hand, plops against the larger side of the stomach. The digestive pouch separates the substances it still needs to work on to break them down, from the fluids that it can wave straight on through. The top part of the stomach is called the **fundus** or body, is a compliant reservoir that can allow a pretty large volume of food to remain in the stomach painlessly until it can be slowly emptied into the intestine (Newman '11: 18). The stomach is not simply lop-sided, rather it has two sides with different specializations. One side copes better with fluids, the other with solids (Enders '15: 35-37).

Stomach



Credit: National Institute for Public Health and Environment

The stomach is a glandular digestive and endocrine organ that is divided into four major anatomic regions. The **cardia** is the narrow portion of the stomach immediately distal to the **gastroesophageal junction**. The portion of the proximal stomach that extends above the level of the gastroesophageal junction is called the **fundus**, and the remainder of the stomach proximal to the angle along the lesser curve (incisuria angularis) is the **body** or corpus. The stomach distal to this angle is the **antrum**, demarcated from the duodenum by the **pyloric sphincter**. The surface of the stomach exhibits coarse **rugae**. These infolding of mucosa and submucosa extend longitudinally and are most prominent in the proximal stomach, flattening out when the stomach is distended. The delicate texture of the mucosa is punctuated by gastric "pits" leading to the gastric glands. The entire mucosal surface as well as the lining of the gastric pits is composed of surface "foveolar" cells (Crawford '94: 767).

The stomach has three main layers, the outer serosal coat, absent only along both curvatures and at the gastro-esophageal junction, a muscular coat those fibers run in three definite layers – outer longitudinal, middle circular fibers (most prominent at the pylorus where it forms the pyloric sphincter) and inner oblique coat (most prominent in the body); the inner lining is the mucous membrane. Especially in the body along the greater curvature, the mucosa is thrown up into folds called rugae, so that the surface area of the mucosa is very much greater than that of the muscular wall of the stomach. When the rugae are flattened by gastric distension, the mouths of innumerable gastric pits can be seen. Between three and seven glands open into each gastric pit. The neck cells are responsible for the replacement of surface epithelium, which has a turnover of 2-3 days. The mucous neck cells (goblet cells) are found most commonly around the cardia and in the antrum. The chief (or peptic) cells are situated mainly in the deeper parts of the glands and are readily identified by their prominent zymogen granules, which contain pepsinogen. The parietal (oxyntic) cells, which are mainly sited in the more superficial parts of the glands, contain intracellular canaliculi and secrete hydrochloric acid.

The secretion of **hydrochloric acid** has two functions (1) the hydrolysis of food and (2) the activation of pepsinogen that splits protein into polypeptides and peptones. Gastric juice undiluted by food has a pH of about 2.0 and this is sufficient to render gastric juice sterile. In the antrum, there are large numbers of pyloric glands, secreting mucus) and G cells. G cells secrete gastrin, of which the two major forms are little gastrin G17 and big gastrin G34 (the numbers indicate the umber of amino-acid residues in the peptide chain). G cells are also present in the proximal duodenum, mainly producing G34. The junction between antral and body mucosa may be visible but is more precisely drawn by measuring surface pH. Gastric ulcers mostly occur on or below this mucosal junction, which migrates with age, also associated gradual atrophic changes in the gastric mucosa. Gastric emptying depends on the contraction of the antrum, about 3% of gastric contents are released per minute, and emptying is completed in 1-4 hours, usually two hours, but fatty meals delay emptying (Jones et al '85: 70-74).

Mitoses are extremely common in this region because the entire gastric mucosal surface is totally replaced every 2 to 6 days. The cardiac glands in the gastric cardia are lined by mucinous cells indistinguishable from the neck cells of the gastric glands. The gastric (oxyntic) glands in the body and fundus are composed in the upper regions of mucous neck cells. The bases of the glands are a mixture of parietal cells and chief cells. Chief cells are responsible for the secretion of pepsinogen I and II in the proenxyme form. Pyloric (antral) glands are composed largely of mucous cells resembling those of the neck regions of the gastric glands. Scattered neuroendocrine cells are present along the glandular epithelial layer and are more abundant in the antral region. The process of gastric acid secretion is relevant to the later consideration of peptic ulcer disease. Gastrin is produced by the G cells in the antral, pyloric and duodenal mucosa.

Histamine is a potent acid secretagogue. The gastric mucosa, where intraluminal concentration of hydrogen ion is 3 million times greater than that of blood and tissue, is protected from auto-digestion by a "mucosal barrier". Mucus secreted in the stomach is impermeable to large molecules such as pepsin, bicarbonate secretion creates a relatively alkaline microenvironment immediately adjacent to the cell surface. Gastric bicarbonate secretion is about 5 to 10% of maximal acid secretion. Mucosal epithelial cells are bound by intercellular tight junctions, providing a barrier to the back-diffusion of hydrogen ions, that is repaired rapidly. The gastric mucosa has a rich blood supply and is protected by neural and muscular components that can trigger a protective reflex vasodilation when toxins or acid breach the epitheal barrier. Most gastric varices lie within 2 to 3 cm of the gastroesophageal junction (Crawford '94: 767).

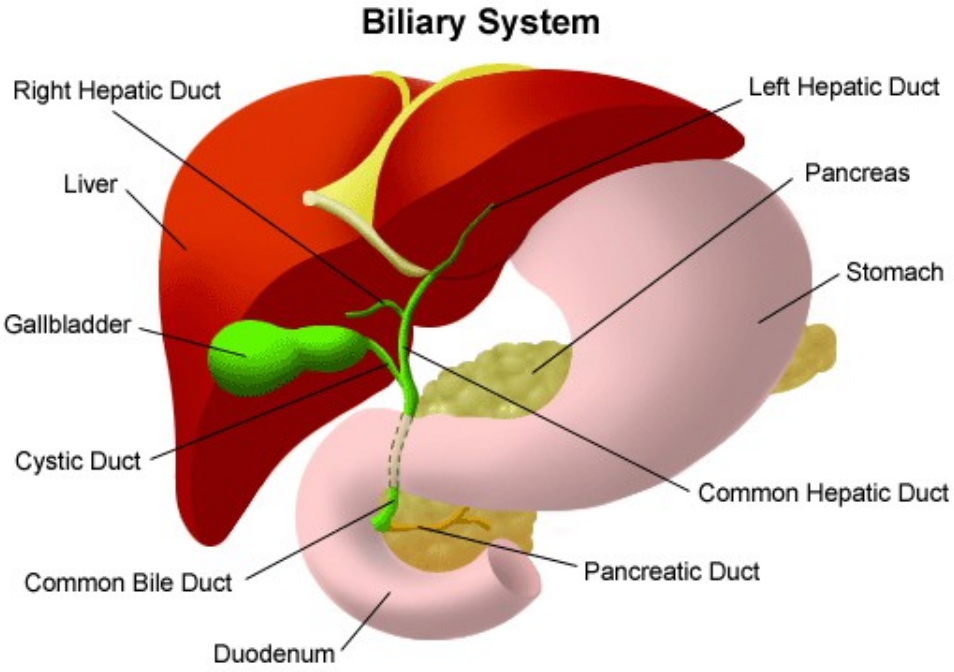
Hormones Secreted by the Stomach: Gastrin (Primarily) is secreted by G cells for the secretion of gastric acid by parietal cells. Ghrelin is secreted by P/D1 cells to stimulate appetite. Secretion of growth hormone from anterior pituitary gland. Neuropeptide Y (NPY) increases food intake and decreased physical activity, is associated with obesity. Somatostatin is secreted by D cells to suppress release of gastrin, cholecystokinin (CCK), secretin, motilin, vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP), enteroglucagon. Lowers rate of gastric emptying Reduces smooth muscle contractions and blood flow within the intestine. Histamine is secreted by ECL cells to stimulate gastric acid secretion. Endothelin is secreted by X cells to stimulate smooth muscle contraction of stomach. **Digestive enzymes f**ound in the stomach: Protease, found in the stomach juices and also in the pancreatic and intestinal juices, helps to digest protein. Pepsin also helps the stomach to digest protein. Lipase, found in the stomach and pancreatic juices, and also present in fats in foods, aids in fat digestion. While not technically an enzyme, hydrochloric acid interacts with digestive enzymes.

Shortly before the bolus arrives the stomach relaxes to accommodate it, and keeps relaxing and stretching to accommodate up to two pounds (one kilo) of foodstuff. Emotions like fear or stress an reduce the ability of the smooth muscle to stretch, making us feel full, or even nauseous, after eating just a small portion of food. Once the bolus arrives, the walls of the stomach speed up their movements. Food is pushed in an elegant arc; it is lobbed against the stomach wall, where it bones off ad plops bak down, in a process called retropulsion. This acceleration, push and plop process is what causes the gurgling sound that can be heard pressing an ear against the top of someone's belly, right after eating. The stomach will churn for about two hours, grinding the mouthfuls into tiny particles, most of them less than one-twelfth of an inch (about 2 millimeters) in size. Scraps of that size are no longer lobbed against the stomach wall, but slip through a little hole at the end of the stomach. This hole is the sphincter to the small intestines. Simple carbohydrates such as cake, rice or pasta make it through to the small intestine pretty quickly. There, they are digested and rapidly cause an increase in the levels of sugar in our blood. Proteins and fats are detained in the stomach for considerably longer. A piece of steak may easily be churned fro six hours before all of it has disappears into the small intestine. This explains why we often fancy a sweet dessert after eating meat or fatty, fried food. Blood sugar levels are impatient and want to rise quickly and dessert provides a quick blood sugar fix. Meals rich in carbohydrates are metabolized more quickly, but they do not sustain the full feeling as long as meaty or fatty meals (Enders '15: 87).

4. Liver and gallbladder

The **liver** weighs 1500 g, about 2.5% of body weight, and is by far the largest solid-intra-abdominal organ. The liver is almost entirely contained in the lower part of the right rib cage. The edge of the normal liver may sometimes be felt emerging from beneath the costal margin

during inspiration on palpation lateral to the right rectus abdominis muscle. If the liver edge is felt one or two finger-breadths inferior to the costal margin it may not be abnormally enlarged, but three or more finger-breadths raises suspicion of abnormal enlargement. Emphysema may cause the liver to be pushed downwards. The texture of the liver may be assesses as its edge rolls on to the palpating fingers in deep inspiration, and the abnormal hardness of cirrhosis of malignant infiltration may be apparent. In the midline, the liver is covered by the thick recti abdominis muscles and its edge cannot easily be felt, though a mass in the left lobe of the liber may palpable in the epigastrium. The liver may be divided into two true anatomical lobes of roughly equal mass and with independent blood supply and biliary drainage, running from the gall-bladder fundus inferiorly to the left margin of the inferior vena cava superiorly. Large liver resection may temporarily compromise liver function, but the liver has the capacity to regenerate to its original mass over several months. In the resting state, the liver receives a large blood supply of approximately 1500 ml/min from two sources: the hepatic artery (25%) and the portal vein (75%). Venous blood drains from the liver into the inferior vena cava through three man hepatic veins and the liver is suspended by these large venous attachments to the vena cava and by adjacent peritoneal reflections (Jones et al '85: 141-143).



Credit: Ohio State University Wexner Medical Center

The **gallbladder** is a small pouch that sits just under the liver. The gallbladder stores bile produced by the liver. After meals, the gallbladder is empty and flat, like a deflated balloon. Before a meal, the gallbladder may be full of bile and about the size of a small pear. In response to signals, the gallbladder squeezes stored bile into the small intestine through a series of tubes called ducts. In contrast to the rest of the gastrointestinal tract, the gallbladder lacks a muscularis mucosa nd submucosa and consists only of (1) a mucosal lining with a single layer of columnar cells (2) a fibromuscular layer (3) a layer of subserosal fat with arteries veins, lymphatics, nerves and paraganglia and (4) a peritoneal covering except where the gallbladder lies adjacent to, or is embedded in the liver. In the neck of the gallbladder numerous interlacing folds of mucosal eopthelium for the spiral valves of Heister, which extend into the cystic duct. Sometimes small

tubular channels (ducts of Luschka) are found buried within the gallbladder wall adjacent to the liver. Small outpouching of the gallbladder mucosa may penetrate into and through the muscle wall (Rikitansky-Aschoff sinuses) and their prominence in the settings of inflammation and gallstone formation suggests that they are acquired herniations. The confluence of the biliary tree is the common bile duct, which courses through the head of the pancreas for about 2 cm before disgorging its contents through the ampulla of Vater into the duodenal lumen. In approximately 60 to 70% of individuals, the main pancreatic duct joins the common bile duct to drain through a common channel, in the remainder, the two ducts run in parallel without joining. Scattered along the length of both intrahepatic and extrahepatic the biliary tree are mucin secreting submucosal glands (Crawford'94: 891, 893, 883).

Incoming blood arrives via the portal vein (60 to 70%) of **hepatic blood flow**) and hepatic artery (30 to 40%) through the porta hepatis; bile exits via the common hepatic bile duct. The vast expanse of hepatic parenchyma is serviced via terminal branches of the portal vein and hepatic artery. Blood collected into the hepatic vein, exits into the inferior vena cava. Classically the liver is divided into 1 to 2 mm diameter hexagonal lobules, also called acini, oriented around the terminal tributaries of the hepatic vein. The parenchyma of the hepatic acinus is divided into three zones, zone 1 being closest to the vascular supply, zone 3 abutting the terminal hepatic venule, and zone 2 being intermediate. Zonation is of considerable metabolic consequence because a lobular gradient exists for many hepatic enzymes and many forms of hepatic injury exhibit a zonal distribution. Between cords of hepatocytes are vascular sinusoids. Hepatocytes are among the most richly profused cells in the body, bathed on two sides by well-mixed portal venous and hepatic arterial blood, representing 25% of the cardiac output. The sinusoids are lined by festrated and discontinuous endothelial cells, which demarcate an extrasinusoidal space of Disse, into which protrude abundant microvilli of hepatocyte, scattered Kupffer cells and occasional fat-containing lipocytes (Ito cells). Between abutting hepatocutes are bile canaliculi, 1 to 2 μm in diameter that drain into the canals of Hering that flow into interlobular bile ducts within the portal tracts (Crawford '94: 831-833).

The liver substance consists of fenestrated plates of hepatocytes, seen in histological sections as rows of cells radiating out from a central venous radicle to form a roughly hexagonal liver lobule at each corner of which lie the portal tracts containing small branches of the hepatic artery, the portal vein, and a bile ductile ensheathed by a small amount of connective tissue. The hepatocyte plates are separated by blood sinusoids lined by fenestrated endothelial cells showing intercellular spaces. Plasma escapes through these fenestration to bathe the hepatocyte. Some of the cells lining the sinusoids (Kupffer cells) are capable of phagocytic activity and form part of the reticulo-endothelial system. The bile canaliculi are channels formed by matching grooves in adjacent hepatocytes. Anastomosing canaliculi form the finest biliary ductules, which drain into the larger ducts in the portal tract. The **gall bladder** is not normally palpable, but the distended fundus may be felt near the tip of the ninth costal cartilage in obstruction of the cystic duct or common bile duct. The peritoneum covering the undersurface of the liver passes smoothly over the gall bladder, which may be partly embedded within the liver substance. Anatomical variation so the biliary tree are fairly common and, during cholecystectomy, the anatomy must be carefully defined before division of the cystic duct is begun lest the common bile duct be damaged. The walls of the bild ducts contain only small amounts of smooth muscle. The lower end of the common duct and the main pancreatic duct most often share a common opening (the ampulla of Vater), and are surrounded by a complex sphincter (the sphincter of Oddi). The liver and biliary tract are supplied with both parasympathetic and sympathetic fibres, carried around the hepatic artery from the coeliac plexus. The preganglionic parasympathetic fibres reach the plexus in the vagal trunks. Preganglionic sympathetic cell bodies are in the 7^{th}-9^{th} thoracic segments and reach

the coeliac plexus via the sphanchnic nerves. Afferent pain fibres from the liver and biliary tract probably run in the sympathetic nerves (Jones et al '85: 143-144).

The liver has the enormous job of maintaining the body's **metabolic homeostasis**. This includes the processing of dietary amino acids, carbohydrates, lipids and vitamins; phagocytosis of particulate material in the splanchnic circulation; synthesis of serum proteins; biotransformation of circulating metabolites; and detoxification and excretion into bile of endogenous waste products and pollutant xenobiotics (Crawford '94: 831). The liver has metabolic, excretory and manufacturing functions. The major metabolic functions of the liver are carbohydrate metabolism, elimination of nitrogenous waste and formation of urea, lipid metabolism and cholesterol synthesis, formation and elimination of bile salts, and degradation of hormones. The excretory functions of the liver include excretion of bilirubin, and manufacturing functions include primarily protein production, cholesterol and phospholipid production and bile salt secretion. The liver is essential for the metabolic functions of glycose homoeostasis and maintenance of blood sugar. Extensive liver resection and severe liver failure lead to profound hypoglycaemia. After carbohydrate ingestion and glucose uptake, the liver stores of carbohydrate in the form of glycogen are increased by glycogenesis. There may also be glycolysis and disposal of glucose via the hexose monophosphate shunt. Carbohydrate (glucose) intolerance is a common feature of chronic liver disease. A variety of mechanisms may be involved, including an increase in peripheral insulin resistance, impaired insulin action and circulating insulin agonists. There may also be increased levels of diabetogenic hormones, including growth hormone, cortisol, and glucagon.

Hormones Secreted by the Liver: **Insulin-like growth factor** (or somatomedin) (Primarily)(IGF) is secreted by Hepatocytes with insulin-like effects. Regulates cell growth and development. Angiotensinogen and **angiotensin** are secreted by Hepatocytes for Vasoconstriction. Release of aldosterone from adrenal cortex dipsogen. **Thrombopoietin** (THPO) is secreted by Hepatocytes to stimulate megkaryocytes to produce platelets. **Hepcidin** is secreted by Hepatocytes to inhibit intestinal iron absorption. **Nitogenous wastes** are eliminated and urea is formed when the products of protein digestion are taken via the portal vein to the liver and metabolized. Amino acids are transaminated and then the carbon skeletons are metabolized by several pathways, including the Krebs citrate cycle. The amino groups are converted, via glutamate and ammonia, to **urea** Failure of these processes, leads to brain toxicity and neuro-encephalopathy. Lipid metabolism and cholesterol synthesis occur in the liver. Cholesterol is synthesized from acetyl CoA in the microsomal fraction of the hepatocytes, is a constituent of cell membranes and a precursor of steroids hormones and bile acids. Cholesterol may occur free or esterified with long-chain fatty acids. Triglycerides, esters of glycerol and fatty acids, are convenient energy stores. Phospholipids (such as lecithin) found in cell membranes are also formed in the liver.

Protein production is a prime liver function; all the circulating proteins apart from gamma globulin are made in the liver. Albumin is required to two functions; (1) maintenance of plasma colloid osmotic pressure and (2) transport of insoluble plasma constituents. The normal liver manufactures some 10-12 g of albumin daily but this forms part of a large continuous turnover within an exchangeable pool of some 300 g. The normal half-life of albumin is about three weeks. Synthesis is impaired by liver disease, in fever, and in cachexia. Albumin levels are usually well maintained in the early stages of biliary obstruction. Apart from impaired formation there are other important causes of a low plasma albumin. Hypoalbuminaemia is therefore associated with movement of fluid into extracellular spaces and the formation of edema. Many drug are hepatoxic. The liver also produces specialized carrier proteins including glycoproteins, haptoglobins, transferrins and caeruluplasmin. All the proteins concerned with blood

coagulation, with the exception of Factor VIII are produced in the liver, i.e. fibrinogen, prothombin, factors II, V, VII, IX, X, XI, XII, and XIII (Jones et al '85: 151-152, 144-146).

Bile is a dilute aqueous solution produced at an approximate rate of 0.5-1.5 litres per day. Active secretion of bile salts by the hepatocytes into the biliary canaliculi is the main determinant of bile flow, and water and electrolytes (mainly Na^+) follow passively along osmotic and electrical gradients. The lipids lecithin and cholesterol also enter the canaliculi according to variations in bile salt secretion. The ductular cells secrete a fluid rich in HCO_3. Bile flow is augmented during a meal by increased turnover of bile salts in the enterohepatic circulation. Bile is stored in the gall bladder, where it undergoes approximately a ten-fold concentration. Bile flow into the duodenum is regulated by hepatic secretion, by gall bladder contraction, and by bile-duct sphincter. During fasting the pressure in the common bile duct is 5-10 cm water, and bile is diverted into the gall bladder. After a meal, the gall bladder contracts, mainly as a result of the humoral action of the hormone cholecystokinin-pancreozymin, which is released from the duodenal mucosa by intraluminal fat and lipolytic products. At the same time the sphincter relaxes and bile squirts into the duodenum as the ductal pressure rises to 15-20 cm water and intermittently exceeds sphincteric resistance. Two primary bile salts, cholate and chenodeoxycholate, are formed in the hepatocytes from cholesterol. Before excretion, their solubility is increased by conjugation with glycine or taurine. These salts are altered by intestinal bacteria to produce the secondary bile salts, deoxycholate and lithocholate. Deoxycholate is reabsorbed to reenter the bile, but lithocholate is less soluble and is excreted in the faeces. Bile salts are detergents and their function is to facilitate absorption of lipids. In aqueous solution they aggregate into groups of several molecules called micelles. Micelles can incorporate lipids and remain in aqueous solution. Lecithin and cholesterol are transported in bile within the icelles. Bile salts, lecithin and cholesterol make up about 90% of the solids in bile and the remainder consist of bilirubin, fatty acids, and inorganic salts. Bile salts participate in fat absorption in the small bowel and are reabsorbed partly by passive transport in jejunum but mainly by an active transport system in the distal ileum, so that about 95% of the secreted bile salts are returned to the liver in the portal venous blood. The entire bile-salt pool of 2.5-4 g circulates twice through the enterohepatic circulation during each meal, and no less than 6-8 cycles are made each day. About 10-20% of the bile-salt pool is lost daily in the faeces and is restored by hepatic synthesis. Insulin, glucagon, glucocorticoids, thyroxine and growth hormone are all metabolized in the liver (Jones et al '85: 152, 153, 146-148).

Bile helps digest fats, but the gallbladder itself is not essential. Removing the gallbladder in an otherwise healthy individual typically causes no observable problems with health or digestion yet there may be a small risk of diarrhea and fat malabsorption. Humans excrete around 0.5 to 1.0 liters of bile daily. Between meals bile is stored in the gallbladder, which in the adult has a capacity of about 50 ml. Storage is facilitated by fivefold to tenfold concentration of bile through the coupled active absorption of electrolytes, with passive movement of water. In preparation for fat digestion, the gallbladder releases stored bile into the gut. Newly secreted bile is a bicarbonate-rich fluid containing by weight about 3% organic solutes, of which two-thirds are bile salts. Bile acids are the major catabolic products of cholesterol. Bile salts act as highly effective detergents, solubilizing water-insoluble lipids secreted by the liver into the biliary tree and dietary lipids within the gut lumen. The principal secreted lipids (more than 95%) are lecithins (phosphatidylcholine) which are hydrophobic. These insoluble amphiphiles, enhance the cholesterol-solubilizing capacity of bile salts in the bile. The solubility of cholesterol in bile is increased several million fold by the presence of bile salts and lecithin. About 95% of secreted bile salts are avidly reabsorbed in the intestines, primarily in the ileum and returned to the liver via the portal blood. The enterohepatic circulation of bile salts

constitutes a highly effective mechanism for reuse of these essential physiologic molecules. Nevertheless, the obligatory fecal loss of about half a gram of bile slats per day constitutes the major route for elimination of body cholesterol (Crawford'94: 891, 883, 884).

There are several liver function tests. Transaminases (aminotransferases) reflect liver and other tissue damage especially in cardiac and skeletal muscle. Alanine transaminase (ALT; serum glutamic pyruvic transaminase, SGPT) is more specifically related to liver damage, but it is not more sensitive than aspartate transaminase (AST; serum glutamic oxaloacetic transaminase, SGOT) and the latter is more generally used. Very high levels (over 1000 units) are found in hepatic necrosis, e.g. severe hepatitis. Numerous other enzymes e.g. lactic dehydrogenase, ornithine carbamoyl transferase) are not widely applicable. LDH isoenzymes are highly specific Gamma gutamyl transpeptidase (GGT) is an enzyme of induction, it is a sensitive enzyme widely used as a screening test and, in conjunction with alkaline phosphatase, to establish the hepatic origin of the later, with which it rises in concert. Some drugs, and particularly alcohol, cause modest to major rises in GGT (50-500 units). Alkaline phosphatase (AP) is an important duct enzyme of several origins but is normally mostly derived from biliary ductular epithelium. Modest rises (up to twice normal) are common, they often reflect liver damage but may be difficult to interpret. Elevation sin excess of 2-3 times normal occur in biliary tract obstruction. Space-occupying lesions can cause levels of AP in excess of 6 times normal. Mild elevations of bilirubin (up to 4-5 time normal) may reflect increased production (haemolysis), impaired transport of conjugation (e.g. Gilbert's disease) or mild cellular damage. Significant rises reflect a failure of excretion. Almost all will be conjugated bilirubin and will be soluble in water and excreted in urine. High bilirubin levels occur in drug-induced and cholestatic viral hepatitis. In established liver disease high levels of bilirubin and jaundice denote a poor prognosis. Albumin tends to be low where protein synthesis is impaired or protein lost, e.g. cirrhosis, malignant disease or severe infection. Prothrombin time (PT) is a sensitive and useful indicator of hepatic function. In simple obstructive jaundice, prolongation may be rapidly reversed with parenteral vitamin K. In drug damage and hepatitis a lengthening or very prolonged PT suggests a poor prognosis. There are many viral markers but the single most important is hepatitis B surface antigen. A positive alpha-feto-protein test strongly suggests primary hepatoma. Mitochondrial antibodies are useful for primary biliary cirrhosis (positive in 98% cases). Smooth muscle antibodies suggest chronic active hepatitis, but are not specific. Ultimately a histological diagnosis should be made in most cases (with the exception of gallstone disease and the relief of extrahepatic obstruction) (Jones et al '85: 175-178).

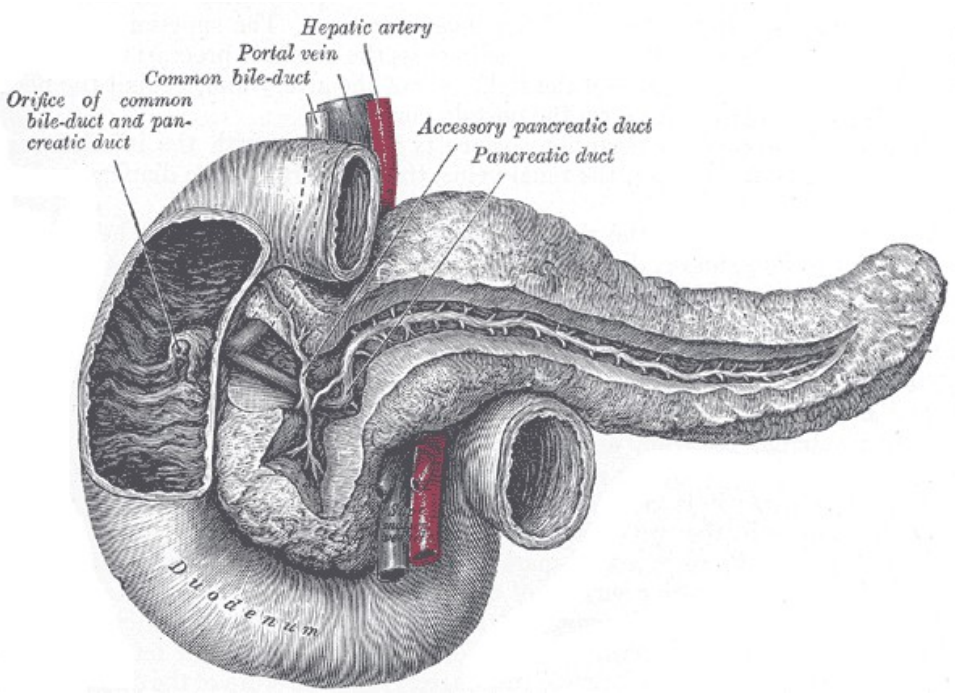
5. Pancreas

The **pancreas** produces 1.5-2.0 liters of juice in 24 hours, this juice is rich in bicarbonate (and is therefore alkaline), enzymes (which are proteins), and electrolytes (Jones et al '85: 102-104). In the adult, the average pancrea**s** is about 15 cm in length, weights 60 to 140, and consists of a head, a body and a tail. It is located on the left side of the body. The pancreas arises from the duodenum in the form of a dorsal bud and a shorter ventral bud. Fusion of the two creates the composite head, with the dorsal bud being the primary source of the tapering tail. The ductal drainage systems anastomose, and the definitive pancreatic duct (the duct of Wirsung) is formed by fusion of the ventral duct with the distal portion of the dorsal duct. Occasionally, the proximal portion of the dorsal duct persists as the accessory duct of Santorini. Although there is much variability in the ductal system, in two-thirds of adults the major pancreatic duct does not empty directly into the duodenum but into the common bile duct just proximal to the ampulla of Vater, thus providing a common channel for pancreatic and biliary drainage. The pancreas is immediately proximate to the duodenum, ampulla of Vater, common bile duct, superior

mesenteric artery, portal vein, spleen and its vascular supply, stomach, transverse colon, and left lobe of the liver. Histological, the pancreas has two separate components, the exocrine and endocrine glands. The exocrine portion, constituting 80 to 85% of the organ is made up of numerous small glands (acini). The endocrine portion consists of about 1 million microscopic cellular units – the islets of Langerhans – and a few scattered cells within the small pancreatic ducts. In aggregate the islets in the adult human weigh only 1 to 1.5 gm (Crawford and Cotran '94: 897, 898, 907).

The pancreas lies retroperitoneally on the posterior abdominal wall, within the duodenal loop and behind the stomach. The splenic vein lies behind the pancreas and runs medially to join with the superior esenteric vein to form the portal vein. The normal texture of the gland is soft and fleshy. Histologically, the pancreas consists of clusters of acini which form lobules separated from each other by areolar tissue. Each acinus is a sphere of pyramidal cells, their apices ending in the central lumen. Each acinus is drained by a pancreatic ductile, the ductular epitherlium extending into the central lumen to form the centro-acinar cell. The ductule drains into an intralobular duct: these unite to form the main pancreatic duct. The nerve supply of the pancreas comes from both the sympathetic (via the coeliac plexus) and the parasympathetic (via branches of the vagus nerve). The delicate and important portal circulation within the pancreas occurs whereby blood in the arterioles goes initially to the capillaries of the islets of Langherans and then to supply the adjacent acinar cells. There is a tendency to think of the pancreas in two distinct entities, namely the exocrine and endocrine elements. The overall volume of endocrine tissue within the pancreas is approximately 1%, with the number of individual islets varying from several hundred thousand to two million, evenly distribute throughout the pancreas (Jones et al '85: 100-102).

Pancreas



Credit: Gray's Anatomy

Under basal conditions the pancreas secretes 1.5-2.0 liters of juice in 24 hours, this juice is rich in bicarbonate (and is therefore alkaline), enzymes (which are proteins), and electrolytes. In response to various stimuli the volume of secretion can rise to 4 liters. The principal enzymes are amylase, lipase and trypsin. Amylase hydrolyses glycogen and starch. Lipase together with the essential protein cofactor co-lipase, this hydrolyses neutral fat to fatty acids and glycerides in the presence of bile salts (provided the latter are present in the correct concentrations). Trypsinogen, chymotrypsinogen and procarboxyypeptidase are protein-splitting enzymes secreted in an inactive form from the zymogen granules within the acinar cells and are activated mainly by enterokinase secreted in the small intestine (notably duodenum). Enterokinase splits a small peptide fraction off the trypsinogen molecule, converting it to the active trypsin. Once for the trypsin activates the other pancreatic proteases. Trypsin and chemotrypsin break up proteins within food into oligopeptides comprising 2-4 amino acids, which are hydrolysed further into individual amino acids during transport through the small intestinal cells. Although efficient pancreatic exocrine secretion is essential to health, it is well documented that up to 40% of ingested fat and protein may be absorbed when there is little or nor remaining pancreatic function (either due to disease or surgical resection). This is because amylases, lipases and peptidases are secreted in small quantities into the gut from sources other than pancreas, allowing survival in hopeless clinical situations (Jones et al '85: 102-104).

Pancreas is a mixed endocrine and exocrine gland and it secretes both enzymes and hormones. The endocrine pancreas consists of islet cells scattered in the larger exocrine pancrease, which lies adjacent to the stomach. The endocrine pancreas contains cells which secrete the hormones: (1) insulin; (2) glucagon;(3) somatostatin; and (4) pancreatic polypeptide (Greenstein '94: 9). Insulin (Primarily) is secreted by β Islet cells to stimulate intake of glucose, glycogenesis and glycolysis in liver and muscle from blood. Intake of lipids and synthesis of triglycerides in adipocytes. Other anabolic effects. Glucagon (Also Primarily) is secreted by α Islet cells for glycogenolysis and gluconeogenesis in liver. Increases blood glucose level. Somatostatin is secreted by δ Islet cells to inhibit release of insulin. Inhibits release of glucagon. Suppress the exocrine secretory action of pancreas. Pancreatic polypeptide is secreted by PP cells to self regulate the pancreas secretion activities and effect the hepatic glycogen levels (Greenstein '94: 9).

The pancreas secretes 1.5 to 3 liters per day of an **alkaline fluid** containing enzymes and proenzymes (zymogen). The regulation of this process involves the hormones secretin and cholecystokinin, produced in the duodenum. The former stimulates water and bicarbonate secretion and the latter enhances the discharge of zymogens by acinar cells. The pancreas also elaborates the enzymes trypsin, chymotrypsin, aminopeptidases, elastase, amylases, lipases, and phospholipases. Trypsin is a key enzyme because it catalyzes activation of the other enzymes. The islets of Langerhans consist of four major and two minor cell types. The four main types are B (beta), A (alpha), D (delta), and P (pancreatic polypeptide) cells. These make up about 70, 20, 5 to 10 and 1 to 2% of the islet cell population. The B cell (beta) produces insulin and hyperplasia or neoplasia of these care responsible for hyperinsulinism. A cells (alpha) secrete glucagon which induces hyperglycemia by its blycogenolytic activity in the liver. D cells (delta) conatin somatostatin, which suppresses both insulin and glucagon release. PP (pancreatic polypeptide) exert a number of gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes and inhibition of intestinal motility. The two rare cell types are D1 cells and enterochromaffin cells. D1 cells elaborate vasoactive intestinal polypeptide (VIP), that induces glycogenolysis and hyperglycemia and also stimulates gastrointestinal fluid secretion and cases secretory diarrhea. Enterochromaffin cells synthesize serotonin and are the source of pancreatic tumors that induce the carcinoid syndrome (Crawford and Cotran ’94: 898, 908-909).

All the **pancreatic enzymes** are secreted from the acinar cells at a very rapid rate. Energy in the form of ATP is needed for this movement. Once in the vacuoles, the enzyme proteins are concentrated. The final step is exocytosis whereby the apical cell membrane ruptures to allow rapid release of zymogen contents into the acinar lumen. Pancreatic secretion is under hormonal and nervous control. The principal hormones controlling pancreatic secretion are secretin, vasoactive intestinal peptide (VIP) and cholecystokinin/pancreozymin (CCK/PZ). Secretin and VIP are both secreted in the duodenum in response to hydrogen ions entering the duodenum from the stomach, particularly after a meal. Reaching the pancreas through the blood stream, they stimulate the pancreas to release fluid rich in bicarbonate and water, with a low enzyme content. The main result is to neutralize acid entering the duodenum. CCK/PZ is released into the blood from the gastric antrum and duodenum by the presence of food and stimulates the acinar cells to secrete a juice rich in enzymes (amylase, lipase and trypsinogen) but low in volume and bicarbonate content. In the duodenum, trypsin is liberated from trypsinogen by the action of enterokinase, which is secreted in the duodenal mucosa. The effects of gastrin, glucagon, somatostatin, calcitonin, bombesin, motilin and other peptides on pancreatic secretion are complex. Neurohormonal interactions are important, and the rate rate of gastric emptying has a measurable effect on pancreatic secretion. There is a also a cephalic phase of secretion on sight and smell of food (Jones et al '85: 102-104).

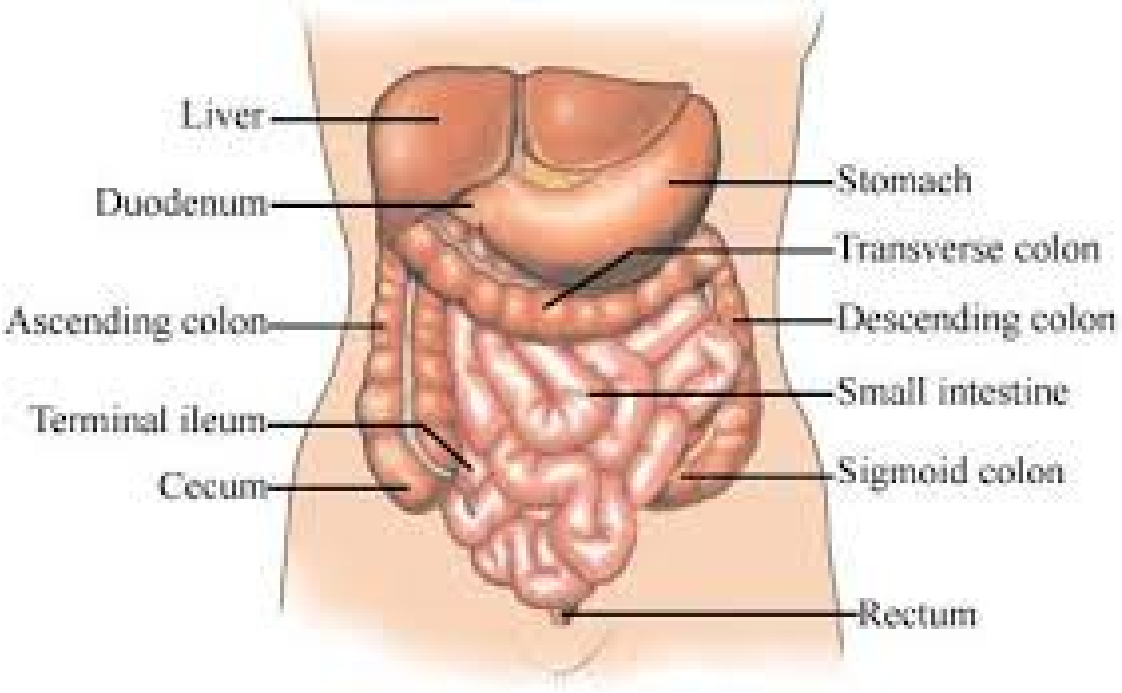
6. Intestines and rectum

The **intestines** in an adult are approximately 7.5 meters (22 feet) long The small intestine in the human adult is approximately 6 meters (18ft) in length, and the colon (large intestine) is approximately 1.5 meters, (5 ft) ending in the rectum, which passes between the crura of the peroneal muscles before reaching the anus. The appendix is an underdeveloped residuum of the otherwise voluminous cecum. The adult appendix averages 7 cm in length, is partially anchored by a mesenteric extension form the adjacent ileum, and has no known function. The most distinctive feature of the small intestine is its mucosal lining, which is studded with innumerable villi. These extend into the lumen as finger-like projections covered by epithelial lining cells. Between the bases of the villi are the pit-like crypts, which extend down to the muscularis mucosa. In normal individuals, the villus-to-crypt height ratio is about 4 to 5:1. Within the duodenum are abundant submucosal mucous glands, termed Brunner's glands that secrete bicarbonate ions, glycoproteins and pepsinogen II and are virtually indistinguishable from the pyloric mucous glands. The villi and are the sites for terminal absorption of foodstuffs by columnar absorptive cells. The crypts secrete ions and water, deliver immunoglobulin A (igA) to the lumen, and serve as the site for cell division and renewal. The purpose of the colon is to reclaim luminal water and electrolytes. The colonic mycosa has no villi and is flat. The mucosa is punctuated by numerous straight tubular crypts that extend down to the muscularis mucosa. Within the small intestine, cells migrate out of the crypts and upward to the tips of the villi, where they are shed into the lumen. This journey normally takes between 96 and 144 hours, leading to normal renewal of the epithelial lining every 4 to 6 days. Turnover of the colonic surface epithelium takes 3 to 8 days. The small bowel has the fastest turnover of any body tissue. Its lining cells (enterocytes) acquire their highly specialized functions, mature, perform a vital role in completing digestion and effecting absorption, die and are shed into the gut lumen in 4-6 days. The rapid renewal of intestinal epithelium provides a remarkable capacity for repair but also renders the intestine particularly vulnerable to agents that interfere with cell replication, such as radiation and chemotherapy for cancer (Jones et al '85: 18, 19).

The small intestine is divided into three areas: duodenum, jejunum, and ileum. The top part is the **duodenum**, it receives food from the stomach. In this part of the intestine, both pancreatic juice and bile are squirted into the intestine, and they mix with the food to help with the digestion

of large molecules – proteins, starches, and dietary lipids – breaking them down into smaller particles that can be absorbed. The middle part of the small intestine in the **jejunum** (from the Latin word for "empty", is a long tube designed to absorbed food by virtue of its structure: finger-like projections called villi markedly increase the surface area – something like the extra absorbency of terry-cloth bath towels. The lowest part of the small intestine is the **ileum**, which is also a place of absorption. In this area, vitamin B_{12} and bile salts are absorbed. Disease or absence of the ileum can result in vitamin B_{12} deficiency and a particular kind of post-infectious diarrhea. The large intestine, the **colon** has two purposes: to remove water from intestinal contents and to propel these contents toward the rectum. The diameter of the colon progressively narrows from the cecum on the right side, via the transverse colon to the sigmoid colon on the left. The contents of the colon are released into the rectum, where waste collects until defecated through the sphincter muscle of the anus. Structure of the intestinal wall: The wall of the intestine has several layers. The innermost layer is called the mucosa, which is responsible for absorption and secretion, and the outside layer is called the submucosa. Outside of these are two layers of muscles – one that is circular and one that is longitudinal – called the muscularis mucosa. The muscle layers are for the propulsion of food through the intestine (Newman '11: 18, 19, 20). The superior and inferior mesenteric arterial supply of the intestine is characterized by the progressive division of the vessels as they approach the gut, with rich arterial interconnections via arching mesenteric arcades. Numerous collaterals connect the mesenteric circulation with the celiac arterial axis proximally and the pudendal circulation distally. The venous drainage shares the proximal and distal anastomoses, the latter via the superior and inferior hemorrhoidal veins. The lymphatic drainage essentially parallels the vascular supply, without the intricate pattern of arcades. Because the colon is a retroperitoneal organ in the ascending and descending portions, it derives considerably accessory arterial blood supply and lymphatic drainage from a wide area dot the posterior abdominal wall (Crawford '94: 787).

Large and Small Intestine in Relation with Abdominal Organs



Credit:Google Images

The **small intestine** meanders about in the abdominal cavity, twisting and turning for a distance of between 10 and 20 feet (3 and 6 meters). The inside of the small intestine is moist and pink with a velvety sheen and delicate appearance, it is surprisingly clean and largely smell-free. The gut wants to offer as much surface area as possible. That is why it folds. Without folds, the small intestine would need to be an estimated 60 feet (18 meters) long to provide us with enough surface area for digestion. Each square inch of its surface contains about 20,000 tiny fingerlike projections (or about 30 projections per square millimeter). These projections, called **villi**, protrude out into the mush of partly digested food, called chyme. The villi's size means they appear as a velvety structure. Under the microscope, the little villi look like large waves made of out of cells, very similar to velvet. Even greater magnification reveals that each and every one of those cells is itself covered with little protrusions, the microvilli. The microvilli are in turn, covered with a velvety meshwork made of countless sugar based structures that look a little bit like antlers. These are called the glycocalyxes. If all this, the fold, the villi and the microvilli were ironed out to a smooth surface, the small intestine would be about 4 ½ miles (7 kilometers) log. In total the surface area of the digestive system is about one hundred times greater than the area of the skin.

The real process of **digestion** begins in the small intestine. The small intestine squeezes, hashes it from all sides, wiggles its villi, and when the bolus is thoroughly mixed, moves it on down the digestive line. After digestion, only a few rough leftovers remain in the stomach and small intestine. An hour after the intestine has digested something, it begins the cleanup process. The scientific name for this process is migrating motor complex, and is nicknamed the little housekeeper. The stomach opens to allow these leftovers into the small intestine. It then moves them along with a wave powerful enough to sweep everything along with it, causing a rumbling belly. If more is eaten before the cleanup is finished, the housekeeper stops working and returns to waiting mode. Constant snacking means there is no time for cleaning, wherefore some nutritional scientists recommend five hours between meals (Enders '15: 89-90). Right at the start of the small intestine there is a small opening in the its wall, this is the duodenal papilla – similar to the salivary papillae in the mouth, but bigger. It is is through this little hole in that digestive juices are squirted onto the chyme. The liver and pancreas being to produce these juices and deliver them to the papilla, as soon as something is eaten. These juices contain digestive enzymes and fat solvents. Each individual villus contains a tiny blood vessel, a capillary, that is fed with the absorbed molecules. All the small intestine's blood vessels eventually come together and carry the blood to the liver, where the nutrients are screened for harmful substances and toxins. Any dangerous substances can be destroyed here before the blood passes into the main circulatory system. The liver is where the first energy stores are created if eating too much. The nutrient-rich blood then flows from the liver directly to the heart. There, it receives a powerful push and is pumped to the countless cells of the body. In this way, a sugar molecule an end up in a skin cell, where it absorbed along with oxygen, that releases energy, which the cell uses to stay alive, with heat and tiny amounts of water created as by-products, this happens inside so many cells at the same time that the heat produced keeps out body at a constant temperature of 97 to 99 degrees Fahrenheit (36 to 37 degrees Celsius). Nature requires energy to ripen an apple on the tree, animals come along and break the apple down to its constituent molecules and metabolize them for energy, that is released to keep us alive. There is no burst of energy right after eating a meal, the food has not yet reached the small intestine, although no longer hungry because the stomach is expanded by the food eaten, still feel as sluggish as before the meal. Furthermore, a large quantity of blood is delivered to the digestive organs resulting in reduced blood supply to the brain. Digestion is more efficient for resting or sedentary people, rather than stressed out workers (Enders '15: 37-42).

Survival is possible with as little as 25 cm of surviving **bowel** following resection, as the result of hypertrophy and elongation of the existing villi in adaptation. The small bowel has a central role in the immunoprotective system of the body. In the villus muscle fibers running from the muscularis mucosae to the lacteals contract during absorption and pump lymph from the lacteal into the lymphatic vessels whence it passes into the mesenteric lymphatics. The villous capillary network is supplied by a central arteriole and drained by venules discharging into the portal vein radicles. Diffusion of oxygen from the arteriole low down in the villus means that the tip is more liable to hypoxia contributing to death and shedding of cells from the tip. Maturation and elaboration of function can be related to specific micro-anatomical structures. The **glycocalyx** consists of glycoproteins, manufactured by the enterocytes themselves, which bind certain nutrients (e.g. trace metals and vitamin B^{12}) and also pancreatic enzymes. Microvillus 'Brush Border' contains enzyme is responsible for carbohydrate and protein digestion. The Brush Border membrane permits solute to cross this membrane barrier. The basolateral membrane contains the energy generating enzyme, sodium potassium adenosine triphosphatase (Na-K-ATPase), responsible for active nutrient uptake. This enzyme uses the hydrolysis of ATP to pump sodium into the intercellular space in exchange for potassium, leading to a concentration gradient across the brush border membrane. Carriers for sodium across this membrane also transport nutrients, e.g. glucose, the combined action being termed a 'symport system' (Jones et al '85: 113-116).

Digested **protein** is ether endogenous or exogenous. Some protein macromolecues are absorbed intact, while other must be broken down into amino acids. In some pathological states, protein is lost from the gut, sometimes in quantities large enough to cause considerable hypoalbuminaemia. Some causes of protein-losing enteropathy are: (1) in the stomach; increased secretions due to Menetrier's disease, tumors or increased glandular secretion; (2) in the duodenum; hyperplastic enteropathies, coeliac disease, allergic gastroenteropathy and tropical sprue; (3) in the jejunum and ileum; lymphatic occlusion from lymphangiectasia, retroperitoneal fibrosis, lymphoma or cardiac failure, venous occlusion or arterial insufficiency; and (4) in the ileum and colon; inflammation due to gastroenteritis, parasitic infestation, contaminated bowel syndrome, chronic inflammatory bowel disease. To achieve effective intraluminal digestion, **lipid droplets** need to be broken up, when the surface area available for lipolysis is increased, this is done by the churning action of the gastric antrum and by forceful ejection through the pylorus. The resultant emulsion is stabilized by the bile acids, which aggregate on the surface of the droplets and prevent them from coalescing into larger droplets. Lingual and gastric lipases release medium and short chain fatty acids which have a carbon chain length of 12 or less and are water-soluble. Medium-chain triacylglycerols (MCTs) are also taken up actively by the enterocyte, where an intracellular lipase degrades them to glycerol and constituent fatty acids. The digestion and absorption of the hydrophobic lipid is dependent upon the bile salts. These are synthesized from cholesterol, in the liver, and are stored and concentrated in the gall bladder. Bile acids possess a carbon skeleton which is soluble in lipids, and hydroxyl and carboxyl groups which are water-soluble. Formation of polymeric aggregates known as micelles is aided by the preliminary concentration of the bile salts in the gall bladder; the intracellular bile salt concentration at which micelles are formed is called the 'critical micellar concentration' (CMC). The CMC is influenced also by the intraduodenal and jejunal pH; the normal pH (6.5) of the lumen becomes too acid, the bile salts precipitate out of solution and if hepatic production is impaired, and lipid digestion is impaired. Another important feature of the actin of bile salt is that they facilitate the intractin of some of the pancreatic liplytic enzymes, which are water-soluble. After absorption, lipid molecules are incorporated into two water-soluble lipoprotein complexes, chylomicrons and very

low-density lipoproteins (VLDLs) for passage to the lymphatics. The chylomirone and VLDLs enter the lacteals through gaps between endothelial cells (Jones et al '85: 118-121).

Although some **bile salts** are reabsorbed passably along the small intestine, most are reabsorbed actively by specific carriers in the terminal ileum and return via the portal circulation to the liver. This enterohepatic circulation completes at least two cycles with each meal. If the salvage mechanism is interrupted by disease or resection of the terminal ileum, bile salts pass into the colon and are lost. The liver can increase its synthesis of bile salts 8-10 fold and it can therefore compensate only for the loss of 4-5 g of bile salts daily. Any loss in excess of this depletes the bile acid pool and jeopardizes the digestion and absorption of fat and fat-soluble vitamins. Patients with gross deficiencies in bile salts or pancreatic lipolytic activity are best managed with special food supplements containing MCT, these are hydrolized by gastric and lingual lipases to produce water-soluble products, which do not require bile salts for their absorption. The fat soluble vitamins A, D and K may need to be given parenterally, in severe cases (Jones et al '85: 118-121).

Metals can be absorbed throughout the small intestine. Up to 80% of the daily calcium intake (approximately 800 mg) is absorbed via mucosal binding proteins, the synthesis of which is regulated by 1,25-dihydroxycholecalciferol. The α-hydroxylation of 25 hydroxycholecalciferol (vitamin D) in the kidneys is regulated by parathyroid hormone (PTH) and is related inversely to plasma calcium concentrations. Calcium is also lost into the intestine, and the resultant net daily absorption is 200 mg; calcium homeostasis is maintained by the adjustment of its excretion in the urine. Iron is best absorbed in the organic complex haem. Inorganic iron is probably taken up by the duodenum most efficiently as ferrous iron. Gastric secretion facilitates the absorption and this may be achieved by reduction of)ferric) iron in the diet to ferrous iron. Most becomes bound to an intracellular protein, apoferritin, to form ferritin. The release of ferritin iron to the tissues depends on the individual's iron status. Cells loaded with ferritin are unable to absorb further iron and this 'mucosal block' prevents any more uptake of the metal. Water-soluble vitamins are probably absorbed by carrier mediated mechanisms of the small intestine. The uptake of riboflavin and pyridoxine may be by diffusion. Dietary folic acid is conjugated with glutamic acid (pteroylpolyglutamate) and hydrolysed at the brush border to a mixture of tri, di and monoglutamates. The mucosal hydrolysis and absorption of folate conjugate is especially sensitive to mucosal disease. Folate deficiency can be screened for by measuring the plasma folate content (usually >2ng/ml) or, more reliably, the red cell folate content (normally 200-8000 ng/l). The absorption of vitamin B^{12} is susceptible to numerous interferences, and severe impairment of absorption can be present without any deficit being apparent in the plasma concentrations because of the large stores of the vitamin in the liver. Following resectin of ileum or in diseases principally affecting the ileum, the jejunum cannot take over the specific functions of the ileum (to absorb vitamin B^{12} and bile salts). Loss of ileal function (either by disease or surgery) is therefore much more serious than loss of jejunal function (Jones et al '85: 121, 122).

As a population **gut endocrine cells** exhibit cytoplasm that contains abundant fine eosinophilic granules, which harbor secretory products. Gut endocrine cells are generally positive by immunoperoxidase stains for chromogranin, synaptophysin and neuron-specific enolase. These cells are marked by the diversity of their secretory products. The various secretory products, act as chemical messengers and modulate normal digestive functions by a combination of endocrine, paracrine and neurocrine mechanisms. Each endocrine cell type exhibits a distribution tailored to meet the physiologic needs pertinent to a gut segment. Although the discovery of secretin by Bayliss and Starling in 1902, and of gastrin by Edkins in 1905, marked the beginning of endocrinology as a separate discipline, it is only in recent years that the importance of the gut to

the endocrine system has been appreciated. Secretin is secreted by S cells to stimulate secretion of bicarbonate from liver, pancreas and duodenal Brunner's glands. Enhances effects of cholecystokinin, stops production of gastric juice. Cholecystokinin is secreted by I cells to stimulate the release of digestive enzymes from pancreas and the release of bile from the gallbladder, hunger suppressant. More recently-established hormones include pancreatic polypeptide (PP), gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), motilin, enteroglucagon, somatostatin, substance P, neurotensin, bombesin and the endorphins. Unlike other endocrine organs, the hormone-producing cells of the gut are diffusely scattered and not collected into recognizable glands and extracts of a piece of gut mucosa may contain may different hormones (Jones et al '85: 18, 19).

Enzymes Found in the Intestine

Type	Products	Stomach	Small Bowel	Large Bowel
		Corpus - antrum	Duodenum-Jejunum-Ileum	Colon rectum
G	Gastrin, ACTH, Metenkephalin,	X	x	
IG	Gastrin		x	
TG	Tetrin		X	
D	Somatostatin	x X	x	-
S	Secretin		X	
I	Cholecystokinin		x	
K	Gip		x	
M_0	Motilin		x -	
N	Neurotonin		- x X	-
L	Enteroglucagon		- - x	- x
EC_1	5 H-T, Substance P, Leu-Enkephalin		x x x	x x x
EC_2	5-HT, Motilin-like, Leu-enkephalin		x -	
EC_n	5-HT, unknown	x x	-	-
ECL	Unknown	X		
D_1	VIP-like	x	-	x -
P	Bombesin-Like	- x	- -	
PP	Pancreatic Polypetide	-	-	- X
PYY	PYY			- X
X	Unknown	X		

Source: Crawford ’94: Figure 17-26 785

Small intestinal **peristalsis**, both antero-grade and retrograde, mixes the food stream and promotes maximal contract of nutrients with the mucosa. Colonic peristalsis prolongs contact of the luminal contents with the mucosa. Both small and large intestinal peristalsis are mediated by

intrinsic (mysenteric plexus) and extrinsic (autonomic innervation) neural control. Meissner's plexus resides at the base of the submucosa, and Auerback's plexus lies between the inner circumferential an outer longitudinal muscle layers of the muscle wall, lesser neural twigs extend between smooth muscle cells and ramify within the submucosa. Throughout the small intestine and colon are nodules of lymphoid tissues, which either lie within the mucosa or span the mucosa and a portion of the submucosa macroscopically visible called Peyer's patches. The surface epithelium contains M cells which serve the intestinal immune system that is attributed with being responsible for as much as 80% of the body's immune response. Through the intestines, T lymphocytes are scattered within the surface epithelium (intra-epithelial lymphocytes) generally of cytotoxic phenotype ($CD8^+$). The lamina propria contains helper T cells ($CD4^+$) and educated B cells. The lymphoid nodules and mucosal lymphocytes which constitute the Mucosa-Associated Lymphoid Tissue (MALT) (Crawford '94: 785).

To diagnose **appendicitis,** important symptoms are fever in combination with pain below and to the right of the belly button. Often pressing on that side of the lower abdomen will cause pain, while, pressing on the other side will relieve it. This is because abdominal organs are surrounded by a supporting fluid. When pressure is applied to the left-hand side, extra support fluid is pushed over to the right, where it provides additional cushioning for the inflamed gut, which relives pain. Other signs of appendicitis are pain when raising the right leg against a resistant pressure. The appendix, officially known as the vermiform, or worm-shaped, appendix, has a reputation for being useless. The appendix is not only too small to deal with chyme, it is positioned in a location that partly digested food hardly ever reaches, just below the junction between the small and large intestines, and is completely bypassed. Although far removed from the Waldeyer's ring, the appendix is part of the tonsillar immune tissue. The vermiform appendix is placed far enough away so that it is not bothered by all the digestion going on above it, but close enough to monitor all foreign microbes .Although the walls of the large intestine include large deposits of immune cells, the appendix is made almost entirely of immune tissue. So, if a bad germ comes by, it is totally surrounded. However, that also means that everything around it an become infected – 360 degree panoramic inflammation. If this inflammation causes the appendix to swell, the little tube has problems sweeping itself clean of those bed germs – leading to more than 270,000 appendectomies every year in the United States alone. In 2007 American researchers Randal Bollinger and William Parker discovered that the appendix acts as a storehouse for all the best, most useful bacteria. Its practicality comes into play after a heavy bout of diarrhea, that will flush away many of the typical gut microbes, leaving the terrain free for other bacteria to settled, this is where the appendix steps in an spreads beneficial bacteria protectively throughout the entire large intestine. In areas with few diarrhea-producing pathogens appendectomy is not very worrisome. The immune cells in the rest of the large intestine may not be quite so closely packed, but in total, they are many times more numerous than those in the appendix, and they are competent enough to do the job. After a bout of diarrhea one can buy good bacteria at a pharmacy to repopulate their gut. (Enders '15: 43-46)

At the end of the small intestine is a structure known as **Bauhin's valve**. It separates the small and large intestine. The large intestine is much more leisurely, and shifts food backward as well as forward, depending on what feels right at the time. The large intestine is home to gut flora, which deals with anything that gets swept into the large intestine undigested. The brain is picky about when it wants to got to the toilet, the bacteria in the gut want time to deal with undigested food, and the rest of the body wants to get back the fluids lent to the digestive system. By the time the bolus reaches the large intestine it no longer resembles the food it started as. Although the large intestine is a smooth tube, it is always shown in diagrams looking like a lumpy string of beads. Just like the small intestine, it bulges as it processes the food it receives. However, it

tends to remain in one position for a long time without moving. Every now and then, it relaxes and then forms bulges in another place. Then it remains in that position for a while. Two or three times a day , the large intestine gives an enthusiastic shove to the concentrated food mush to push it forward. Those who consume enough bulk may even have to go to the toilet two or three times a day. For most people the content of their large intestine is enough for one bowel movement a day. Three times a day is also a healthy frequency. Women's large intestines are generally slightly more lethargic than men's. The journey from fork to toilet takes approximately one day on average. Faster guts accomplish this journey in eight hours, slower digesters can take three and a half days. Some particles may linger in the large intestine for twelve hours while others from the same meal take forty-two hours (Enders '15: 91-92).

The **large intestine** takes care of things that cannot be absorbed in the small intestine. It does not have the same velvety texture. The large intestine is home to most gut bacteria, which can break down the last nutritious substances. The large intestine does not wind like about like its smaller counterpart. It surrounds the small intestine on the outside, like a picture frame. The large intestine takes its time with all the leftovers and digests them thoroughly. The small intestine can get on with processing the next meal, or even the next two in the meantime, without affecting the large intestine's work, doggedly processing leftovers for sixteen hours or so. In doing so substances are made available that would have been lost if the gut were more hurried, including calcium that can only be absorbed in the large intestine. The large intestine and its flora also provide an extra-helping of energy-rich fatty acids, vitamin K, vitamin B12, thiamine (vitamin B1) and riboflavin (vitamin B2). In the final three feet (last meter) of the large intestine, water and salt levels are finely tuned. The saltiness of feces remains the same, saving the body an entire quart (liter) of fluids. All the nutrients absorbed by the large intestine are transported first to the liver before entering the main blood stream. The final few inches (centimeters) of the large intestine, however, do not send their blood to the detoxifying liver; blood from their vessels goes straight into the main circulatory system. This is because, generally, nothing more is absorbed in this section because everything useful has been removed. The important exception is substances contained in a medical suppository. Suppositories contain much less medication than pills and take effect more quickly. Tablets and fluid medications often have to contain large doses of the active agent because much of it is removed by the liver before it even reaches the area of the body it is meant to act upon. (Enders '15: 45 - 47).

Large volumes of fluid are handled by the gut daily, most of it endogenously produced and most reabsorbed. **Water flux** is free in the small intestine, both into and out of the lumen. In the duodenum net flux is into the lumen. Most carbohydrate, protein and medium-chain fatty acids are absorbed in the proximal 1.5 m of jejunum. Appreciable reabsorption of water and sodium occurs in combination with other solutes such as D-hexoses and L-amino acids. This mechanism is exploited in the oral treatment of cholera and other choleraic syndromes by giving large volume of balanced solution of saline and glucose or sucrose or by commercial electrolyte solutions such as Dioralyte. In the distal ileum and colon, single sodium carriers predominate, and only water enters between the cells. Potassium is passively absorbed in the proximal gut in response to chemical gradients and also by paracellular solvent drag, but is secreted by the terminal ileum and colon. Intraluminal hydrolysis of carbohydrate polysaccharides commences with the action of salivary and pancreatic amylases and is completed by small bowel mucosal oligosaccharidases. Absorption occurs throughout the small bowel via the sodium-linked symport systems. This process is efficient, up to 120 g of carbohydrate can be handled in one hour, and extensive impairment of the digestive and absorptive mechanisms for carbohydrates can be tolerated due to the efficiency of the enzyme amylase. Fermentation of the saccharides produces volatile organic acids (e.g. lactic, acetic, butyric and proprionic) which are either

absorbed by the colon or are passed in the feces, producing a pH of less than 6.0. the colonic microflora are able to metabolize considerable amounts of carbohydrate and the colon is able to absorb the resultant organic acids and gases (Jones et al '85: 117, 118).

The major function of the **anal canal** is to provide a continent passage through which there can be a controlled evacuation of flatus and feces. The anal canal is about 3 cm long in the adult; the lower 2 cm is lined by squamous epithelium, which terminates at the pectinate line. Here a number of anal valves, or crescentic folds, mark the junction between the sensitive modified skin of the anal canal and the rectal mucosa. Above the anal valves are a number of pockets, the anal crypts, into some of which open the anal glands. Immediately deep to the lining of the anal canal lies the vital and sphincter mechanism. This consists of an inner smooth muscle tube (the internal sphincter), which is a condensation of the circular muscle of the gut, and the outer striated muscle ring (the external sphincter). At its upper border the external sphincter is in continuity with the pelvic diaphragm, i.e. the levator ani muscle. An important part of this muscle is the puborectalis sling, which is attached to the bak of the symphysis pubis and pulls the junction of rectum and anal anal (the anorectal ring) forwards, so creating a valvular mechanism important in maintaining continence. On either side of the puborectalis, the levator ani muscle fans out radially as the pelvic diaphragm and is attached to the walls of the pelvis (Jones et al '85: 245).

There are two **sphincter** muscles in the rectum, internal and external. When what's left of the food reaches the internal sphincter, that muscle's reflex response is to open. But it does not just open the floodgates and let everything out, leaving the outer sphincter to deal with the deluge. First, it allows a small taster through. The space between the internal and external sphincter muscles is home to a large number of sensor cells. They analyze the product delivered to them, test it to find out whether it is solid or gaseous, and send the resulting information up to the brain. The external sphincter gets the message and dutifully squeezes itself closed even more tightly than before. The internal sphincter gets the message. The two muscles work together and maneuver the taster back into a holding pattern (Enders '15: 13-14). Except when defecation has to be postponed, and the striated muscle of the levator ani and external sphincter is voluntarily contracted, continence depends on the unconscious working of several factors: (1) normally, the lower rectum is empty and the puborectalis sling maintains an angle of 70-80° between anal canal and rectum. Intra-abdominal pressure therefore tends to press the anterior rectal wall against the posterior wall and prevent passage of feces and flatus. (2) The resting tone in the internal anal sphincter maintains a pressure zone in the anal canal which is higher than the intrarectal pressure. (3) A vital aspect of anal continence is the sensory mechanism by which rectal filling is recognized, and discrimination between flatus and faeces is achieved. The sensation of flatus or feces entering the rectum is perceived in the stretch receptors sited in the levator ani, rather than the rectal wall itself. 'Sampling' of the contents is carried out by a relaxation of the anal sphincter mechanism which allows the rectal contents to come into contact with the sensory epithelium of the anal canal: this enables the individual to decide whether it is safe to pass flatus without fear of soiling – a process which may go awry when the stool is fluid (Jones et al '85: 246).

Several studies have indicated that squatting is the most effective method of **defecation**. Israeli doctor Dov Sikirov asked twenty-eight test subjects to defecate in three alternative positions: enthroned on a normal toilet; half-sitting, half-sitting, half-squatting on an unusually low toilet; and squatting with no seat beneath them at all. In a squatting position, the subjects took an average of 50 seconds and reported a feeling of full, satisfactory bowel emptying. The average when seated was 130 seconds and the resulting feeling was deemed to be not quite so

satisfactory. Reason being, the closure mechanism of the gut is designed in such a way that it cannot open the hatch completely when seated. There is a muscle that encircles the gut like a lasso when we are sitting or, standing, and it pulls the gut in one direction, creating a kink in the tube, in addition to the sphincters. Japanese researchers fed volunteers luminous substances and x-rayed them while they were defecting in various positions. They found that squatting does indeed lead to a nice straight intestinal tract, allowing or a direct, easy exit. Hemorrhoid, digestive diseases like diverticulitis and constipation are common only in countries where people generally sit on some kind of chair to pass their stool. Sitting on a toilet is not the only cause of hemorrhoids and diverticula, however, it remains a fact that the 1.2 billion people in this world who squat have almost no incidence of diverticulosis and far fewer problems with hemorrhoids. In the West people squeeze their gut tissue until it comes out and has to be removed by a doctor (Enders '15 : 17-18).

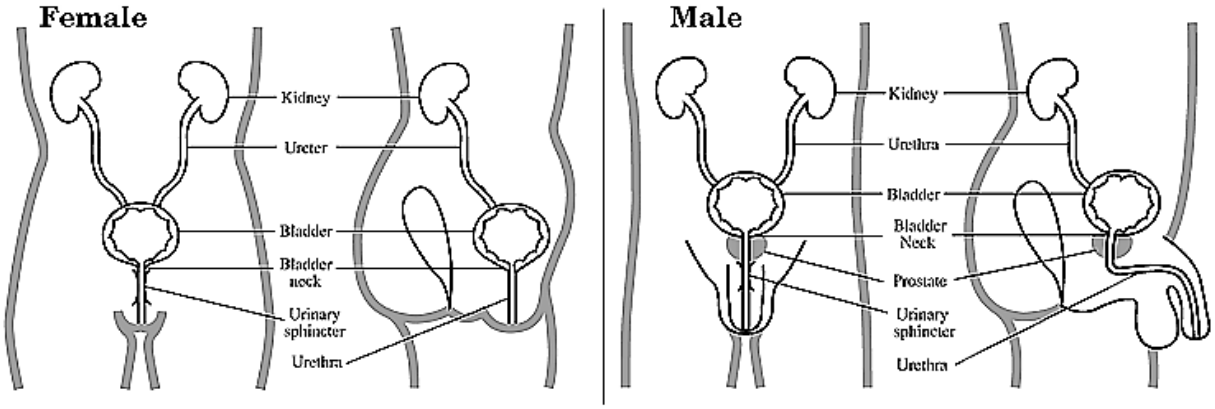
Transit through the small bowel takes 4-5 hours but on average it takes a further 12-18 hours for feces to travel from caecum to rectum, about 24 hours in total. About 1.5 liters of liquid chime passes through the ileocaecal valve each 24 hours, but only about 100-200 grams of stool is evacuated, of which 60-80% is water. Whereas peristaltic activity is more-or-less constant in the small bowel, two separate types of movement can be distinguished in the colon. Segmentation produces mixing of the contents, whereas propulsion is a mass movement which on three or four occasions in the day (generally after a meal) propels feces down the colon. On a typical western diet a daily stool weight in excess of 300 g would be considered pathological unless exceptional quantities of dietary fibre were being eaten. Only 1 in 100 Western citizens have fewer than three bowel movements a week or more than three per day (Jones et al '85: 301). Feces are three-quarters water. Around 3 ½ ounces (100 milliliters) of fluid are lost everyday. During a passage though the digestive system, some 10 quarts (9.8 liters) are reabsorbed. Whatever fluid is left in the feces belongs there. This optimal water content makes our feces soft enough to ensure metabolic waste products an be transported out of the body safely. A third of the solid components are bacteria, that have died or otherwise are exiting the digestive system. Another third is made up of indigestible vegetable fiber. The more fruit and vegetables eaten, the more feces excreted per bowel movement. Increasing the proportion of that food group can raise the weight of a bowel movement from the average 3 ½ to 7 ounces (100 to 200 grams) to as much as 178 or 18 ounces (500 grams) per day. The remaining third is made up of substances the body wants to get rid of, such as the remains of medicines, food coloring or cholesterol (Enders '15: 70, 71).

B. Urinary Tract

Urology deals with disease and disorders of the male and female genitourinary tract. Surgical diseases of the adrenal gland are also included. Each **kidney** is capped by an adrenal gland, and both organs are enclosed within Gerot's (perirenal) fascia. Each adrenal weights about 5 g The right adrenal is triangular in shape; the left is more rounded and crescentic Each gland is composed of a cortex, chiefly influenced by the pituitary gland, and a medulla derived from chromaffin tissue. The right adrenal lies between the liver and the vena cava. The left adrenal lies close to the aorta and is covered on its lower surface by the pancreas; superiorly and laterally, it is related to the spleen. The adrenal cortex is composed of 3 distinct layers: the outer zona glomerulosa, the middle zona fasciculate, and the inner zona reticularis. The medulla lies centrally and is made up of polyhedral cells containing eosinophilic granular cytoplasm. The chromaffin cells are accompanied by ganglion and small round cells. Each adrenal receives 3 arteries; one from the inferior phrenic artery, one from the aorta, and one from the renal artery. Blood from the right adrenal is drained by a very short vein that empties into the vena cava; the

left adrenal vein terminates in the left renal vein. The lymphatic vessels accompany the suprarenal vein and drain in to the lumbar lymph nodes (Tanagho '88: 1).

Urinary Tract



Human **kidneys** serve to convert more than 1700 liters of blood per day into about 1 liter of a highly specialized concentrated fluid called urine. In so doing, the kidney excretes the waste products of metabolism, precisely regulates the body's concentration of water and salt, maintains the appropriate acid balance of plasma, and serves as an endocrine organ, secreting such hormones as erythropoietin, renin and prostaglandins. Each human adult kidney weights about 150 gm. Although both kidneys make up only 0.5% of the total body weight they receive about 25% of the cardiac output. Of this, the cortex is by far the more richly vascularized, receiving 90% of the total renal circulation. As the **ureter** enters the kidney at the hilus, it dilates into a funnel-shaped cavity, the pelvis, from which derive two to three main branches, the **major calyces**; the latter subdivide again into about three to four minor calyces. There are about **12 minor calyces** in the human kidney. On cross-section the kidney is made up of a cortex and a medulla, the former 1.2 to 1.5 cm in thickness. The **medulla** consists of renal pyramids, the apices of which are called papillae, each related to a calyx. **Cortical tissue** extends into spaces between adjacent pyramids as the renal columns of Bertin. From the standpoint of diseases, the kidney can be divided into four components: blood vessels, glomeruli, tubules and interstitium.

The tips of the minor calices (8-12 in number) are indented by the projecting pyramids. These calices unite to form 2 or 3 major calices which join the renal pelvis. The pelvis may be entirely intrarenal or partly intrarenal and partly extrarenal. Inferomedially, it tapers to form the ureter. The adult ureter is about 30 cm long, varying in direct relation with the height of the individual. It follows a rather smooth S curve. Areas of relative narrowing are found (1) at the ureteropelvic junction, (2) where the ureter crosses over the iliac vessels, and (3) where it courses through the bladder wall. As followed form above downward, the ureters lie on the psoas muscles, pass medially to the sacroiliac joints, and then swing laterally near the ischial spines before passing medially to penetrate the base of the bladder. In the female, the uterine arteries are closely related to the juxtavesical portion of the ureters. The ureters are covered by the posterior peritoneum; their lowermost portions are closely attached to it, while the juxtavesical portions are embedded in vascular retroperitoneal fat. In males the vasa deferentia, as they leave the internal inguinal rings, sweep over the lateral pelvic walls anterior to the ureters. They lie medial to the latter before joining the seminal vesicle and penetrating the base of the prostate to become the ejaculatory ducts. The walls of the calices, pelvis and ureters are composed of transitional cell epithelium under which lies loos connective and elastic tissue (lamina propria). External to these are a mixture of spiral and longitudinal smooth muscle fibers They are not arranged in

definitive layers. The outermost adventitial coat is composed of fibrous connective tissue. The renal calices, pelvis and upper ureters derive their blood supply from the renal arteries; the mid ureter is fed by the internal spermatic (or ovarian) arteries. The lowermost portion of the ureter is served by branches form the common iliac, internal iliac (hypogastric) and vesical arteries. The veins of the renal calices, pelvis and ureters are paired with the arteries. The lymphatics of the upper portion of the ureters as well as those from the pelvis and calices enter the lumbar lymph nodes. The lymphatics of the mid ureter pass to tht internal iliac (hypogastric) and common iliac lymph nodes; the lower ureteral lymphatics empty into the vesical and hypogastric lymph nodes (Tanagho '88: 3-5).

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The **penis** is composed of 2 corpora cavernosa and the corpus spongiosum, which contains the urethra, whose diameter is 8-9 mm. The average American man's penis measures 5.6 inches, or 14.2 cm, long when erect. The penises measured in the study ranged from 2.75 inches to 7 inches (7 to 18 centimeters) long in a flaccid-but-stretched state, and from 3.93 inches to 7.87 inches (10 to 20 cm) when erect. Girth ranged from 2.75 inches to 5.11 inches (7 to 13 cm) when flaccid and from 3.54 inches to 6.69 inches (9 to 17 cm) when erect (Pappas '13). The adult **female urethra** is about 4 cm long and 8 mm in diameter. It is slightly curved and lies beneath the public symphysis just anterior to the vagina. The epithelial lining of the female urethra is squamous in its distal portion and pseudostratified or transitional in the remainder. The submucosa is made up of connective and elastic tissues and spongy venous spaces. Embedded in it are many periurethral glands, which are most numerous distally; the largest of these are the periurethral glands of Skene, which open on the floor of the urethra just inside the meatus. External to the submucosa is a longitudinal layer of smooth muscle continuous with the inner longitudinal layer of the bladder wall. Surrounding this is a heavy layer of circular smooth muscle fibers extending from the external vesical muscular layer. They constitute the true involuntary urethral sphincter. External to this is the circular striated (voluntary) sphincter surrounding the middle third of the urethra. The arterial supply to the female urethra is derived from the inferior vesical, vaginal and internal pudendal arteries. Blood from the urethra drains into the pudendal veins. Lymphatic drainage form the external portion of the urethra is to the inguinal and subinguinal lymph nodes. Drainage from the deep urethra is into the internal iliac (hypogastric) lymph nodes (Tanogho '88: 13, 14).

With diminished renal function, the ability of the kidneys to concentrate urine lessens progressively until the specific gravity of the urine reaches 1.006-1.010. Patients uric acid stones rarely have a urinary pH over 6.5 (uric acid is soluble in alkaline urine). Patients with calcium stones, nephrocalcinosis, or both may have renal tubular acidosis and will be unable to acidify urine below pH 6.0. With urinary tract infections caused by urea splitting organisms (most commonly *Proteus* species), the urinary pH tends to be over 7.0. Urine obtained within 2 hours of a large meal or left standing at room temperature for several hours tends to be alkaline. Persistently elevated protein levels in the urine may indicate significant disease, e.g., glomerulopathy or cancer; proteinuria can be determined by the protein: creatinine ratio. The normal ratio is 0.2 mg or less of protein per milligram of creatinine and that a ratio of 3.5 or more represents significant proteinuria (more than 1 g of protein excreted every 24 hours). Serum creatinine levels will remain within the normal range (0.8-1.2 mg/dL in adults; 0.4-0.8 mg/dL in young children) until approximately 50% of renal function has been lost. Unlike most excretory products serum creatinine is not generally influenced by dietary intake or hydration status.

The **endogenous creatinine clearance test** is the most accurate and reliable measure of renal function available without resorting to infusion of exogenous substances such as inulin or

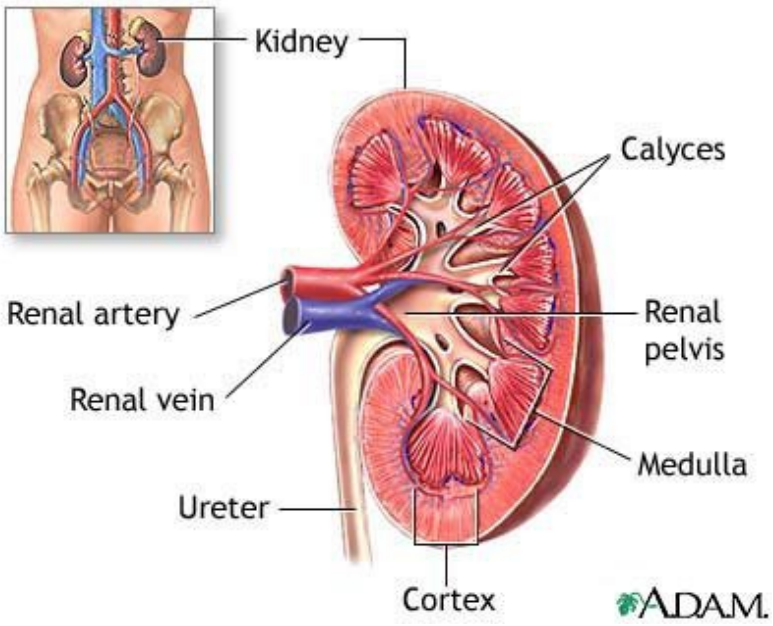
radionuclides. Determination of creatinine clearance requires the collection of a times (usually 24 hour) urine specimen and a serum specimen. The clearance can then be calculated as follows: Clearance = UV/P where U= creatinine in urine (mg/dL); P=creatinine in plasma (mg/dL); V=mL or urine excreted per minute or per 24 hours. The resulting clearance is expressed in milliliters per minute, with 90-110 mL/min considered normal. Because muscle mass differs among individuals further has been achieved by using the following formula UV/P x 1.73 m^2/estimated surface area = corrected clearance. A corrected clearance level of 70-140 mL/min is considered normal. The blood urea nitrogen level is related to the glomerular filtration rate. Urea is the primary metabolite of protein catabolism and is excreted entirely by the kidneys. Blood urea nitrogen is influenced by dietary protein intake, hydration status ,gastrointestinal bleeding, urinary obstruction. Approximately two-thirds of renal function must be lost before a significant rise in blood urea nitrogen level will be evident. The blood urea nitrogen: creatinine ratio is normally 10:1 in dehydrated patients and those with bilateral urinary obstruction or urinary extravasation, the ratio may range from 20:1 to 40:1, and patients with advanced hepatic insufficiency and overhydrated patients may exhibit a lower than normal blood urea nitrogen level and blood urea nitrogen: creatinine ratio. Patients with renal insufficiency may develop extremely high blood urea nitrogen levels that can be partially controlled by a decrease in dietary protein. (Williams '88: 48, 54, 55).

1. Kidneys

The **kidneys** lie obliquely along the borders of the psoas muscles. The position of the liver causes the right kidney to be lower than the left. The adult kidney weighs about 150 g. The kidneys are supported by the perirenal fat (which is enclosed in the perirenal fascia), the renal vascular pedicle, abdominal muscle tone, and the general bulk of the abdominal viscera. The average descent on inspiration or on assuming the upright position is 4-5 cm. Lack of mobility suggests abnormal fixation (e.g., perinephritis), but extreme mobility is not necessarily pathologic. On longitudinal section, the kidney is seen to be made up of an outer cortex, a central medulla, and the internal calices and pelvis. The cortex is homogeneous in appearance Portions of it project toward the pelvis between the papillae and fornices and are called the columns of Bertin. The medulla consists of numerous pyramids formed by the converging collecting renal tubules, which drain into the minor calices. The functioning unit of the kidney is the nephron, which is composed of a tubule that has both secretory and excretory functions. The secretory portion is contained largely within the cortex and consists of a renal corpuscle and the secretory part of the renal tubule. The excretory portion of this duct lies in the medulla. The renal corpuscle is composed of the vascular glomerus, which projects into Bowman's capsule, which, in turn, is continuous with the epithelium of the proximal convoluted tubule (Tanagho '88: 1-3).

The secretory portion of the renal tubule is made up of the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule. The excretory portion of the nephron is the collecting tubule, which is continuous with the distal end of the ascending limb of the convoluted tubule. It empties its contents through the tip (papilla) of the pyramid into a minor calix. The renal stroma is composed of loose connective tissue and contains blood vessels, capillaries, nerves and lymphatics. Usually there is one renal artery, a branch of the aorta, that enters the hilum of the kidney between the pelvis, which normally lies posteriorly, and the renal vein. It may branch before it reaches the kidney, and 2 or more separate arteries may be notes. It is usual for each renal segment to have its own arterial supply. The renal artery divides into anterior and posterior branches and are all end arteries. The renal artery further divides into interlobar arteries, which ascend in the columns of Bertin (between the pyramids) and then arch along the base of the

pyramids (arcuate arteries). The renal artery then ascends as interlobular arteries. From these vessels, smaller (afferent) branches pass to the glomeruli. From the glomerular tuft, efferent arterioles pass to the tubules in the stroma. The renal veins are paired with the arteries, but any of them will drain the entire kidney if the others are tied off. The renal nerves derived from the renal plexus accompany the renal vessels throughout the renal parenchyma. The lymphatics of the kidney drain into the lumbar lymph nodes (Tanagho '88: 1-3).



The **main renal artery** divides into anterior and posterior sections at the hilus. From these, interlobar arteries emerge, course between lobes, give rise to the arcuate arteries, which arch between cortex and medulla, in turn giving rise to the interlobular arteries. From the interlobular arteries, afferent arterioles enter the glomerular tuft, where they progressively subdivide into 20 to 40 capillary loops arranged in several units or lobules. Capillary loops merge together to exit from the glomerulus as efferent arterioles. **Efferent arterioles** from superficial nephrons form a rich vascular network that encircles cortical tubules (peritubular vascular network), while deeper juxtamedullary glomeruli give rise to the vasa recta, which descend as straight vessels to supply the out and inner medulla. These descending arterial vasa recta then make several loops in the inner medulla and ascend the venous vasa recta. Occlusion of any branch results in an infarction of the specific area it supplies. Glomerular disease that interferes with blood flow through the glomerular capillaries has profound effects on the tubules, within both the cortex and the medulla, because all tubular capillary beds are derived from the efferent arteries. The renal medulla is especially vulnerable to ischemia. The major characteristics of glomerular filtration are an extraordinary high permeability to water and small solutes, accounted for by the highly fenestrated endothelium and impermeability to molecules the size of **albumin** (+3.6-nm radius; 70,000 kd) call the **glomerular barrier function** (GBM). The proximal tubular cells reabsorb two-thirds of filtered sodium and water as well as glucose, potassium, phosphate, amino acids and proteins. The proximal tubule is particularly vulnerable to ischemic damage (Saunders '94: 927-931, 978).

The **kidney** is an excretory organ, filtering soluble waste products and drugs from the circulation. It also produces hormones involved in the control of blood pressure and in erythropoiesis (production of red blood cells): (1) renin and (2) erythropoietin (Greenstein '94: 9). Hormones Secreted by the Kidney: **Renin** (Primarily) is secreted by the Juxtaglomerular

cells to activate the renin-angiotensin system by producing angiotensin I of angiotensinogen. **Erythropoietin** (EPO) is secreted by the Extraglomerular mesangial cells to stimulate erythrocyte production. **Calcitriol** (1,25-dihydroxyvitamin D_3) is an active form of vitamin D_3 that increases absorption of calcium and phosphate from gastrointestinal tract and kidneys. Inhibits the release of PTH. **Thrombopoietin** stimulates megakaryocytes to produce platelets (Greenstein '94: 9).

The **adrenal glands** are situated just above the kidneys, and are composed of an outer layer, or cortex, and an inner layer, or medulla. The two layers have different functions: the cortex produces steroid hormones and the medulla produces the catecholamines. The adrenal medulla is a modified ganglion (Greenstein '94: 9). Hormones Secreted by the **Adrenal cortex**: **Adrenaline** (epinephrine) (Primarily) is secreted by Chromaffin cells for fight-or-flight response: Boost the supply of oxygen and glucose to the brain and muscles (by increasing heart rate and stroke volume, vasodilation, increasing catalysis of glycogen in liver, breakdown of lipids in fat cells). Dilate the pupils. Suppress non-emergency bodily processes (e.g., digestion). **Noradrenaline** (norepinephrine) is secreted by Chromaffin cells for fight-or-flight response: Boost the supply of oxygen and glucose to the brain and muscles (by increasing heart rate and stroke volume, vasoconstriction and increased blood pressure, breakdown of lipids in fat cells). Increase skeletal muscle readiness. **Dopamine** is secreted by Chromaffin cells to increase heart rate and blood pressure. **Enkephalin** is secreted by Chromaffin cells to regulate pain. **Glucocorticoids** (chiefly cortisol) are secreted by zona fasciculata and zona reticularis cells imulates gluconeogenesis to stimulates fat breakdown in adipose tissue. Inhibits protein synthesis and inhibits glucose uptake in muscle and adipose tissue. Inhibits immunological responses (immunosuppressive). Inhibit inflammatory responses (anti-inflammatory). **Mineralocorticoids** (chiefly aldosterone) are secreted by zona glomerulosa cells to stimulate active sodium reabsorption in kidneys. Stimulates passive water reabsorption in kidneys, thus increasing blood volume and blood pressure. Stimulates potassium and H^+ secretion into nephron of kidney and subsequent excretion. **Androgens** (including DHEA and testosterone) are secreted by Zona fasciculata and Zona reticularis cells. In males: Relatively small effect compared to androgens from testes. In females: masculinizing effects.

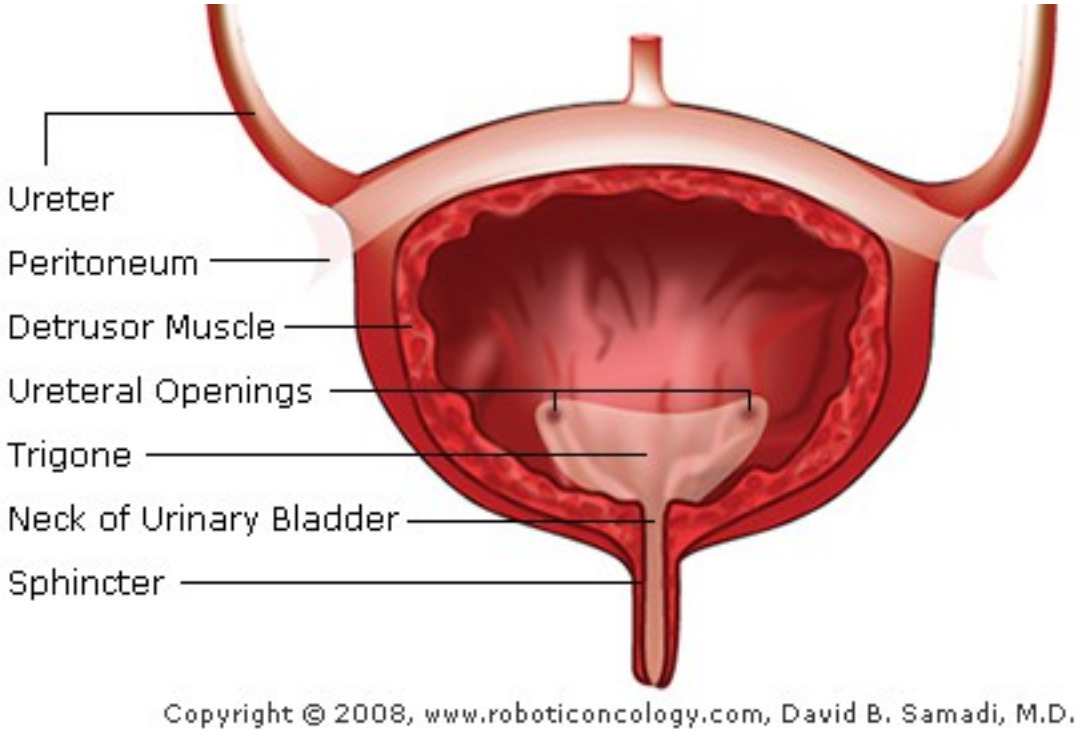
2. Bladder and genitals

The **bladder** is a hollow muscular organ that serves as a reservoir for urine. In women, its posterior wall and dome are invaginated by the uterus. The adult bladder normally has a capacity of 350-450 mL. When empty, the adult bladder lies behind the pubic symphysis and is largely a pelvic organ. In infants and children, it is situated higher. When it is full, it rises well above the symphysis and can readily be palpated or percussed. When over-distended, as in acute or chronic urinary retention, it may cause the lower abdomen to bulge visibly. Extending from the dome of the bladder to the umbilicus is a fibrous cord, the medial umbilical ligament, which represents the obliterated urachus. The **ureters** enter the bladder posterio-inferiorly in an oblique manner and at these points are about 5 cm apart. The orifices, situated at the extremities of the crescent-shaped interureteric ridge that forms the proximal border of the trigone, are about 2.5 cm apart. The trigone occupies the area between the ridge and the bladder neck. The internal sphincter, or bladder neck, is not a true circular sphincter but a thickening formed by interlaced and converging muscle fibers of the detrusor as they pass distally to become the smooth musculature of the urethra.

In males, the bladder is related posteriorly to the seminal vesicles, vasa deferentia, ureters and rectum. In females, the uterus and vagina are interposed between the bladder and rectum. The

dome and posterior surfaces are covered by peritoneum; hence, in this area the bladder is closely related to the small intestine and sigmoid colon. In both males and females, the bladder is related to the posterior surface of the pubic symphysis, and, when distended, it is in contact with the lower abdominal wall. The mucosa of the bladder is composed of transitional epithelium. Beneath it is a well-developed submucosal layer formed largely of connective and elastic tissues. External to the submucosa is the detrusor muscle, which is made up of a mixture of smooth muscle fibers arranged at random in a longitudinal, circular and spiral manner without any layer formation or specific orientation except close to the internal meatus, where the detrusor muscle assumes 3 definite layers: inner longitudinal, middle circular and outer longitudinal. The bladder is supplied with blood by the superior, middle and inferior vesical arteries, which arise from the anterior trunk of the internal ilia (hypogastric) artery, and by smaller branches from the obturator and inferior gluteal arteries (Tanagho '88: 7).

Bladder



In the female, the uterine and vaginal arteries also send branches to the bladder. Surrounding the bladder is a rich plexus of veins that ultimately empties into the internal iliac (hypogastric) veins. The lymphatics of the bladder drain into the vesical, external iliac, internal iliac (hypogastric) and common iliac lymph nodes (Tanagho '88: 7). In the female, the uterine arteries are closely related to the juxtavesical portion of the ureters. The ureters are covered by the posterior peritoneum; their lowermost portions are closely attached to it, while the juxtavesical portions are embedded in vascular retroperitoneal fat. In males the vasa deferentia, as they leave the internal inguinal rings, sweep over the lateral pelvic walls anterior to the ureters. They lie medial to the latter before joining the seminal vesicle and penetrating the base of the prostate to become the ejaculatory ducts. The walls of the calices, pelvis and ureters are composed of transitional cell epithelium under which lies loose connective and elastic tissue (lamina propria). External to these are a mixture of spiral and longitudinal smooth muscle fibers They are not arranged in definitive layers. The outermost adventitial coat is composed of fibrous connective tissue. The renal calices, pelvis and upper ureters derive their blood supply from the renal

arteries; the mid ureter is fed by the internal spermatic (or ovarian) arteries. The lowermost portion of the ureter is served by branches form the common iliac, internal iliac (hypogastric) and vesical arteries. The veins of the renal calices, pelvis and ureters are paired with the arteries. The lymphatics of the upper portion of the ureters as well as those from the pelvis and calices enter the lumbar lymph nodes. The lymphatics of the mid ureter pass to the internal iliac (hypogastric) and common iliac lymph nodes; the lower ureteral lymphatics empty into the vesical and hypogastric lymph nodes (Tanagho '88: 3-5).

The testis is the major male reproductive gland, and produces (1) testosterone; (2) inhibin; (3) Müllerian regression (or inhibiting) factor (fetus) (Greenstein '94: 9). Androgens (chiefly testosterone) are secreted by Leydig cells to stimulate anabolic growth of muscle mass and strength, increased bone density, growth and strength. Virilizing: maturation of sex organs, formation of scrotum, deepening of voice, growth of beard and axillary hair. Estradiol is secreted by Sertoli cells to prevent apoptosis of germ cell. Inhibin is secreted by Sertoli cells to inhibit production of FSH. The **penis** is composed of 2 corpora cavernosa and the corpus spongiosum, which contains the urethra, whose diameter is 8-9 mm. The average American man's penis measures 5.6 inches, or 14.2 cm, long when erect. The penises measured in the study ranged from 2.75 inches to 7 inches (7 to 18 centimeters) long in a flaccid-but-stretched state, and from 3.93 inches to 7.87 inches (10 to 20 cm) when erect. Girth ranged from 2.75 inches to 5.11 inches (7 to 13 cm) when flaccid and from 3.54 inches to 6.69 inches (9 to 17 cm) when erect (Pappas '13).

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IV. Indigestion

1. Birth Defects

Higher animals develop from three tubes. The first tube runs right through with a knot in the middle, this is the cardiovascular system. The second tube develops more or less parallel to the first, forms a bubble that floats to the top, this is the nervous system. The third tube runs from end to end, this is our intestinal tube. It grows buds that that bulge out farther and farther into the right and left. These buds will later develop into lungs. A little bit lower down, the intestinal tube bulges again and the liber begins to develop. It also forms the gall bladder and pancreas. The tube itself beings to grow increasingly clever. It is involved in the complex construction of the mouth, creates the esophagus, with its ability to move and develops a little stomach pouch to store food for a couple of hours. And, last but not least, the intestinal tube completes the eponymous intestine or gut (Enders '15: 10). Babies are germ free in the womb. As soon as there is any breach in the protective amniotic sac, colonization begins. While 100 percent of the cells that make us up when we start life are human cells, we are soon colonized by so many microorganisms that only 10 percent of our cells human, with microbes accounting for the remaining 90 percent. Human cells are much larger than microbes. When born the first microbes ingested are from the vaginal flora, a particularly acidic Lactobacillus, this is mixed with a few skin-dwelling and hospital germs. Breast-feeding promotes *Bifidobacteria*. Some bacteria are beneficial, others less so. Breast feeding shifts the balance toward the beneficial. Breast milk is so beneficial that a mother does not need to do more than suckle her baby to ensure it is receiving a healthy diet. Breast milk provides everything that dietary scientists believe children need to thrive, including antibodies. African children have bacteria that break down fibrous plant based foods. Japanese children have marine bacteria to help digest seafood. Children born by caesarean section take months or even longer to develop a normal population of gut bacteria, and have increased risk of allergies or asthma until age seven. Studies have shown that administering *Lactobacillus* to these children can reduce risk (Enders '15: 163).

All parts of the alimentary tract, from the mouth to the anus, can be the site of a **malformation** which has arisen in utero. The incidence of malformation varies considerably within and between countries and races, but congenital abnormalities o the alimentary tract have an incidence of about in every 1000 births and produce about one-third of all admissions to a neonatal surgical unit. The need for these units have become generally recognized over the last 30 years. Almost all of these babies are nursed in individual incubators. The aim in western Europe and North America is to produce a neonatal surgical unit for every 3 million people and in practice this means that each Area Health board supports one unit. With rapid medically-supervised transport in a portable incubator, these babies can be safely transferred considerable distances. In the four-week fetus the hind-gut ends in the cloaca. In the following weeks, the cloaca is split vertically into an anterior urogenital sinus and a posterior rectum. Anomalies are divided into high and low deformities. High deformities – those lying above the levator ani – are associated with disordered division of the cloaca by incomplete descent of the urogenital fold. Low deformities, which only affect the rectum and anus below the levator ani and pelvic diaphragm, are associated with abnormalities in the disappearance of the cloacal membrane. There usually appears to be no anus, but if a probe is passed, and the skin ridge cut back, a normal anus is revealed. Half the lesions can be relieved by minor surgery. High anomalies are more serious because no part of the rectum exists at or below the level of levator ani.

In **exomphalos** all or most of the epigastric abdominal wall fails to develop and there is a major herniation of liver and gut through a wide deficit which is covered only a by a glistening

transparent avascular membrane composed of amnion and peritoneum. This begins to disintegrate as it dries out and loses the nourishment derive din utero from amniotic fluid, and so repair is an urgent matter. The hernia is often too big to allow a full-scale repair of the abdominal wall. Sometimes a temporary repair can be effected by excising the sac and dissecting up the skin of the abdomen and using this as a cover for the abdominal contents. This creates a skin-covered hernia, and the muscle layers can be repaired when the child has grown and is fit, around one year of age. A **gastroschisis** is an open defect of the abdominal wall, beside the umbilicus, which has allowed intestine to spill out of the abdomen in utero: this appears to happened days or weeks before delivery. At birth there is a striking prolapse of small bowel through the deficiency and urgent repair is needed. If the bowel is cleansed and replaced in the abdomen, and the defect repaired most of these babies do remarkably well (Jones et al '85: 268-270, 271).

Clefts of the lip and palate are due to a failure of the maxillary and nasal growth centres to fuse in a normal manner. These deformities cause little actual medial disability, but if a palate is not skillfully repaired the social disadvantage of cleft palate type of speech are severe, and the appearance of an uncorrected cleft lip is very unpleasant. With timely and expert plastic surgery during the first two year, these disabilities are nowadays almost completely overcome (Jones et al '85: 259, 260). **Esophageal atresia** occurs in about one in every 3000 births. In the normal course of events the trachea and larynx split off from the foregut about the fourth to sixth week of fetal life, and this must be the stage at which esophageal anomalies develop. Associated anomalies in the heart and renal tracts and in the rectum occur in about half of babies with oesophageal atresia. The commonest deformity (85%) is a complete atresia of the upper oesophagus with a fistula between the tracheal bifurcation and the lower oesophagus. A few (10%) babies have a long gap between the two esophageal pouches and no fistula. These newborns cannot swallow, cough and splutter. Whenever this is noted, a stiff catheter should be passed through the mouth, it will be found to arrest about 10 cm below the incisor teeth. Since the first successful repair of an esophageal atresia in a neonate in 1941, this has become a regular operation for pediatric surgeons. The right chest is entered extra-pleurally, the trachea-esophageal fistula is divided and oversewn, and the two blind ends of oesophagus mobilized and joined together. In good risk babies, over 2 kg in weight, mortality is now negligible. **Neonatal intestinal obstruction** can occur at any level form the duodenum to the anus. The higher deformities in the duodenum and small bowel tend to present quickly, during the first 24-48 hours, with characteristic bright green vomiting differing from the yellow vomit which many babies produce. Duodenal obstruction may be of intrinsic or extrinsic causation. Intrinsic obstruction is a blockage of the lumen due either to a membrane, or to actual discontinuity of the lumen (atresia). In atresia the usual treatment is to anastomose jejunum to the distended duodenum above the obstruction. There is a strong associated of these anomalies with mongolism, which occurs in 25%. In extrinsic obstruction the rotation of the midgut has gone awry. These babies tend to feed normally for a few days after birth, and then volvulus occurs, followed by green vomiting, but this an occur later in life. Treatment entails division of Ladd's band, untwisting the volvulus, and placing the small bowel on the right, and colon to the left side of the abdomen. The caecum then lies in the mid-abdomen, so the appendix should be removed (Jones et al '85: 260-262).

Meckel's diverticulum, a small remnant of the vitello-intestinal duct, is the commonest congenital deformity of the alimentary, being present in 2-3% of the population: only about one-third of diverticula, however, prove to be pathogenic. The majority exist as an unattached diverticulum projecting from the antimesenteric surface of the ileum, sited some 60 cm above the ileocaecal valve (in the adult) and averaging 5 cm in length. There is characteristically blood

supply via the omphalomesenteric artery. A few diverticular are attached to the back of the umbilicus and of these a minority are patent, so intestinal juices are discharged through the navel. Between 50-60% of diverticular contain ectopic gastric mucosa, secreting acid and pepsin. Most diverticular remain silent and may be found incidentally through a laparotomy. Of the one-third which produce symptoms, 80% will present during childhood, and of these 5 out of 6 exist in boys. Meckel's diverticulum can prove pathogenic if (2) the gastric secretions may cause a peptic ulcer to gorm in the adjacent ileum, (2) acute inflammation of a diverticulum can occur, similar to acute appendicitis, and (3) small intestinal obstruction can occur if an unattached diverticulum forms the leading point of an intussusception or an attached diverticulum acts as a peritoneal band or is the point of rotation of a voluvulus. In all these situations, treatment involves excision of the diverticulum with closure of the defect in the wall of the ileum (Jones et al '85: 272).

Megacolon describes a condition in which the colon is grossly dilated and distended. Most patients with megacolon suffer from a congenital malformation known as **Hirschsprung's disease** which occurs one in every 5000 neonates whereby the autonomic innervation migration down the gut stops short of the anal canal, leaving a length of colon devoid of ganglia. This deformity may affect only a few centimeters of rectum or, more commonly, the whole rectum and part of the sigmoid colon. Boys outnumber girls by 5 to 1. It is important that all infants with Hirschsprung's disease should have either a colostomy fashioned, or definitive surgery completed, before leaving hospital because of the danger of enterocolitis developing. The definitive operation is usually delayed until, with the bowel decompressed and evacuating normally via the colostomy, the baby has grown and is an otherwise normal 9-12 month-old child. In **Swenson's operation** all aganglionic bowel is excised and the mobilized ganglionic colon is anastomosed end-to-end to the anal canal by a pull-through operation. In **Duhamel's operation** the rectum is retained, the ganglionic colon is joined to the posterior half of the anorectal ring, and then the common wall between rectum and colon is destroyed, so forming a capacious new rectum. Both operations require considerable expertise but yield excellent long-term results (Jones et al '85: 262-268).

Wilson's disease, hepatolenticular degeneration, is an autosomal recessive disorder of copper metabolism marked by the accumulation of toxic levels of copper in many tissues and organs, principally the liver, brain and eye. Wilson's disease has a gene frequency of 1: 200 to 400 and a disease incidence of 1:200,000. When hepatic involvement remains subclinical, the condition comes to attention as a Parkinson-like movement disorder, as a psychiatric disturbance ranging from behavioral disorders to frank psychoses, or because of the ocular changes. Early recognition permits the long-term use of copper chelators (e.g.) penicillamine) to prevent the accumulation of copper and thsue arrest the progression of organ damage. Fulminant hepatitis and unmanageable cirrhosis necessitate liver transplantation which appears to be curative. **Alpha$_1$Antitrypsin (α_1-AT) deficiency** is an autosomal recessive disorder marked by abnormally low serum levels of protease inhibitor (Pi). The deficiency leads to the development of pulmonary disease (emphysema) and hepatic disease (cholestasis or cirrhosis). Pulmonary emphysema develops owing to a relative lack of antiprotease in the lungs, thus permitting tissue-destructive enzymes to run amok (Crawford '94: 861-864). Inability to synthesize **apolipoprotein B** is a rare inborn error of metabolism that is transmitted by autosomal recessive inheritance. It is characterized by a defect in the synthesis and export of lipoproteins from the intestinal mucosal cells. Free fatty acids and monoglycerides resulting from hydrolysis of dietary fat enter the absorptive epithelial cells and are re-esterified in the normal fashion but cannot be assembled into chylomicrons. Consequently triglycerides are stored within the cells, creating lipid vacuolation, visible under the light microscope with special fat stains.

Concomitantly there is complete absence in plasma of all lipoproteins containing apolipoprotein B (chylomicrons, very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL). The failure to absorb certain essential fatty acids leads to systemic lipid membrane abnormalities (Crawford '94: 800).

A unique, very small subgroup of pregnant patients (0.1%) develops hepatic complications directly attributable to pregnancy. **Preeclampsia** occurs in 7 to 10% of pregnancies and characterized by maternal hypertension, proteinuria, peripheral edema, coagulation abnormalities and varying degrees of disseminated intravascular coagulation. When hyperreflexia and convulsions occur the condition is called eclampsia. Hepatic disease is distressingly common in preeclampsia, usually as part of a syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). In mild cases, patients may be managed conservatively, definitive treatment in severe cases requires termination of the pregnancy. Acute fatty liver of pregnancy presents in the latter half of pregnancy, Symptoms may be directly attributable to hepatic failure, including bleeding, nausea, and vomiting, jaundice or coma. In 20 to 40% of cases, the symptoms coexist with preeclampsia. Although it usually runs a mild course patients can progress within days to hepatic failure and death. The primary treatment for **acute fatty liver of pregnancy** is termination of the pregnancy. **Intrahepatic cholestasis** of pregnancy being with pruritis in the third trimester, followed by darkening of the urine and occasionally light stools and jaundice. Although generally a benign condition, the mother is at risk for gallstones and malabsorption and the incidence of fetal distress, stillbirths, and prematurity is modestly increased (Crawford '94: 875-876).

Extrahepatic biliary atresia (EHBA) occurs in 1: 10,000 live births, one-third of infants with neonatal cholestasis. EHBA is defined as a complete obstruction of bile flow owing to destruction or absence of all or part of the extrahepatic bile ducts. It is the single most frequent cause of death from liver disease in early childhood and accounts for 50 to 60% of children referred for liver transplantation, owing to the rapidly progressing secondary biliary cirrhosis. Most infants with EHBA are born with an intact biliary tree, which undergoes progressive inflammatory destruction in the weeks following birth. Without surgical intervention death usually occurs within 2 years of birth. Prolonged conjugated hyperbilirubinemia in the neonate, termed neonatal cholestasis, affects approximately 1 in 2500 live births. **Neonatal cholestasis and hepatitis** are not specific entities, nor are the disorders necessary inflammatory but the diagnosis should bring about a diligent search for recognizable toxic, metabolic and infectious liver diseases. Affected infants have jaundice, dark urine, light or acholic stools and hepatomegaly. 50 to 60% of cases are idiopathic and 20% are due to extrahepatic biliary atresia (EHBA) and 15% to Alpha$_1$Antitrypsin (α_1-AT) deficiency. **Choledochal cysts** are congenital dilations of the common bile duct presenting most often in children before age 10 with the nonspecific symptoms of jaundice or recurrent abdominal pain typical of biliary colic or both. Approximately 20% of patients become symptomatic only in adulthood. The female-to-male ratio is 3 to 4:1 (Crawford '94: 890, 867, 891). **Cystic fibrosis** (mycovisciododi, fibrocystic disease of pancrease) is by far the common cause of pancreatic disease in childhood and is possibly the commonest lethal single-gene disease. It is transmitted as an autosomal recessive trait and the incidence is of the order of 1 in 1500-1800 live births in the West. Treatment is wholly supportive, and death usually supervenes from the respiratory complications during adolescence or early adulthood. The pancreas is from birth hard and knobbly with fibrosis and cystic dilatation of the ducts. Cirrhosis of the liver is a later feature. The lungs are normal at birth but repeated infection with produces bronchitis, bronchiectasis, fibrosis, emphysema and cor pulmonale. Almost all patients eventually develop an almost ineradicable pulmonary infection with *Pseudomonas auruginosa* (Jones et al '85: 106-109).

About 10% of all people are born with potentially significant malformations of the urinary system. Renal dysplasias and hypoplasias account for 20% of chronic renal failure in children. **Congenital renal disease** can be hereditary but is most often the result of an acquired developmental defect that arises during gestation. Genetic abnormalities may also cause enzymatic or metabolic defects in tubular transport, such as syctinuria and renal tubular acidosis. All except horseshoe kidney are uncommon. **Horseshoe kidney** is caused by fusion of the upper or lower poles of the kidneys produces a horseshoe-shaped structure that is found in 1 in 500 to 1,000 autopsies. Ninety percent of such kidneys are fused at the lower pole and 10% are fused at the upper pole. **Agenesis of the kidney** can be bilateral, which is incompatible with life, usually encountered in stillborn infants, and is often associated with other congential disorders and leads to early death. Unilatera agenesis is compatible with normal life if no other abnormalities exist. The opposite kidney is usually enlarged as a result of compensatory hypertrophy. Some patients eventualy develop progressive glomerular sclerosis in the remaining kidney. **Hypoplasia** refers to a failure of the kidneys to develop to a normal size. This anomaly may occur bilaterally, resulting in renal failure in early childhood, but it is more commonly encountered as a unilateral defect. Most cases probably represent acquired scarring but a truly hypoplastic kidney shows no scars and has a reduced numer of renal lobes and pyramids, usually six or fewer. In one form of hypoplastic kidney, oligomeganephronia, the kidney is small with fewer nephrons that are markedly hypertrophied. **Ectopic kidneys** lie either just above the pelvic brim or within the pelvis. They are usually normal or slightly small in size but otherwise not remarkable, because of their abnormal position, kinking or tortuosity of the ureters may cause some obstruction to urinary flow, which predisposes to bacterial infection. **Multicystic renal dysplasia** is characterized by the persistence in the kidney of abnormal structures-cartilage, undifferentiated mesenchyme and immature collecting ductures, and by abnormal lobar organization. Most cases are associated with ureteropelvic obstruction, ureteral agenesis or atresis and other anomalies of the lower urinary tract. Dysplasia, enlargement of the kidney, can be unilateral or bilateral and is almost always cystic. When unilateral surgical nephrectomy is performed, when bilateral renal failure may ultimately result (Alper '10: 954-956).

Congenital anomalies of the kidney occur more frequently than in any other organ. Some cause no difficulty, but many, for example, hypoplasia, polycystic kidneys, cause impairment of renal function. A significant incidence of renal agenesis ectopy, malrotation and duplication has been observed in association with congenital scoliosis and kyphosis. Unilateral agenesis, hypoplasia and dysplasia are often seen in association with superlevator imperforate anus. Renal dysplasia present protea manifestations. **Simple cysts** of the kidneys are usually unilateral and single but may be multiple. As a simple cyst grows, it compresses and thereby may destroy renal parenchyma, but rarely does it destroy so much renal tissue that renal function is impaired. A solitary cyst may compress the ureter, causing progressive hydronephrosis. Infection may then complicate. The differential diagnosis is with cancer. Cysts are generally left alone, if they become infected antimicrobials are used. Metronidazole may reduce post-streptococcal kidney infection, malabsorption and antibiotic associated colitis. Surgical drainage is often required. Surgical excision of the extra-renal portion of the cyst wall and drainage will prove curative. About one in a thousand individuals has some type of renal fusion, the most common being the horseshoe kidney. **Congenital ectopic kidney** is a low kidney on the proper side that failed to ascend normally. It may lie over the pelvic brim or in the pelvis. Rarely in the chest. It usually causes no symptoms unless complications such as ureteral obstruction or infection develop. **Medullary sponge kidney** is a congenital autosomal recessive defect characterized by widening of the distal collecting tubules. The only symptoms are those arising from infection and stone formation. A single renal artery is noted in 75-85% of individuals and a single renal vein in an

even higher percentage. Aberrant veins and arteries can cause obstruction, aneurysm, renal infarcts due to arterial occlusion, thrombosis of the renal vein, Arteriovenous fistula may be congenital (25%) or acquired. A thrill can often be palpated and a murmur heard both anteriorly and posteriorly (McAninch '88: 493-511).

Cystic diseases of the kidney may be hereditary, developmental or acquired disorders. **Adult polycystic kidney disease** is an autosomal dominant hereditary condition and almost always bilateral(95% of cases). The patient is placed on a low-protein diet (0.5-0.75 g/kg/d of protein) and force fluids to 3000 mL or more per day. Reasonable physical activity is permitted, but not overstrenuous. Hypertension should be controlled. Hemodiaysis may be indicated. Besides Multicystic renal dysplasia, polycystic kidney disease is a hereditary disorder. **Polycystic kidney disease** can be autosomal-dominant (adult) polycystic disease (ADPKD) or autosomal-recessive (childhood) polycystic disease (ARPKD). ADPKD is characterized by multiple expanding cysts of both kidneys that ultimately destroy the renal parenchyma and cause renal failure. It is a common condition affecting roughly 1 of every 400 to 1000 live births and accounting for 5-10% of cases of chronic renal failure requiring transplantation or dialysis. The likelihood of developing renal failure with a PKD1 mutation is less than 5% by 40 years of age, rising to more than 35% by 50, more than 70% at 60 and m ore than 95% by 70. With a PKD2 mutation the odds of renal failure are less than 5% by 50, 15% at 60, and about 45% at 70. Progression is accelerated in blacks (largely correlated with the sickle cell trait), in males, and in the presence of hypertension. Individuals with PKD tend to have extra-renal congenital anomalies and about 40% have one to several cysts in the liver (polycystic liver disease) that are usually asymptomatic. Cysts are derived from biliary epithelium. Cysts occur much less frequently in the spleen, pancreas, and lungs. Intracranial berry aneurysms arise in the circle of Willis, and subarachnoid hemorrhages from these account for death in about 4-10% of individuals. Mitral valve prolapse and other cardiac valvular anomalies occur in 20-25% of patients, but most are asymptomatic. Patients may survive for many years with azotemia slowly progressing to uremia. Ultimately, about 40% of adult patients die of coronary or hypertensive heart disease, 25% of infection, 15% of a ruptured berry aneurysm or hypertensive intra-cerebral hemorrhage, and the rest of other causes. ARPKD is genetically distinct. Patients who survive infancy may develop a peculiar type of congenital hepatic fibrosis. In older children the hepatic disease is the predominant clinical concern. Such patients may develop portal hypertension with splenomegaly (Alper '10: 956- 959).

The three major types of medullary cystic disease are medullary sponge kidney, a relatively common and unusually innocuous structural change, and nephronophthisis and adult-onset medullary cystic disease, which are almost always associated with renal dysfunction. **Medullary sponge kidney** is restricted to lesions consisting of multiple cystic dilations of the collecting ducts in the medulla. The condition occurs in adults and is usually discovered radio-graphcially. The papillary ducts in the medulla are dilated, and small cysts may be present. The cysts are lined by cuboidal epithelium or occasionally by transitional epithelium. **Nephronophthisis** and adult-onset medullary cystic disease is a group of progressive renal disorders. The common characteristic is the presence of a variable number of cysts in the medulla, usually concentrated at the cortico-medullary junction, cortical tubulo-interstitial damage is the cause of the eventual renal insufficiency. Some forms are inherited as autosomal recessive traits and usually become manifest in childhood or adolescence. As a group, the nephronophthisis complex is now thought to be the most common genetic cause of end-stage renal disease in children and young adults. Adult-onset medullary cystic disease has an autosomal dominant pattern of transmission and is now considered a distinct entity. Affected children present first with polyuria and polydipsia, reflecting a defect in the concentrating ability

of the renal tubules. Sodium wasting and tubular acidosis are also prominent. The kidneys are small and show cysts in the medulla and small cysts in the cortex. The expected course is progression to terminal renal failure during a period of 5 to 10 years (Alper '10: 959, 960).

Hypertrophic pyloric stenosis of infancy is not generally considered congenital abnormality, there is usually no hint of the existence of this condition until the baby begins to vomit in the third or fourth week of life. In the established case, the pathological anatomy is most striking – a dilated thickened stomach with huge hypertrophy of the pyloric circular muscle sufficient to produce severe obstruction to the gastric outlet. The pyloris is an ovoid mass 1.5-2.0 cm long and about 1 cm in diameter which, when contracted, is hard and readily palpable through the abdominal wall. Hypertrophic pyloric stenosis of infancy is a fairly common condition and occurs at the rate of about 3 per 1000 births. As soon as the diagnosis is confirmed the child will be operated on: the circular muscle ring is divided longitudinally in Ramstedt's operation (Pyloromyotomy). This is now a very safe and successful operation although, as recently as 1940, it carried a 25% mortality: this was almost entirely due to cross-infection and subsequent gastroenteritis (Jones et al '85: 271).

2. Dental caries, gingivitis, periodontitis and oral cancer

Dental caries, also described as "tooth decay" or "dental cavities", is an infectious disease, caused 95 percent of the time by sugar, which damages the structures of teeth. The disease can lead to pain, tooth loss, infection, and, in severe cases, death. Today caries are one of the most common diseases throughout the world. In total, more than 95 percent of adults in the United States are afflicted with dental caries. Between 6 and 18 years of age, approximately 75 to 90 percent of children have some kind of malocclusion. Among children in the United States and Europe, 60-80% of cases of dental caries occur in 20% of the population. Twenty-five percent of Americans are without any natural teeth when they die. Teeth infected with caries may no longer jeopardize life as they did before antibiotics, but they compromise its quality. Left untreated, caries can cause excruciating pain and result in loss of teeth. This affects appearance and self-esteem, ability to chew, speak, and occasionally even how well-nourished. Treating caries and its consequences with restorations, crowns, bridges, dentures, root canal therapy, and implants consumes a substantial percentage of the personal expenditures that are spent on dental services, which were almost $41 billion in the United States in 1994 (Smith ’97: 9, 149, 150, 86).

Plaque is a biofilm consisting of large quantities of various bacteria that form on teeth. If not removed regularly, plaque buildup can lead to dental cavities (caries) or periodontal problems such as gingivitis. Given time, plaque can mineralize along the gingiva, forming *tartar*. A process, known as "demineralization", leads to tooth destruction. When the pH drops below 5.5 at the tooth surface, the calcium phosphate in the apatite of the enamel surface dissolves. When 30 percent of the calcium is lost the teeth decay. Saliva gradually neutralizes the acids which cause the pH of the tooth surface to rise above the critical pH. This causes 'remineralization', the return of the dissolved minerals to the enamel. If there is sufficient time between the intake of foods then the impact is limited and the teeth can repair themselves. Saliva is unable to penetrate through plaque, however, to neutralize the acid produced by the bacteria. Dental health organizations advocate preventative and prophylactic measures, such as regular oral hygiene and dietary modifications, to avoid dental caries. The basic diet for oral health is to eat plenty of animal products and brush within ten minutes of eating sugar (Smith '97) and not for half an hour after acidic foods that weaken the enamel. Meat and milk are necessary to provide the teeth with nutritional support for the formation of dental **calcium phosphorus apatite**. Vegans and antibiotic consumers who develop dental problems must take probiotic supplements. Vegans

should probably go vegetarian, because it is doubtful they can get enough phosphorus from the vegetable sources of soy and mung beans and calcium from green leafy and cruciferous vegetables. Use natural chalk (calcium carbonate) based, pH balancing, tooth powder (sold by Uncle Harry's Natural Products), when not entirely satisfied with normal toothpaste.

Caries is a destructive infectious disease instigated by bacteria. For caries to develop, three things have to be present: specific bacteria, fermentable carbohydrates for them to feed on, and a tooth surface that is susceptible to the products that bacteria form. The most cariogenic (caries-producing) bacterial species *Streptococcus mutans*, which feeds on the sugars in foods, is the primary organism involved. It releases lactic, formic and other acids, some of which are capable of dissolving the enamel on the teeth, beginning the disease process. Other organisms play lesser roles: *Lactobacilli* are associated with caries of the pits and fissures on the biting surfaces and *Actinomyces* with root caries. Most children acquire the *S. mutans* infection between 19 and 28 months of age, 83 percent are infected by the age of four years (Smith '97: 81, 87, 88). If the root area is invaded, causing abscesses, the infection may spread throughout the body. In addition to *Streptococcus*, organisms of *Actinomyces*, *Rothia* and *Arthrobacter* predominate in caries of both root and crevicular areas. Antibiotic resistant yeast *Candida albicans* is a common oral infection that can become extremely painful long before the white "thrush" can be seen in the cheeks. (Lewis & Elvin-Lewis '77: 226-228). *C. albicans* is easily treated with OTC anticandidal preparations.

About 20 of the 300 or so different types of bacteria that have been found in the mouth are associated with specific types of **periodontal disease**. Most of the bacteria associated with periodontal diseases are anaerobic, meaning they survive without oxygen. Gingivitis is the first stage of the disease, begins as the plaque below and above the gum-line builds up and the toxins released by the bacteria lead to gum inflammation. As the inflammation continues, the area below the gum-line is colonized by bacteria, and the destructive types proliferate. According to a recent survey of the National Institute of Dental research, almost 44 percent of adults have bleeding gums, an indication of gingivitis, about 15 percent have gum pockets greater than 4 millimeters, and fewer than 2 percent have a pocket depth greater than 7 millimeters indicative of advanced periodontitis. Chronic adult periodontal disease usually begins in adults over the age of 35 (Smith '97: 106, 160).

Measurement of Severity of Periodontal Condition

Healthy gums 1 to 3 millimeters
Gingivitis 2 to 4 millimeters
Mild periodontitis 3 to 5 millimeters
Moderate periodontitis 4 to 6 millimeters
Advanced periodontitis 7+ millimeters

There are **four major forms of periodontitis**, all of which are associated with specific strains of bacteria. (1) Chronic adult periodontitis directly related to deposits of plaque and tartar. Faulty, large or numerous restorations and teeth that are issuing or out of alignment contribute to the retention of plaque and can make an adult more prone to developing this form of periodontitis. (2) Prepubertal periodontitis is found in fewer than 1 percent of children. Juvenile periodontitis occurring ages 11-13 is most associated with the bacteria *Actinobacillus actinomycetermcomitans.* (3) Rapidly progressive periodontitis that affects people older than twenty is usually associated with *Porphyromonas gingivalis* and *Bacteroides forsythus*. (4) Refractory periodontitis includes the antibiotic resistant strains of bacteria, five percent of treated

patients do not benefit from. The traditional way of detecting periodontal disease s to insert a manual probe between the gum and the root surface of the tooth to determine whether the gum is losing its attachment to the tooth. If attachment has been lost, the depth of the pocket increases. The dentist then checks whether and how much the tooth can be moved, whether the gums bleed when they are probed, and whether the gum margin has receded. In general, the measurements of pocket depth listed correlate with the following periodontal conditions (Smith '97: 114, 115, 116). Carafate (Sucralfate) is effective for duodenal and mouth ulcers in conjunction with a broad spectrum of antibiotics.

The total incidence of **oral cancers** is about 50,000 cases per year with 8,000 deaths. Surgeries to remove some of these cancers are traumatic and destroy the victim's quality of life (Jerome '00: 402). In the United States men between the ages of 40 and 65 have the highest rate of oral cancers. The most common sites are the lip, the floor of the mouth and the lateral tongue. Oral cancer makes up between 2 and 5 percent of all cancers. Signs of oral cancer are a sore in your mouth that bleeds easily and does no heal. A lump or thickening in you cheek that you can feel with your tongue. A white or red patch on your tongue, gums, or oral mucosa. Soreness of the throat or the sensation that something is caught in your throat. Difficulty chewing or swallowing. Numbness in your tongue or elsewhere in your mouth. For a number of reasons, including the loss of teeth, dependence on caregivers, and difficulty getting to appointments, many older persons do not routinely visit the dentist. As a result, they miss regular screenings for oral cancer. In general, if you have any sore in or around your mouth that does not heal within 10 to 14 days, you should have it checked by your dentist. Pain and numbness develop later. Between 70 and 90 percent of oral cancers are squamous cell carcinomas. They are treated most often surgically by a head and neck cancer specialist. In many instances surgery is followed with radiation therapy and chemotherapy. In 1991 20 percent of high-school-aged boys either chewed tobacco or placed it in their cheeks. An eightfold increase from 15 years earlier before smoking areas were abolished. Chronic users have 50 times the risk of developing cancers of the gums and lower lip, 4 times the chance of developing oral cancer and an increased risk of developing high blood pressure, heart attacks, kidney disease, and strokes. Smokeless tobacco can erode the enamel of teeth and irritate the gums, cause them to whiten and recede (Smith '97: 153, , 171, 161, 162).

Leukemia is a group of cancers that affect the blood. Both the condition and the powerful chemicals and drugs used to treat it can cause oral changes, including swelling, inflammation and bleeding of the gums, candidiasis, and lesions in the soft tissues of the mouth. Patients whose leukemia is in remission can receive dental treatment, although the clotting time of the blood should be tested before scaling or surgery and antibiotics used pre-op. Leukopenia results from drugs, radiation or disease where there is an abnormal decrease in the numbers of one or all kinds of white blood cells. As a consequence, the individual is susceptible to infection and may warrant premedication with antibiotics. **Radiation** that is used to treat cancers of the head and neck can cause a number of acute and chronic dental problems – it can destroy the salivary glands so that the mouth is very dry, swallowing becomes difficult, and dental caries is rampant, mucositis, candidiasis, sensitivity of the teeth, loss of taste, and damage to the bone (Smith '97: 201, 202, 171)(Sanders '12: 28).

3. Vomiting, reflux, hiatal hernia, varices and esophageal neoplasm

Vomiting occurs when the brain responds to the alarm, activates the area responsible for vomiting and switches the body to emergency mode. The blood drains from the cheeks and is sent to the abdomen. Blood pressure drops and heart rate falls. Finally, the unmistakable sign: a lot of saliva to protect the teeth from the corrosive effects of gastric acid. To begin the stomach and gut move in small, nervous waves, shoving the contents in completely opposite directions. An empty stomach is no defense against vomiting, sine the small intestine is just as able to expel its contents. The stomach opens the gate to allow the contents of the small intestine back in, stimulating sensitive nerves. The lungs take a particularly large breath before the airway is closed. The stomach and the opening of the esophagus relaxes and the diaphragm and abdominal muscles abruptly press upward, propelling the entire contents of the stomach from the body. Vomit that contains recognizable bits of food is almost certainly to have come from the stomach. The smaller the particles, the more bitter the taste, and the more yellow the color, the more likely it is to be from the small intestine (Enders '15: 98-107).

Sudden vomiting, almost without warning is likely to be caused by a gastrointestinal virus. Food and alcohol poisoning also cause vomiting in surges, after being warned by nausea. Motion sickness is caused when the information sent to the brain from the eyes is at odds with that sent by the ears, the brain cannot understand what is going on and panics. Vomiting can also be caused by intense feelings of stress and anxiety for which the body synthesizes the stress-response hormone CRF (corticotropin-releasing factor) in the brain and gut. When gastrointestinal cells register large amounts of CRF, the body reacts with diarrhea, nausea or vomiting. Strategies for reducing vomiting attacks are keep eyes fixed on the horizon ahead, ginger is soothing, anti-vomiting drugs are similar to anti-allergy medicine, and stroking P6 in acupuncture point effective against vomiting located two to three finger-breaths below the wrist, right between the two prominent tendons of the lower arm. The human, apes, dogs, cats, pigs and birds are especially designed to be able to vomit. Those that are not able to vomit are mice, rats, guinea pigs, rabbits, and horses. Their esophagus is too long and narrow and they lack the nerves. Animals that cannot vomit have to have different eating habits. Rats and mice nibble their food to test their suitability. Rodents are better at breaking down toxins because their liver has more of the necessary enzyme, and are even able to digest feces. If something bad ends up in the intestine of horses, the results can often be life-threatening (Enders '15: 98-107).

Vomiting (known medically as **emesis** and informally as throwing up and numerous other terms) is the forceful expulsion of the contents of one's stomach through the mouth and sometimes the nose. Vomiting can be caused by a wide variety of conditions; it may present as a specific response to ailments like gastritis or poisoning, most commonly overconsumption of alcoholic beverages or as a non-specific sequela of disorders ranging from brain tumors and elevated intracranial pressure to overexposure to ionizing radiation. The feeling that one is about to vomit is called **nausea**, which often precedes, but does not always lead to vomiting. Antiemetics are sometimes necessary to suppress nausea and vomiting. In severe cases, where dehydration develops, intravenous fluid may be required. Vomiting is different from regurgitation, although the two terms are often used interchangeably. **Regurgitation** is the return of undigested food back up the esophagus to the mouth, without the force and displeasure associated with vomiting. The causes of vomiting and regurgitation are generally different. Vomiting can be dangerous if the gastric content enters the respiratory tract. Under normal circumstances the gag reflex and coughing prevent this from occurring, however these protective reflexes are compromised in persons under the influences of certain substances such as alcohol or anesthesia. The individual may choke and asphyxiate or suffer an aspiration pneumonia.

The vomiting act has two phases. In the **retching phase**, the abdominal muscles undergo a few rounds of coordinated contractions together with the diaphragm and the muscles used in respiratory inspiration. For this reason, an individual may confuse this phase with an episode of violent hiccups. In this retching phase nothing has yet been expelled. In the next phase, also termed the **expulsive phase**, intense pressure is formed in the stomach brought about by enormous shifts in both the diaphragm and the abdomen. These shifts are, in essence, vigorous contractions of these muscles that last for extended periods of time - much longer than a normal period of muscular contraction. The pressure is then suddenly released when the upper esophageal sphincter relaxes resulting in the expulsion of gastric contents. Individuals who do not regularly exercise their abdominal muscles may experience pain in those muscles for a few days. The relief of pressure and the release of endorphins into the bloodstream after the expulsion causes the vomiter to feel better.Gastric secretions and likewise vomit are highly acidic. Recent food intake appears in the gastric vomit.

Irrespective of the content, vomit tends to be malodorous. The content of the *omitus* (vomit) may be of medical interest. Fresh blood in the vomit is termed hematemesis ("blood vomiting"). Altered blood bears resemblance to coffee grounds (as the iron in the blood is oxidized) and, when this matter is identified, the term "coffee ground vomiting" is used. **Bile** can enter the vomit during subsequent heaves due to duodenal contraction if the vomiting is severe. Fecal vomiting is often a consequence of intestinal obstruction or a gastrocolic fistula and is treated as a warning sign of this potentially serious problem ("signum mali ominis"). If the vomiting reflex continues for an extended period with no appreciable vomitus, the condition is known as non-productive emesis or **dry heaves**, which can be painful and debilitating. Bright red in the vomit suggests bleeding from the esophagus. Dark red vomit with liver-like clots suggests profuse bleeding in the stomach, such as from a perforated ulcer. Coffee ground-like vomit suggests less severe bleeding in the stomach, because the gastric acid has had time to change the composition of the blood. Yellow vomit suggests bile. This indicates that the pyloric valve is open and bile is flowing into the stomach from the duodenum. (This is more common in older people.).

Prolonged and excessive vomiting depletes the body of water (dehydration), and may alter the electrolyte status. Gastric vomiting leads to the loss of acid (protons) and chloride directly. Combined with the resulting alkaline tide, this leads to hypochloremic metabolic alkalosis (low chloride levels together with high HCO_3^- and CO_2 and increased blood pH) and often hypokalemia(potassium depletion). The hypokalemia is an indirect result of the kidney compensating for the loss of acid. With the loss of intake of food the individual may eventually become cachectic. A less frequent occurrence results from a vomiting of intestinal contents, including bile acids and HCO_3^-, which can cause metabolic acidosis. Repeated or profuse vomiting may cause erosions to the esophagus or small tears in the esophageal mucosa (Mallory-Weiss tear). This may become apparent if fresh red blood is mixed with vomit after several episodes.Recurrent vomiting, such as observed in bulimia nervosa, may lead to destruction of the tooth enamel due to the acidity of the vomit. Digestive enzymes can also have a negative effect on oral health, by degrading the tissue of the gums.

Vomiting is a common symptom having many causes inside and outside the gastrointestinal tract. An **emetic,** such as syrup of ipecac, is a substance that induces vomiting when administered orally or by injection. An emetic is used medically where a substance has been ingested and must be expelled from the body immediately (for this reason, many toxic and easily digestible products such as rat poison contain an emetic). Inducing vomiting can remove the substance before it is absorbed into the body. Ipecac abuse can cause detrimental health effects

(Lewis and Elvin-Lewis ’77: 279-280). An **antiemetic** is a drug that is effective against vomiting and nausea. Antiemetics are typically used to treat motion sickness and the side-effects of medications such as opioids and chemotherapy. Antiemetics act by inhibiting the receptor sites associated with emesis. Hence, anticholinergics, antihistamines, dopamine antagonists, serotonin antagonists, and cannabinoids are used as anti-emetics. Antiemetics include: 5-HT_3receptor antagonists – these block serotonin receptors in the central nervous system and gastrointestinal tract. As such, they can be used to treat post-operative and cytotoxic drug nausea & vomiting. However, they can also cause constipation or diarrhea, dry mouth, and fatigue. Dolasetron (Anzemet) - can be administered in tablet form or in an injection. Granisetron (Kytril, Sancuso) - can be administered in tablet (Kytril), oral solution (Kytril), injection D(Kytril), or in a single transdermal patch to the upper arm (SANCUSO). Ondansetron (Zofran) - administered in an oral tablet form, orally dissolving tablet form, orally dissolving film, or in an IV/IM injection. Tropisetron (Setrovel, Navoban) - can be administered in oral capsules or in injection form. Palonosetron (Aloxi) - can be administered in an injection or in oral capsules. NK1 receptor antagonis are Aprepitant (Emend) Commercially available NK1 Receptor antagonist and Casopitant Investigational NK1 receptor antagonist. Antihistamines (H_1 histamine receptor antagonists), effective in many conditions, including motion sickness, morning sickness in pregnancy, and to combat opioid nausea, such as Cyclizine, Diphenhydramine (Benadryl), Dimenhydrinate (Gravol, Dramamine), Doxylamine, Meclozine (Bonine, Antivert), Promethazine (Pentazine, Phenergan, Promacot) can be administered via a rectal suppository for adults and children over 2 years of age.

One of the most direct ways to prevent vomiting is to inhibit the hyperactivity of the vomiting center by using **anticholinergic drugs**. Antihistamines such as Dramamine or hydramine have mild antiemetic effects. Two synthetic compounds are the phenothiazines (chlorpromazine, piperazine) and othopramides (metoclopramide), they work in three minutes. To sooth the stomach there are Aristolochiaceae, *Aristolochia serpentine* (Virginia snakeroot), Nyrtaceae, *Eugenia caryophyllata* (clove tree). Lamiaceae, *Menthe piperita* (peppermint), *Monarda puncata* (horsemint), Rosaceae, *Rubus* spp. (blackberry and thimbleberry) (Lewis and Elvin-Lewis ’77: 279-280). **Cannabinoids** are used in patients with cachexia, cytotoxic nausea, and vomiting, or who are unresponsive to other agents. These may cause changes in perception, dizziness, and loss of coordination. Cannabis - Medical marijuana, in the U.S., it is a Schedule I drug. Dronabinol (Marinol) – a Schedule III drug in the U.S. Some synthetic cannabinoids such as Nabilone (Cesamet) or the JWH series. Sativex is an oral spray containing THC and CBD. Propofol given intravenously. It has been used in an acute care setting in hospital as a rescue therapy for emesis. Peppermint is claimed to help nausea or stomach pain when added into a tea or peppermint candies. Ginger - contains 5HT3 antagonists gingerols and shogaols. The traditional home remedy for vomiting, like diarrhea, is to eat **plain white rice**, the nausea tends to subside as soon as this food hits the stomach, but patients tend to not have any appetite and if vomiting or diarrhea are very severe, such as in cholera, are to hydrate by drinking white rice water made with one cup of rice to three cups water boiled for the normal amount of time, about 20 minutes. Antibiotic resistant *Helicobacter pylori* , the most common dangerous pathogen infecting the stomach and esophagus, responds only to metronidazole, that is essential to the curative treatment of anyone suffering from esophagitis and reflux (joint or digestive disease), but women in their first trimester of pregnancy when it can impair neural development of the fetus. Metronidazole (Flagyl ER) cures *H. pylori*.

Injury to the esophageal mucosa with subsequent inflammation is common worldwide. In northern Iran, the prevalence of esophagitis is more than 80%, it is also extremely high in regions of China. In the United States and other Western countries, **esophagitis** is present in about 10%

to 20% of the adult population. The inflammation may have many origins (1) reflux esophagitis, (2) prolonged gastric intubation, (3) ingestion of irritants, such as alcohol, corrosive acids or alkalis (in suicide attempts), excessively hot fluids (i.e. hot tea in Iran), and heavy smoking, (4) Cytotoxic anticancer therapy, with or without superimposed infection, (5) infection, usually antibiotic resistant *H. pylori* cured with **metronidazole**, following bacteremia or viremia; herpes simplex viruses and cytomegalovirus are the more common offenders in the immunosuppressed, (6) fungal infection in debilitated or immunosuppressed patients or during broad-spectrum antimicrobial therapy. Candidiasis is the most common; mycomycosis and aspergillosis may occur, (7) uremia, (8) radiation, (9) systemic conditions associated with decreased LES tone, including hypothyroidism, systemic sclerosis and pregnancy, (10) in association with systemic desquamitive dermatologic conditions such as pemphigoid and epidermolysis bullosa and (11) graft-versus-host disease. Patients with a frequent and persistent feeling that there is a lump in their throat even when they are not eating may well be suffering from a globus problem.

To call the problem a **globus**, it must be ascertained that there is never any difficulty in swallowing and that there is no weight loss, association with acid reflux, or any demonstrable motility disturbance of the esophagus. Sometimes the best approach is an empirical trial of a proton pump inhibitor (PPI) taken once a day, in the morning before breakfast, for 4 to 6 weeks (Newman ’11: 112). Protonix (Pantoprazole) is also useful for minor abrasion of the esophagus. Aciphex (Rabeprazole Sodium) is an anti-ulcer drug useful for treating inflammation of the esophagus. **Developmental defects** are uncommon and must be corrected early because they are incompatible with life – absence of an esophagus is extremely rare, in atresia a segment of the esophagus is represented by a thin, non-canalized cord, with a blind pouch connected to the pharynx and another to the stomach. Non-neoplastic constrictions may occur as developmental defects. Because the gut and respiratory tract begin as a single tube embryonically, it is not uncommon to have a fistula connecting the lower pouch with a bronchus or the trachea. Often associated anomalies are congenital heart disease and malformations of other portions of the GI (Crawford ’94: 762).

Acid reflux, technically known as gastro-esophageal reflux disease (GERD), a chronic form of heartburn is common. Up to 25% of the population experiences heartburn regularly. GERD occurs when the esophageal sphincter, which normally keeps food and acid in the stomach where they belong, repeatedly fails to close tightly enough, allowing stomach acid to flow back, or reflux, into the esophagus and create that burning feeling. As obesity increases the number of people with GERD increases as well. The classic symptoms are burning and regurgitation, bringing up food without retching, especially when bending over or lying down. Other symptoms of GERD include hoarseness, cough and a raspy voice. GERD patients often express an intolerance to citric drinks, like orange and grapefruit juices and to chocolate. Surprisingly they often tolerate spicy foods. Empirical treatment with a daily potent acid suppressor, such as a protein pump inhibitor (PPI) before breakfast is quite dramatic in controlling GERD symptoms. If a patient has burning and does not respond to a PPI, the most likely diagnosis is FD (Newman ’11: 71). The link between GERD and asthma is pretty clear, with as many as 70 percent of people with asthma also suffering from GERD compared with 20 to 30% in the general population. Useful in the treatment of GERD are antacids and the proton pump inhibitors (PPIs) Prilosec (Omeprazole) and Nexium (Esomeprazole Magnesium) as well as the antiemetic and gastroprokinetic agent Reglan (Metoclopramide). It may be necessary to modify the acid-base balance with antacids and bicarbonate. Essentially, small meals that are rich in vegetables and include modest servings of complex carbs and lean protein are usually best. A protein elimination diet is usually best (Berger ’04: 62, 142).

Reflux is the regurgitation of gastric acid and digestive enzymes into the pharyngeal area; in the case of heartburn, those juices travel no farther than the end of the esophagus, causing a burning sensation in the chest. When the nerves of the digestive system receive incorrect information, they fail to keep gastric juices where they belong and allow them to move in the wrong direction. The junction between the esophagus and the stomach is an area that is particularly susceptible. Despite safety measures that include a narrow esophagus, a steadied position in the diaphragm, and the curve at the entrance to the stomach, things sometimes still go wrong. Around a quarter of people regularly experience such problems. The nervous system of the brain and the gut work together. The sphincter muscle between the esophagus and stomach is under control of nerves from the brain. The brain also influences gastric aid production. The nerves of the digestive tract ensure that the esophagus moves things in a downward wave, keeping it clean by swallowing a thousand times a day or so. Practical tips to help with heartburn and reflux are based on trying to get those two nervous systems back on the right path. Chewing gum or sipping tea can help the digestive tract because small, repeated swallows help nudge the nerves in the right direction – down toward the stomach, not back up. Relaxation techniques can also help.

There is a strong relation with GERD and chest pain, probably due to **asthma**. This is why poor air quality, smoke and strong smells, even some others find pleasant, can be so nauseating to people suffering reflux. Asthma predisposes people to dietary GERD, indigestion of foods other people enjoy manifests as nausea, the reflux can run concurrently with the asthma or be as curative as brackish water to eliminate indigestible particles. One half of all patients who have asthma also have esophageal reflux. Evidence suggests that treatment of esophageal reflux decreases the medication required to treat asthma. Forced expiration during asthma attacks may increase intraabdominal pressure and cause esophageal reflux. Asthma medications such as theophylline and beta-adrenergic drugs given orally decrease lower esophageal sphincter pressure and may predispose the patient to esophageal reflux. A systemic abnormality may alter both airway smooth muscle function and lower esophageal sphincter function. Esophageal reflux may lead to microaspiration of stomach contents into the airways, thereby inducing asthma attacks. Esophageal reflux may stimulate sensory nerve endings in the distal esophagus, which causes bronchoconstriction through vagal reflex pathways. Often asthma is most severe in the middle of the night. A disproportionate number of asthmatic patients die in their sleep. Aspiring nonsteroidal anti-inflammatory drugs, and acetaminophen cause severe bronchoconstriction in a subpopulation of persons with asthma. The association of aspirin sensitivity, nasal polyps and asthma is often known as "triad asthma". Nonselective beta-adrenergic blockers precipitate severe bronchoconstriction in many asthmatics. Cholinesterase inhibitors used in the treatment of myasthenia gravis, may precipitate asthma attacks. Many food preservative and dyes have been implicated in causing acute asthma attacks. Sulfites, including bisulfites and metabisulfites, precipitate acute attacks in some asthmatics. However, food dyes such as tartrazine and food additives such as monosodium glutamate are questionable in causing asthma attacks. Anxiety and stress may exacerbate asthma. Persons who have asthma should be wary of using gas ranges, which produce NO_2 and should use them only with exhaust fans as a partial protective measure (Bethel '89: 165, 166, 174).

Cigarette smoke stimulates the areas of the brain that are also activated by eating. This may lead to a sense of satisfaction, but it also tricks the brain into producing more gastric aid for no practical reason, as well as causing the sphincter between the esophagus and the stomach to relax. Giving up smoking often helps reduce reflux and heartburn complaints. Pregnancy hormones intended to keep the womb relaxed and cozy, may have a similar effect on the sphincter of the esophagus. The result is a leaky connection to the stomach, which, combined

with the pressure of the bulging belly from below, causes acid to rise. Contraceptives containing female hormones an cause reflux as a side effect. Doctors recommend avoiding foodstuffs that can reduce the strength of the sealing sphincter: chocolate, hot spices, alcohol, sugary sweets, coffee and monosodium glutamate. Antacids may provide relief but should not be relied on for more than four weeks. When symptoms continue despite the use of antacids, doctors will take blood tests. If blood tests and thorough physical examination yield no abnormal results a doctor may prescribe a drug called a proton pump inhibitor (PPI). PPIs inhibit the production of acid and its secretion into the stomach. Short term use of the PPI may leave the stomach laking a little avid, but gives patients a chance to recover from acid attacks. If attacks strike at night it is a good idea to prop the upper body up at an angle of 30 degrees, that is also good for the cardiovascular system. When symptoms such as difficulty swallowing, weight loss, swelling or any sign of blood appears, it is time to explore the stomach with a camera. The real danger with reflux comes not from burning acid, but from bile reaching the esophagus from the small intestine via the stomach. Bile does not cause a burning sensation but can seriously confuse the cells of the esophagus to change into small intestine cells. Mutating cells can make mistakes and no longer grow in a controlled way like other cells, however this serious repercussion affects only a small percentage of people who suffer from acid reflux (Enders '15: 95-97). Clinicians must make sure that antibiotic resistant *Helicobacter pylori* is treated with metronidazole.

Functional dyspepsia (FD) is a very common problem in young people, which is another way of saying that true peptic ulcer disease is usually a problem in the middle-aged and the elderly. In the pre-endoscopy days, dyspeptic complaints led to the performance of many upper gastrointestinal (UGI) series, tests that occasionally showed enough of a deformity of the duodenum for the radiologist to call it an ulcer. Peptic ulcer surgery, either removing a large chunk of stomach or cutting the nerves to the stomach, often with dire consequences, such as dumping syndrome-post-vagotomy diarrhea, or severely prolonged gastric emptying. There are several symptoms of functional dyspepsia that should be investigated with some urgency. Because the diagnosis of FD is most comfortably made in patients younger than 55 serious investigations must be undertaken if an older patients presents with dyspepsia symptoms. In younger patients, the doctor should be highly suspicious if the patient presents symptoms of weight loss, difficulty swallowing, with food getting stuck in the esophagus, painful swallowing, with food hurting as it goes down the esophagus, anemia, vomiting blood, family history of stomach cancer, history of previous stomach surgery, jaundice or abnormal physical examination. Inflammation may be caused by an infection, such as *Helicobacter pylori* (Newman ’11: 65, 66, 70). **Achalsia** – failure of relaxation with consequent dilation of the esophagus – is characterized clinically by progressive dysphagia and regurgitation. Studies show three major abnormalities in achalasia (1) aperistalsis, (2) parital or incomplete relaxation of the LES with swallowing and (3) increased resting tone of the LES (Crawford ’94: 761, 762).

Hiatal hernia is characterized by separation of the diaphragmatic crura and widening of the space between the muscular crura and esophageal wall. Pathogenesis of esophagitis begins with the reflux of gastric contents as the result of (1) decreased efficacy of esophageal anti-reflux mechanisms, (2) the presence of a sliding hiatal hernia, (3) increased gastric volume and (4) reduction in the reparative capacity of the esophageal mucosa by protracted exposure to gastric juices. In Barrett’s esophagus, the distal squamous mucosa is replaced by metaplastic columnar epithelium, as a response to prolonged injury. Healing occurs by re-epithelialization and ingrowth of pluripotent stem cells, which in the microenvironment of a low pH in the distal esophagus differentiate into epithelium that is more resistant to injury. Two anatomic patterns are the axial, or sliding hernia and the nonaxial, or paraesophageal, hiatal hernia. The sliding hernia constitutes 95% of cases; protrusion of the stomach above the diaphragm creates a bell-

shaped dilation, bounded below by the diaphragmatic narrowing. Reflux esophagitis is seen in association with 9% of sliding hernias. Hiatal hernia are reported in 1 to 20% of adult subjects, increasing with age (Crawford ’94: 763, 757-761).

Diverticular outpouchings may develop in the proximal or distal esophagus, sometimes reaching several centimeters in size and be the site of food accumulation and regurgitation (and aspiration) during sleep. Longitudinal tears in the esophagus are termed Mallory-Weiss tears and are believed to be caused by severe retching, seen in alcoholics and excessive vomiting. Esophageal lacerations account for 5 to 10% of upper gastrointestinal bleeding, but is usually not profuse and ceases without surgical intervention. Supportive therapy, such as vaso-constrictive medications, transfusions and sometimes balloon tamponade is usually all that is required. Healing is usually prompt, with minimal to no residua (Crawford ’94: 763, 757-761). **Portal hypertension** leads to the formation of collateral bypass channels. The increased pressure in the esophageal plexus produces dilated tortuous vessels called varices. **Varices** appear as tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach. Varices occur in approximately two-thirds of all cirrhotic patients and is most often associated with alcoholic cirrhosis. Varices produce no symptoms until they rupture, when massive bleeding may occur. Once begun, the hemorrhage rarely subsides spontaneously and endoscopic injection of thrombotic agents (sclerotherapy) or balloon tamponade are usually required. When varices bleed, 40% of all patients die during the first episode. Among those who survive, rebleeding occurs in more than half within 1 year, with a similar rate of mortality for each episode (Crawford ’94: 757-761).

Benign tumors of the esophagus are mostly mesenchymal and are typified by the leiomyoma, which rarely exceeds 3 cm in diameter. Fibromas, lipomas, hemagniomas, neurofibromas, and lymphangiomas may arise. In rare instances, a mesenchymal mass of inflamed granulation tissue, called an inflammatory polyp may resemble a malignant lesion, and can be called inflammatory pseudo-tumor. In the United States, carcinomas of the esophagus represent about 6% of all cancers of the gastrointestinal tract but cause a disproportionate number of cancer deaths. With rare exception, **malignant esophageal tumors** arise from the epithelial layer. For many years, most esophageal cancers were of squamous cell origin, but there has been a declining incidence of these tumors coupled with a steadily increasing incidence of adenocarcinomas. Most squamous cell carcinomas occur in adults over age 50. The male-to-female ratio falls in the range of 2:1 to as high 20:1. Provinces of northern and eastern china exhibit annual incidence rates exceeding 100 per 100,000, with deaths from cancer of the esophagus constituting more than 20% of all cancer deaths. Other areas of high incidence include Puerto Rico, Iran, south African and the republics of the former Soviet Union. In the United States, it affects between 2 and 8 persons per 100,000 yearly and is predominantly a disease of men (male-to-female ratio = 4:1). Blacks throughout the world are at a higher risk than are whites, with the incidence being fourfold higher for blacks in the United States. The presence of carcinogens, such as fungus-contaminate and nitrosamine-containing foodstuffs and nutritional deficiencies play a major role. Alcohol consumption and smoking are strongly associated with esophageal cancer in Europe and the United States. Adenocarcinomas now represent one-quarter of all esophageal cancers reported in the United States and more than one-half of this in the distal third of the esophagus, often in the setting of Barrett’s esophagus. The prognosis of esophageal adenocarcinoma is as poor as that for other forms of esophageal cancer with a less than 15% 5 year survival rate. Early diagnosis with definitive resection improves 5 year survival to more than 50%. No medical therapy has been shown to decrease the risk of esophageal cancer in patients with Barrett’s esophagus (Crawford '94: 763-766).

Esophageal cancer is a highly lethal squamous cell carcinoma that represents 1.5% of all cancers, and 7% of all gastrointestinal cancers in the United States. Although in the United States the incidence is relatively low (6 cases per 100,000 males), in other parts of the world, including China, Iran, Finland, Curacao, and part of Africa, the incidence can reach 500 cases per 100,000. In most cases esophageal cancer appears to result from exposure to environmental carcinogens. In high incidence countries it is associated with the ingestion of nitrosamines, other carcinogens, and the presence of diets depleted in riboflavin, nicotinic acid, magnesium and zinc. In the United States the disease is usually seen in the setting of alcohol and tobacco abuse. Esophageal carcinoma is a malignancy of squamous epithelium. Distal esophageal malignancies, however, may be adenocarcinomas, usually arising at the cardioesophageal junction in the areas of gastric metaplasia or in Barrett's esophagus. The major symptom of esophageal carcinoma is dysphagia. Patients may have difficulty swallowing large pieces of food, or there may be complete inability to swallow. The morbidity and mortality associated with esophageal cancer results form both local-regional spread and distant metastases. Invasion of the trachea or bronchus makes a patient inoperable and raises the possibility that a tracheosesophageal fistula may develop. Before considering surgical resection, one must rule out disseminated metastatic disease. A chemistry profile and whole-lung computed tomographic (CT) scan are appropriate. Biopsy of abnormal supraclaviular nodes is mandatory, but if the mediastinal CT scan suggests adenopathy, mediastinoscopy should be considered. An abdominal CT scan helps to rule out hepatic metastases and also to evaluate the celiac lymph nodes, a frequent site of metastases. Some patients with esophageal cancers will have elevated carcinoembryonic antigen (CEA) in the serum, particularly if liver metastases is present (Macdonald '90: 223, 224).

Staging for Esophageal Cancer

Stage I	**Primary Tumor (T)**
T1, N0, M0	T0 No demonstrable tumor T1S Carcinoma in situ T1 Tumor involves 5 cm or less of esophageal length with no obstruction nor complete circumferential involvement nor extraeophageal spread T2 Tumor involves more than 5 cm of esophagus and produces obstruction with circumferential involvement of the esophagus but no extraesophageal spread. T3 Tumor with extensions outside the esophagus involving mediastinal structures
Stage II T1, N1, M0 T1, N2, M0 T2, N0, M0 T2, N1, M0 T2, N2, M0	**Regional Lymph Nodes** Cervical esophagus (cervical and supraclavicular lymph nodes) N0 No nodal involvement N1 Unilateral involvement (moveable) N2 Bilateral involvement (moveable) N3 Fixed node Thoracic esophagus (nodes in the thorax, not those of the cervical, supraclavicular, or abdominal areas) N0 No nodal involvement N1 Nodal involvments
Stage III Any M1 Any T3	**Distant metastases** M0 No metastases M1 Distant metastases. Cancer o thoracic sophagus with cervical,

	supraclavicular, or abdominal lumph node invovlmeent is classified as M1

Source: Macdonald '90: Table 29-1, Pg 224

The maximum 5 year survival of esophageal cancer patients treated by surgery is generally 20%, and the vast majority of patients have less than a 5% to 10% probability of long-term survival with surgery only. Radiation therapy for patients with significant dysphagia can be palliative and can allow patients to eat. However, there is no good evidence, except for cervical esophageal cancer, that radiation alone has been curative. **Chemotherapy** of patients with advanced disseminated disease is clearly only palliative. Chemotherapy regimens utilizing combination of 5-fluorouracil (5-FU) (1000 mg/m^2 per day, IV continuous infusion on days 1 to 4; repeat on days 29 and 32) and cisplatin (75 mg/m^2, IV day 1 and day 29 only), or 5-FU and mitomycin and 3000 cGy of radiation, can be effectively used in the management of patients with esophageal cancer. In one study 17% were shown to have no tumor in the resected esophageal specimens. The median survival of patients achieving pathologic complete remission was 32 months with 67% and 45% at 2 and 3 years after surgery. Placement of intra-luminal esophageal intubation tubes allow the patient to feed and swallow but is associated with significant mortality (10% to 40%), the major life-threatening complication is esophageal rupture and subsequent mediastinitis (Macdonald '90: 225, 226).

4. Gastritis, peptic ulcers, stomach defects and cancer

Gastritis is an inflammation of the gastric mucosa. Inflammation may be predominantly acute, with neutrophilic infiltration, or chronic, with lymphocytes or plasma cells predominating. Acute gastroenteritis is frequently associated with (1) heavy use of non-steroidal anti-inflammatory drugs (NSAIDs) particularly aspirin, (2) excessive alcohol consumption, (3) heavy smoking, (4) treatment with cancer chemotherapeutic drugs, (5) uremia, (6) systemic infections (e.g. salmonellosis), (7) severe stress, (8) ischemia and shock, (9) gastric irradiation, (10) mechanical trauma (e.g. nasogatric intubation), and (11) following distal gastrectomy. Depending on the severity of the anatomic changes, acute gastritis may be entirely asymptomatic, may cause variable epigastric pain, nausea, and vomiting, or may present with overt hemorrhage, massive hematemesis, melena and potentially fatal blood loss. As many as 25% of persons who take daily aspiring develop acute gastritis, many with bleeding. Chronic gastritis is defined as the presence of chronic mucosal inflammatory changes leading eventually to mucosal atrophy and epithelial metaplasia, usually in the absence of erosions. The epithelial changes may become dysplastic and constitute a background for developing carcinomas. The major etiologic associations of chronic gastritis are (1) immunologic, associated with pernicious anemia, (2) chronic infection, especially antibiotic resistant *Helicobacter pylori*, cured with metronidazole (Flagyl ER) (3) toxic, as with alcohol consumption and cigarette smoking, (4) post-surgical, especially antrectomy and gastro-enterostomy with reflux of bilious duodenal secretions, (5) motor and mechanical, including obstruction, bezoars (luminal concretions) and gastric atony, (6) radiation, (7) granulomatous conditions (e.g. Crohn's disease) and (8) miscellaneous, graft-versus-host disease, amyloidosis, uremia etc. (Crawford '94: 770-771).

The top part of the stomach is called the **fundus** or body, is a compliant reservoir that can allow a pretty large volume of food to remain in the stomach painlessly until it can be slowly emptied into the intestine. On occasion, the stomach body is less compliant and really disapproves of holding large volumes of food or liquid. This can be quite uncomfortable or, on occasion, seriously painful. The bottom part of the stomach, called the antrum, is a pump that sends food

into the first part of the intestine in a regulated manner. In many disease states, this pump does no function well and the patient suffers from delayed gastric emptying (Newman '11: 18). **Autoimmune gastritis** also designated diffuse corporal atrophic gastritis, reflects the presence of autoantibodies to the gastric gland parietal cells which leads to loss of acid and intrinsic factor production, it is uncommon and usually associated other autoimmune disorders such as Hashimoto's thyroiditis and Addison's disease. Chronic infection by *Helicobacter pylori* appears to be the major cause of chronic gastritis. *H. pylori* is present in a high percentage of patients with chronic gastritis affecting the antrum and corpus. *H. pylori* colonization rates increase with age reaching 50% of asymptomatic adult Americans older than 50 and is the most common gastrointestinal infection. *H. pylori* colonization of gastric mucosa damaged by other events leads to a state of retarded healing and chronic mucosal inflammation is the most plausible theory. Patients respond well to antimicrobial agents and relapses are associated with reappearance of this organism. Most infected persons remain asymptomatic but are at increased risk for the development of peptic ulcer disease and possibly gastric cancer. The long term risk of gastric carcinoma for persons with gastric atrophy is in the range of 2 to 4% (Crawford '94: 771-773). *H. pylori* is antibiotic resistant; metronidazole is the definitive curative treatment.

Gastric lesions are frequent causes of clinical disease. **Peptic ulcers** have become almost a hallmark of civilized life and develop in up to 10% of the general population in North America. Cigarette smoking, alcohol consumption, and stress gastritis are one of the everyday causes of "indigestion". In the United States approximately 4 million people have peptic ulcers (duodenal and gastric), and 350,000 new cases are diagnosed each year. Around 100,000 patients are hospitalized yearly and about 3,000 people die each year as a result of peptic ulcer disease. The lifetime likelihood of developing a peptic ulcer is about 10% for American men and 4% for American women. Even with healing the propensity to develop peptic ulcers remains. The male-to-female ratio for duodenal ulcers is about 3:1, and for gastric ulcers about 2:1. In recent years there has been a significant decrease in the prevalence of duodenal ulcers but little change in the prevalence of gastric ulcers. At least 98% of peptic ulcers are located in the first portion of the duodenum or in the stomach, in a ratio of about 4:1. Chronic gastritis is virtually universal among patients with peptic ulcer disease, occurring in 85 to 100% of patients with duodenal ulcers and 65% with gastric ulcers. *Helicobacter pylori* infection is almost always demonstrate in patients with gastritis. Gastritis remains after the ulcer has healed; recurrence of the ulcer does not seem related to the gastritis (Crawford '94: 773-775).

Peptic ulcers are chronic, most often solitary, lesions that occur in any portion of the gastrointestinal tract exposed to the aggressive action of acid-peptic juices. The distinctive features of peptic ulcers are that they are (1) usually a single lesion, (2) tend to be less than 4 cm in diameter, (3) by definition penetrate the muscularis mucosa and may perforate the gastric wall, (4) is frequently recurrent, with intermittent healing, (5) is located in the following sites, with decreasing frequency (a) duodenum, first portion, (b) stomach, usually antrum, (c) within Barrett's mucosa, (d) in the duodenum, stomach, or jejunum of patients with Zollinger-Ellison syndrome, (e) within or adjacent to a Meckel's diverticulum that contains ectopic gastric mucosa (Crawford '94: 773-775). Peptic ulcers are produced by an imbalance between the gastro-duodenal mucosal defense mechanisms and the damaging forces. Gastric acid and pepsin are requisite for all peptic ulcerations. The importance of the acid is evidence by the Zollinger-Ellinger syndrome with its multiple peptic ulcerations, owing to the excess gastrin secretion and acid production. The apparent role of *H. pylori* in peptic ulceration cannot be overemphasized. *H. pylori* infection of gastric mucosa is present in 90 to 100% of patients with duodenal ulcer and 70% of those with gastric ulcer. Gastric ulcero-genesis presumably results from the action of bacterial urease, which generates ammonia, and protease, which breaks down glycoproteins in

the gastric mucus. Damage to the protective mucus layer exposes the underlying epithelial cells to the damaging influence of acid peptic digestion and may thus lead to inflammation. Bleeding occurs in 25-33% of patients, it is the most frequent complication, it may be life threatening and accounts for 25% of ulcer deaths and may also be the first indication of an ulcer. Perforation occurs in about 5% of patients, accounts for two-thirds of ulcer deaths and is rarely the first indication of an ulcer. Obstruction from edema or scarring is most often due to pyloric channel ulcers, may also occur with duodenal ulcers, causes incapacitating, crampy abdominal pain, but rarely leads to total obstruction with intractable vomiting. Intractable pain may also be a complication (Crawford '94: 775). Antibiotic resistant *H. pylori* is cured with **metronidazole**.

The original operation for chronic duodenal ulcer, which had great popularity between 1920 and 1940 was **gastrojejunostomy**. However, it soon became clear that the complete failure to control hypersecretion led, in about 50% of cases to recurrent peptic ulceration, usually on or near the soma. This operation is now occasionally used for very elderly or infirm patients with pyloric stenosis. **Partial gastrectomy** was for many years the standard treatment for chronic duodenal ulcer and produced a high level of satisfactory results. The Polya type of gastrectomy was nearly always chosen. By removing the first part of the duodenum and the gastric antrum, all G cells producing gastrin are excised. By removing a substantial part of the body, the level of gastric secretion of acid is reduced by about 70%. Recurrent of peptic ulceration is fairly unusual (about 3%0. In spite of the radical nature of the surgery, at least 80% of patients obtained an excellent result, but the main drawbacks were closure of the scarred duodenum and a leak from the suture line was very serious, with mortality rates of Polya gastrectomy about 5% which was too high to be acceptable, the reduction of gastric capacity, and various functional sequelae such as dumping and bilious vomiting and late anaemia and carcinoma. Dragstedt introduced truncal vagotomy in 1943. Because the whole stomach and duodenum were denervated, many patients showed delayed gastric emptying and so a drainage procedure, either pyloroplasty or gastrojejunostomy, had to be added. A procedure known as 'vagotomy and drainage' has become popular for duodenal ulcer because it is technically simple and safe, with a mortality below 1% and 75% of patients obtain very good result. However many have some looseness of stool, and for a few, diarrhea is a great nuisance, dumping and bilious vomiting occur in about 10% of patients. Recurrence of ulceration, either in the duodenum or at the stoma, is a complication in about 8%. Around 1955-65 vagotomy and antrectomy was developed to denervate the stomach but remove the area of mucosa responsible for gastrin production, thus lowering acid output by about 90% and recurrent ulcer to 1 in 100 patients (Jones et al '85: 88-90.

The most recent operation to be developed is the 'highly selective vagotomy' (HSV) which aims to totally denervate the stomach, with the exception of the pyloric sphincter and the adjacent area of the antrum normally innervated by nerves and as a consequence, the antrum and pylorus can act as a normal emptying mechanism for the stomach, whilst denervation of the mucosa of the body leads to a major drop in the secretion of pepsin and acid. Dumping and biliary reflex into the stomach do not occur through an intact pylorus. HSV has a very low mortality (less than 1%) and a ulcer recurrence rate of about 8%, that is lower in the hands of experienced surgeons, but is not a suitable operation for patients with severe duodenal fibrosis and pyloric stenosis in whom dilatation of the duodenum or a drainage procedure must be added. The chronic gastric ulcer often requires surgical treatment because medical treatment fails to heal a substantial number of gastric ulcers and there is always doubt whether the ulcer is in fact a carcinoma and the complications – hemorrhage and perforation – carry an unduly high mortality. The surgical treatment of chronic gastric ulcer is dominated by the need to establish whether there is carcinomatous change within it (Jones et al '85: 88-90).

The suggested plan for management of peptic ulcer include regular relaxed meals, no tobacco, alcohol, drugs (e.g. salicylates and other NSAIDs (or antibiotics other than metronidazole)). For symptomatic relief of pain, heartburn and discomfort is initially done with antacids with balanced magnesium/aluminum salts preparation. In patients with costive stools, magnesium salts (e.g. Mist, Magnesium Trisil. BPC) 10 ml three times daily 1 hour after food and at night. In patients with loose stools, aluminum salts (e.g. aluminum hydroxide gel, BPC) 10 ml three times daily 1 hour after food and at night. For nausea and vomiting metroclopramide 10 mg three times daily orally or domperidone intramuscularly. For the specific healing of gastric ulcer colloidal bismuth (De-Nol) 5 ml in 15 ml water half-an-hour before meals and at night 4-6 weeks causes no significant side effects; carbenoxolone (Biogastrone) 100 mg three times daily one week, the 50 mg three times daily 5 weeks, watch for oedema, blood pressure and hypokalemia; or cimetidine (Tagamet) 200 mg three times daily 400 mg nightly or ranitidine (Zantac) 150 mg twice daily 4-6 weeks, however as yet the role of H_2 receptor blockers has not been conclusively proven. For the specific healing of duodenal ulcer cimetidine (Tagamet) 200 mg three times daily 400 mg nightly or 400 mg twice daily 6-8 weeks or ranitidine (Zantac 150 mg twice daily 6-8 weeks; colloidal bismuth (De-Nol) 5 ml in 15 ml water or one tablet three times daily and at night 6-8 weeks; or 'high dose' antacid regimes, e.g. Maalox 10 l two-hourly and at night (Jones et al '85: 85). Two derivatives of *Glycyrrhiza glabra* root (common licorice native to Eurasia) carbenoxolone sodium and deglycyrrhizinized licorice, can on the average reduce the size of an ulcer by 70 to 90% after one month of treatment. Healing occurs in patients who are not confined to bed, and many who continue to work during the treatment. Excessive secretion of hydrochloric acid or hyperacidity can lead to ulcerations of the stomach and duodenum. Common neutralizing agents for excessive acid may be prescribed: sodium bicarbonate, calcium carbonate, and magnesium hydroxide (milk of magnesia) are a few examples. A natural remedy used by North American Indians was hops *(Humulus lupulus)*.

Metronidazole is the only antibiotic effective against antibiotic resistant *Helicobacter pylori,* the absolutely most common bacterial cause and infectious agent of peptic ulcers, and is in general very good at healing internal abdominal ulceration. Metronidazole is essential to the curative, professional, treatment of any peptic or gastrointestinal disorder. *Helicobacter pylori* infection and duodenal ulcer disease is treated with the oral administration of 200 or 250 mg three or four times daily at meals and bedtime for fourteen days of metronidazole (Flagyl ER). Metronidazole (Flagyl ER) may be administered in conjunction with tetracycline (500 mg) and bismuth subsalicylate (525 mg) 4 times daily (at meals and at bedtime) for 14 days; these drugs should be given concomitantly with an H_2-receptor antagonist, such as Pepcid (Famotidine) or Zantac (Ranitidine) in recommended dosage for 14 days. In the absence of *H. pylori*, most but not all ulcers are caused by intolerance to anti-inflammatory drugs such a naproxen (Alleve) or ibuprofen (Advil). The key to treating these ulcers that are *H. pylori*- negative is to stop the anti-inflammatory and prescribe potent acid-suppressing medications, such as omeprazole, until the ulcer is healed. Then the anti-inflammatory drug may be restarted along with a gastro-protective agent such as the proton pump inhibitor (PPI) used to heal the ulcer (Newman ’11: 102). Proton pump inhibitors (PPIs): Prevacid (Lansoprazole), Prilosec (Omeprazole), Protonix (Pantoprazole) and Nexium (Esomeprazole Magnesium).

The most notable **congenital defects** of the stomach are pancreatic heterotopia and gastric **heterotopia** where nodules of essentially normal pancreatic tissue may be present in the gastric or intestinal submucosa, in the muscle wall and are rarely larger than 1 cm in size. Weakness in the diaphragm may permit the abdominal contents to herniate into the thorax during in utero development. **Congenital hypertrophic pyloric stenosis** is encountered in infants as a disorder

that affects males three to four times more often than females, occurring in 1 in 300 to 900 live births. Acquired pyloric stenosis in adults is one of the longer term risks of antral gastritis or peptic ulcers close to the pylorus as well as gastric carcinomas, lymphomas, or adjacent carcinomas of the pancreas. **Hypertrophic gastrophaty** is a group of uncommon conditions all characterized by giant cerebriform enlargement of the rugal folds of the gastric mucosa. The rugal enlargement is not caused by inflammation but by hyperplasia of the mucosal epithelial cells. Three variants are recognized (1) Menetrier's disease, (2) Hypertrophic-hypersecretory gastrophaty and (3) Gastric gland hyperplasia secondary to excessive gastrin secretion. **Gastric varices** develop in the setting of portal hypertension but less often than esophageal varices. Most gastric varices lie within 2 to 3 cm of the gastroesophageal junction (Crawford '94: 769, 770, 778).

Gastric cancer, despite its decreasing incidence in the United States, still remains a leading cause of death from cancer (Crawford '94: 669-770). Gastric cancer is currently the third most common malignancy, but its incidence in the Western world is falling, and this is good because 5-year survival is about 10%. In Japan the incidence of gastric carcinoma is higher and much finance and medical effort are directed to its early detection and chemotherapeutic treatment and 5-year survival rates are as high as 90% in patients diagnosed before the tumor as spread beyond the lamina propria. The great majority of malignant tumors of the stomach are adenocarcinomata; sarcomata are less common. The tumor may take the form of a fungating polypoid structure which, when present in the fundus of the stomach, may infiltrate the lower end of the oesophagus causing obstruction and true dysphagia. In other patients the tumor may take the form of an ulcerating lesion, with 'heaped up' or 'rolled' edges, in the antral region, sometimes causing gastric outlet obstruction. In the elderly especially, the tumor may take the form of a diffusely infiltrating scirrhous carcinoma producing the so-called 'leather bottle' stomach or 'linitis plastica'. Gastric cancers arise most frequently on the greater curve of the stomach (Jones et al '85: 90).

The term **polyp** is applied to any nodule or mass that projects above the level of the surrounding mucosa. The use of the term "polyp" in the gastrointestinal tract is generally restricted to mass lesions arising in the mucosa. Gastric polyps are uncommon and are found in about 0.4% of adult autopsies and 3 to 5% of Japanese adults. More than 90% of gastric polyps are non-neoplastic and appear to be of an inflammatory or hyperplastic nature. Numbers by the score are observed in about 20 to 25% of cases. They are regarded as having malignant potential but are nonetheless found in about 20% of stomachs resected for carcinoma. The **adenoma** of the stomach is a true neoplasm representing 5 to 10% of the polypoid lesions in the stomach. By definition, an adenoma contains proliferative dysplastic epithelium and thereby has malignant potential. Adenomatous polyps are much more common in the colon. The most common location is the distal portion of the stomach, particularly the antrum. These lesions are usually single and may grow up to 3 to 4 cam in size before detection. The male-to-female ratio is 2:1. Up to 40% of gastric adenomas contain a focus of carcinoma at the time of diagnosis and the risk of cancer in the adjacent gastric mucosa may be as high as 30%. Among malignant tumors that occur in the stomach, carcinoma is the most common (90-95%). Next in order of frequency are lymphomas (4%), carcinoids (3%) and malignant spindle cells tumors (2%) (Crawford '94: 778-783). **Leiomyoma** is an unusual gastric tumor arising from the muscular wall, that may be benign, or have a sarcomatous element and be locally infiltrative; wide local removal is usually the correct treatment. **Lymphomas** of the gastrointestinal tract are uncommon, about one-half arise in the stomach, but they represent only 1-2% of all gastric neoplasms; in the small bowel, many present as an emergency, either as a perforation with peritonitis, or with intestinal

obstruction; there is an association with coeliac disease; radical surgical resection is the best treatment, adjuvant chemotherapy and radiation are often used (Jones et al '85: 90-99).

Gastric carcinoma is worldwide disease. Its incidence, however, varies widely, being particularly high in Japan, Chile, Costa Rica, Colombia, China, Portugal, Iceland, Finland and Scotland and considerably lower in the United States and Canada. In most countries, there has been a steady decline in both the incidence and mortality of gastric cancer. Since 1930 the annual mortality rate in the United States has dropped from about 38 to 7 per 100,000 population for men an d from 28 to 4 per 100,000 for women. Yet it remains among the leading killer cancers, representing 3% of all cancer deaths because of its dismal 5 year survival rate. The diet is suspected to be the primary offender, and adherence to certain culinary practices is associated with a high risk of gastric carcinoma. The presence of carcinogens, such as nitroso compounds and benzopyrene, appears to be particularly important. Thus, lack of refrigeration, common use of nitrite preservative, water contamination with nitrates, and lack of fresh fruit and vegetables are common themes in high-risk areas. Specific foodstuffs that have been implicated in Japan include pickled raw vegetables, salty sauces, and dried salty fish. Conversely, intake of green, leafy vegetables and citrus fruit, which contain antioxidants is negatively correlated with gastric cancer. An 18 fold increased risk of gastric carcinoma is reported in patients with chronic antral gastritis with atrophy, the cumulative cancer risk in patients older than 50 years is 7 to 10% within 10 years of diagnosis. Infection by *H. pylori* appears to serve as a cofactor in gastric carcinogenesis. Within the United States, blacks, Native Americans and Hawaiians have a higher risk of developing gastric carcinoma. Because only about 4% of patients with gastric carcinoma have a family history of this disease, genetic factors are unlikely to be major influences. The prognosis for gastric carcinoma depends mainly on depth of invasion and the extent onodal and distant metastasis (Crawford ’94: 778-783).

Most carcinomas can be **removed** by excising two-thirds to three-quarters of the stomach, and anastomosing the jejunum to the gastric remnant. In the course of such operation it is not uncommon to remove the body of the pancreas and the spleen along with the specimen, when a carcinoma has involved the pancreas. The great omentum is removed because it is often the site of transcolonic spread of the carcinoma. Total gastrectomy is done when the carcinoma lies close to the esophagogastric junction, the abdominal esophagus must included in the resection to secure clearance of invaded tissue. **Reconstruction** is usually effected by bringing up a loop of upper jejunum through the transverse mesocolon and joining the end of the esophagus to the top of the loop. **Esophago-gastrectomy** is done when the carcinoma invades the gastro-esophageal junction then more oesophagus must be removed and the anastomosis can only be made by extending the abdominal incision into the left chest, which allows the diaphragm to be split down to the esophageal hiatus and reveals the whole of the stomach as well as the lower oesophagus lying in the posterior mediastinum so that a very radical operation can be performed by removing the upper half of the stomach, together with the spleen, and the whole of the left gastric artery and the coeliac lymph nodes. **Reconstruction** is often effected by closing the distal half of the stomach, bringing it up as a tube, and joining the open end of the oesophagus to an incision into the front of the gastric pouch. The diaphragm is carefully closed around the stomach and the chest wall and abdominal incision sutured with an underwater drain to evacuate the left pneumothorax. About 60% of carcinomas of the stomach can be resected by one or other of these rather major procedures. The mortality of the abdominal gastrectomies is about 5% and for the thoraco-abdominal operations it is about 10% (Jones et al '85: 90-99).

The five year survival rate of surgically treated early gastric carcinoma is 90 to 95%, with only a small negative increment if lymph node metastases are present. In contrast, the 5 year survival

rate for advanced gastric cancer remains below 10%. Gastric lymphomas represent 5% of all gastric malignancies and are similar to intestinal lymphomas (Crawford '94: 783). The most reliable surgical method is to remove the ulcer completely by **partial gastrectomy**; a Billroth I gastrectomy is preferred because it allows complete removal of the ulcer and joins the stomach to the duodenal stump by end-to-end anastomosis. This promotes good mixing of the gastric contents with the bile and pancreatic secretions and the great majority of patients secure a satisfactory result. Reasons for an unsatisfactory result include recurrent ulcer, post-vagotomy diarrhea (3-4%), bilious vomiting, dumping, anaemia due to hypochlorhydria which reduces the amount of iron in the jejunum and as many of half of patients have iron deficiency anaemia, and/or vitamins B_{12} deficiency, osteomalacia can result from vitamin D deficiency and weight loss can be a serious complication because there is insufficient stomach to allow a normal meal to be eaten.

5. Gastrointestinal disorder

Gastrointestinal disease accounts for about 10% of all illness, as well as 10% of general practitioner consultations, 8.5% of prescriptions and 8.3% of the cost of inpatient treatment. It is responsible 8.8% of days of certified incapacity to work and 10% of all deaths (Lewis and Elvin-Lewis '77: 272). An estimated 40% of the population (100 million people) suffer acute cases of either vomiting or diarrhea per year in the United States. **Diarrheal diseases** of the bowel are often caused by microbiologic agents; others arise in the setting of malabsorptive disorders and idiopathic inflammatory bowel disease. Among the most common offenders are rotavirus, causing around 600,000 deaths from childhood diarrhea worldwide, and norovirus, causing 28 million cases of "stomach flu" in the United States annually. Enterotoxigenic *Escherichia coli*, is the most common serious cause of bacterial enterocolitis, that can lead to chronic diarrheal disease. Many pathogens, however, can cause diarrhea, and in 40 to 50% of cases, the specific agent cannot be isolated. Any particles in the drinking water will cause diarrhea. Municipal drinking water must be filtered before consumption. While viruses and bacteria are the predominant enteric pathogens in the United States, parasitic disease and protozoal infections collectively affect more than one-half of the world's population on a chronic or recurrent basis. In the United States approximately 4 million people have peptic ulcers (duodenal and gastric), and 350,000 new cases are diagnosed each year. Around 100,000 patients are hospitalized yearly and about 3,000 people die each year as a result of **peptic ulcer disease**. The lifetime likelihood of developing a peptic ulcer is about 10% for American men and 4% for American women. *Helicobacter pylori* is the leading cause of peptic ulcers (Crawford '94: 791, 773-775). *H. pylori* and *Clostridium difficile* are notoriously resistant to all antibiotics except metronidazole.

Metronidazole (Flagyl ER) is the definitive antibiotic treatment for all bacterial and protozoal infections of the digestive tract, urinary tract and joints. All abdominal and joint procedures whose justification fails to try metronidazole, such as fecal transplant are doomed ie. death from *E. coli* contamination, Unlike other antibiotics metronidazole does not disturb the gut, although yoghurt remains prescribed. Metronidazole is contraindicated for use with alcohol and in the first trimester of pregnancy when it can cause neural tube defects. Relief of gastrointestinal disorders emphasizes gastric antacids, indigestion, digestive stimulation, antispasmodics, emetics, anti-emetics, purgatives, antidiarrheal agents, infectious diarrheas, liver, cholangitis, aminosalicylates, anthelmintics, amebicides, hemorrhoids, carminatives (Lewis and Elvin-Lewis '77: 272) and probiotics. Traditionally, the most highly effective remedy for vomiting and acute diarrhea, with or without blood, is white rice water, of white rice cooked for regulation time, around 20 minutes, in three parts water. White rice is much more effective than brown rice,

which is a better maintenance diet because it contains less starch, but for acute vomiting or diarrhea, white rice is medicinal. However, patients seldom have any appetite whatsoever and they are therefore directed to drink the white rice water and eat the white rice when able. Symptoms usually stop the instant the white rice coats the person's digestive tract.

The presence of intestinal **gas** can be a source of discomfort. The adult has 30-300 ml of gas in the gut at any one time. Much of this is acquired by air swallowing and in food; an egg for example, contains 80% by volume of air. Flatulence, is excessive gas in the stomach or intestine, that is relieved by farting. Farting relieves painful gastritis, is not considered a medical emergency although it is embarrassing and may require over-the-counter treatment. Farts can be silent, but typically make noise. Farts can be dry or wet and dirtying to undergarments. The reason for the distressing behavior of beans in the intestinal tract is the presence of complex sugars (oligosaccharides) triggers the creation of methane (Lewis and Elvin-Lewis '77: 294-295). Gastric and intestinal stasis and bacterial overgrowth allow the production in the small bowel of unusual gases which may cause foul eructations. The volume and composition of flatus depends on the amount of unabsorbed carbohydrate, lipid and protein presented for fermentation by the colonic microflora and upon the predominant bacterial type. Nitrogen and carbon dioxide are the predominant gases, with very little oxygen; the amount of hydrogen and methane varies according to the diet. Fructose intolerance can cause flatulence. Once flatulence has started, every phrase, in the "beans, beans, the magical fruit, the more you eat, the more you toot", rhyme has meaning. There are several over-the-counter preparations that are generally instantly effective to treat flatulence: Beano, simethicone, etc. Flatulence is reported to be relieved by Apiaceae, *Anethum graveolens* (dill), *Foeniculum vulgare* (fennel), *Piminella anisum* (anise), Aracea, *Acorus calamus* (sweet flag), Lamiaceae, *Hedeoma pulegioides* (American pennyroyal), *Mentha piperita* (peppermint), *M. spicata* (spearmint), *Monarda fistulosa* (wild bergamot), *M. punctate* (horsemint), *Posmarinus officinalis* (rosemary), Zingiberaceae, *Zingiber officinale* (ginger). Probiotics may be useful if the flatulence was a symptom of antibiotic associated colitis. Excessive eructation (**belching**) is commonly due to behavioral problems such as excessive air swallowing or to consumption of antacids or carbonated drinks which release carbon dioxide in the stomach (Jones et al '85: 201-203). Belching is rarely an indication of disease or cause of esophageal injury or discomfort.

Aminosalicylates are immunosuppressants used to treat ulcerative colitis, proctitis and Crohn's disease (Friedman and Liechtenstein '06: 803-817). **Imodium** (Loperamide) is the standard treatment diarrhea. Traveler's diarrhea caused by *E. coli* infection is treated with Metronidazole (Flagyl ER). For the treatment of peptic and duodenal ulcers there are antacids, antiemetics, Proton pump inhibitors (PPIs) and antihistamine H-2 receptor antagonists. Metronidazole (Flagyl ER) deserves special mention because it is a uniquely useful antibiotic in the treatment of diarrhea and intra-abdominal infections, including ulcers, peritonitis, intra-abdominal abscess, liver abscess and antibiotic associated colitis from *Clostridium difficile*. Prolonged use of any antidiarrheal agent is discouraged (Lewis and Elvin-Lewis '77: 284). Carcinogenesis of the digestive tract does not usually occur without a decade of chronic disease, specifically Hepatitis B and ulcerative colitis (UC), but is always a possibility. Hygiene, diet (elimination diets, probiotics and rice), iron B_{12} and folate multi-vitamins and homeopathic remedies are the mainstay treatment for chronic diarrhea. Fecal transplant seems safe and effective.

Many conditions, such as infections, inflammatory disease, and tumors, affect both the small and large intestines. Collectively, **disorders of the intestines** account for a large portion of human disease. In addition to such rarities as intestinal malrotation and developmental defects of the abdominal wall, several anomalies deserve separate mention. **Congenital intestinal obstruction**

is an uncommon but dramatic lesion that may affect any level of the intestines. The obstruction may be complete (atresia) or incomplete (stenosis). A true diverticulum contains all three layers of the normal bowel wall: mucosa, submucosa and muscularis propria. **Meckel's diverticulum** are present in 2% of the normal population. When peptic ulceration occurs in the small intestinal mucosa adjacent to the gastric mucosa, mysterious intestinal bleeding or symptoms resembling those of acute appendicitis may result. Alternatively, symptoms may be related to inssusception (telescoping of one intestinal segment within another) incarceration or perforation. Congenital megacolon, or **Hischspung's disease**, results when the migration of neural crest cells arrests at some point before reaching the anus. Hence a segment remains that lacks both Meissner's submucosal and Auerback' myenteric plexuses. Loss of enteric neuronal coordination leads to functional obstruction and colonic dilation proximal to the affected segment. Hirshspurng's disease occurs in approximately 1 out of 5000 to 8000 live births and present with increased frequency (3.6%) in siblings. Males predominate 4:1. **Acquired megacolon** is a condition of any age and may result from (1) Chagas' disease in which the trypanosomes directly invade the bowel wall to destroy the enteric plexuss; (2) obstruction of the bowel as by a neoplasm or inflammatory stricture; (3) toxic megacolon complicating ulcerative colitis or Crohn's disease or (4) a functional psychosomatic disorder (Crawford '94: 786-787).

Hemorrhoids is one of the most common conditions to afflict the citizens of Western countries, and there is considerable evidence that it is related to the refined Western diet. Certainly rural Africans, who eat a diet with high fibre content are rarely constipated and hardly ever suffer from hemorrhoids (piles). Hemorrhoids form either in the internal hemorrhoidal plexus (when they are known a internal piles) or in the external plexus (external hemorrhoids). Internal hemorrhoids are much the commoner and may affect as many as 50% of those over 50 years of age living in Western countries. Pressure exerted between the fecal mass and the anal sphincter tends to obliterate the free flow of blood and since arterial blood continues to flow into the internal plexus, it becomes engorged. As time goes on, prolapse of the pile occurs and becomes greater if excessive straining continues, with resultant enlargement of hemorrhoidal masses. As the hemorrhoids become larger, squamous epithelium may extend onto the surface of the hemorrhoid normally covered by columnar epithelium – usually known as squamous metaplasia. Hemorrhoids are normally classified as First degree bleeding only, Second degree prolapsing but reduce spontaneously and Third degree prolapse which does not undergo spontaneous reduction. Itching (pruritis) is common and the discharge of mucus is present if the hemorrhoids are large. Sigmoidoscopy should always be performed since there is a high incidence of coincidental rectal disorders which may be the true cause of the symptoms. The multiplicity of methods for the treatment of hemorrhoids suggest that no one method gives perfect results. For first-degree and some second degree hemorrhoids, an outpatient method such as injection with sclerosing solution of banding of the hemorrhoids gives good results, whereas third-degree hemorrhoids are probably best dealt with by a ligation and excision method.

Over-the-counter treatment of hemorrhoids consists of obtaining easy bowel movement by the use of astringents, lotions and ointments manufactured from vegetable sources such as Preparation H. Herbal remedies incdlue Anacardiaceae, *Rhus glabra*, asteraceae, *Anaphalis margaritacea* (pearly everlasting), *Serretula tincotira* (centaury), Fabaceae, *Copaifera officinalis*, *C. reticulate*, Facaceae, *Quercus infectoria* (dyer's oak) Hamamelidaceae, *Hamamelis virginiana* (witch hazel), *Oleaceae, Fraxinus* Americana (white ash), Rubiaceae, *Cinchona* spp., Simourabaceae, *Brucea javanic* and *B. sumatrana* (Lewis and Elvin-Lewis '77: 293-294). Newer treatments include cryotherapy, manual dilatation of the anus, lateral sphincterotomy and thermocoagulation using the infra-red coagulator. The most commonly used sclerosing solution is the injection of 5% phenol in arachis or almond oil. A proctoscope is

inserted and injections are made in nonsensitive columnar epithelium immediately above the hemorrhoid at the level of the anorectal ring. All the three usual hemorrhoidal sites may be injected in one session. The agent sets up an inflammatory reaction which causes obliteration of the hemorrhoids and allows the mucous membrane lining to adhere to the underlying internal sphincter apparatus. Ligation with rubber bands may be applied through a proctoscope with a special band applicator around the base of an internal hemorrhoid. They produce ischemia with consequent necrosis. If severe pain is to be avoided, it is important that they are not applied to innervated squamous epithelium. Ligation and excision is particularly recommended if there are third-degree hemorrhoids with large skin tags present. The hemorrhoid is dissected off the internal sphincter, commencing in the perineum outside the anal margin. The hemorrhoidal pedicle is transfixed and ligated well up the anal canal and the hemorrhoid excised (Jones et al '85: 247-249).

Obstruction of the gastrointestinal tract may occur at any level, but the small intestine is most often involved owing to its narrow lumen. Tumors and infarction, although the most serious, account for only about 10 to 15% of small bowel obstructions. Four of the entities – hernias, intestinal adhesions, intussusception, and volvulus – collectively account for 80% . The syndrome of intestinal obstruction is marked by abdominal pain and distention, vomiting, obstipation, and failure to pass flatus. If the obstruction is mechanical or vascular in origin, immediate surgical intervention is usually required (Crawford ’94: 808). **Hernias** occur when a weakness or defect in the wall of the peritoneal cavity may permit protrusion of a pouch-like, serosa-lined sac of peritoneum, called a hernia sac. Hernias are of concern chiefly because segments of viscera frequently protrude and become trapped in them. The resultant stasis and edema increase the bulk of the herniated loop, leading to permanent trapping, or incarceration. With time, compromise of arterial supply and venous drainage (strangulation) leads to infarction of the trapped segment. Surgical procedures, infection and even endometriosis often cause localized or more general peritoneal inflammation (peritonitis). As the peritonitis heals, adhesions may develop between bowel segments or the abdominal wall and operative site. These fibrous bridges can create herniation (Crawford ’94: 808).

A **diverticulum** is a small flask-like or spherical outpouching, a blind pouch, leading off the alimentary tract, usually 0.5 to 1 cm in diameter, lined by mucosa that communicates with the lumen of the gut. Although colonic diverticula are unusual in persons under 30 years of age, in Western adult populations over the age of 60, the prevalence approaches 50%. Colonic diverticula generally occur multiply, and so the condition is termed “diverticulosis”. Obstruction or perforation of diverticula leads to inflammation, which dissects into the immediately adjacent pericolic fat, generating “diverticulitis”. In time, the inflammation may lead to marked fibrotic thickening in and about the colonic wall, sometimes producing narrowing sufficient to resemble a colonic cancer. Diverticular infection may lead to pericolic abscesses, sinus tracts, and sometimes pelvic or generalized peritonitis. Most individuals with diverticulosis remain asymptomatic throughout their lives and the lesions are most often discovered incidentally. Only about 20% of those affected ever develop manifestations, intermittent cramping or continuous lower abdominal discomfort, constipation, distention and a sensation of never being able to empty the rectum completely (Crawford ’94: 806-807).

Intussusception occurs when one segment of the small intestine, constricted by a wave of peristalsis, suddenly becomes telescoped into the immediately distal segment of bowel. Once trapped, the invaginated segment is propelled by peristalsis farther into the distal segment, pulling its mesentery along behind it. When encountered in children there is usually no underlying anatomic lesion or defect in the bowel, and the patient is otherwise healthy.

Intussusception in adults, however, signifies an intraluminal mass or tumors at the point of traction. In both settings, intestinal obstruction ensues and trapping of mesenteric vessels may lead to infarction. Twisting of a loop of bowel is known as a volvulus. If the volvulus twists about its mesenteric base of attachment is also produces intestinal obstruction and infarction. Volvulus occurs most often in large redundant loops of sigmoid, followed in frequency by the cecum, small bowel, stomach or rarely transverse colon (Crawford '94: 809).

Bowel infarction is an uncommon but grave disorder that imposes a 50 to 75% death rate largely because the window of time between onset of symptoms and perforation is small. Mucosal and mural infarction by themselves may not be fatal but bowel embarrassment may progress to more extensive infarction and sepsis or serious blood loss may set in. Chronic ischemic colitis may present as an insidious inflammatory disease, with intermittent episodes of bloody diarrhea interspersed with periods of healing, mimicking inflammatory bowel disease. It tends to occur in older individuals, when cardiac and vascular diseases are most prevalent. Ischemic lesions may be restricted to the small or large intestine or may affect both, depending on the particular vessels affected. Acute occlusion of one of the three major supply trunks of the intestines – celiac and superior and inferior mesenteric arteries – may lead to infarction of several meters of intestine. Insidious loss of one vessel may be without effect.

The **severity of injury** ranges from (1) transmural infarction of the gut, involving all visceral areas; (2) mural infarction of the mucosa and submucosa; to (3) mucosal infarction, if the lesion extends no deeper than the muscularis mucosa. Almost always, transmural infarction imlies mechanical compromise of the major mesenteric blood vessels. Mucosal or mural infarction more often results from hypoperfusion, either acute or chronic. Venous thrombosis is a less frequent cause of vascular compromise. The predisposing conditions for ischemia are (1) Arterial thromobosis caused by severe atherosclerosis (usually of at the origin of the mesenteric vessel), systemic vasculitis, dissecting aneurysm, angiographic produces, aortic reconstructive surgyer, surgical accidents, hypercoagulable states and oral contraceptives. (2) Arterial embolism caused by cardiac vegetations, angiopraphic procedures, and aortic atheroembolism (3) venous thrombosis caused by hypercoagulable states, oral contraceptives, antithrombin III deficiency, intraperitoneal sepsis, the postoperative state, invasive neoplasm (particularly hepatocellular carcinoma), cirrhosis and abodominal trauma. (4) Nonocclusive ischemia caused by cardiac failure, shock, dehydration, vasoconstrictive drugs (e.g., digitalis vasopressin, propranolol). (5) Miscellaneous causes such as radiation injury, volvulus, stricture and internal or external herniation (Crawford '94: 787, 789).

In Western Europe, North America, Australia and New Zealand acute appendicitis is the commonest abdominal surgical emergency. Before the **routine appendectomy** three out of four patients died from a perforated appendix (Jones et al '85: 24, 28, 25). The **appendix** is an underdeveloped residuum of the otherwise voluminous cecum. The adult appendix average 7 cm in length, is partially anchored by a mesenteric extension form the adjacent ileum, and has no known function. Diseases of the appendix loom large in surgical practice. Inflammation of the right lower quadrant was considered a nonsurgical disease of the cecum until Fitz recognized acute appendicitis as a distinct entity in 1886. Appendicitis is associated with obstruction in 50 to 80% of cases, usually in the form of a fecalith and, less commonly, a gallstone, tumor or ball of worms (*oxyuriasis vermicularis*). Continued secretion of mucinous fluid in the obstructed viscus leads to a progressive increase in intraluminal pressure sufficient to cause eventual collapse of the draining veins. Ischemic injury favors bacterial proliferation with additional inflammatory edema and exudation, nevertheless, a significant minority of inflamed appendices have no demonstrable luminal obstruction, and the pathogenesis of the inflammation is unknown.

There is general agreement that highly competent surgeons make false-positive diagnoses of acute appendicitis and remove normal appendices about 20 to 25% of the time. The discomfort and risks associated with an exploratory laparotomy and discovery of "no disease: are far outweighed by the morbidity and mortality (about 2%) associated with perforation. Conditions that mimic appendicitis are mesenteric lymphadenitis, caused by Yersinia or a virus (Crawford '94: 822-824). There is a strong need to try Metronidazole (Flagyl ER) before surgery.

Peritonitis may result from bacterial invasion or chemical irritation. The most common causes are bile, pancreatic enzymes, and surgically introduced foreign material. Perforation of rupture of the biliary system evokes a highly irritating peritonitis. Globules of free fat may be found floating in the peritoneal fluid that accumulates. After 24 to 48 hours enzymatic damage and bacterial permeation of the bowel will usually lead to a frank suppurative condition. The common disorders leading to bacterial dissemination are appendicitis, ruptured peptic ulcer, cholecystitis, diverticulitis, strangulation of bowel, and peritoneal dialysis. Virtually every bacterial organism has been implicated, most commonly *E. coli*, alpha-hemolytic and beta-hemolytic streptococci, *Staphylococcus aureus*, enterococci, gram-negative rods, and *Clostridium perfringens.* Among adults, 10% of cirrhotic patients with ascites develop spontaneous bacterial peritonitis during the course of their illness. The usual causal agents are *E. coli* and prenumococci, but the manner by which they invade the peritoneal cavity is unknown. Dense fibromatous overgrowth of the retroperitineal tissues may sometimes develop designated sclerosing retroperitonitis or retroperitoneal fibromatosis. The cause is obscure but in some instances there is a history of methysergide use, an ergot derivative used for migraine. Similar fibrotic changes seen in other sites are mediastinal fibrosis, sclerosing cholangitis, and Riedel's fibrosing thyroiditis, suggesting the disorder is autoimmune and systemic in origin. Tumors and cysts can also develop in the peritoneal cavity (Crawford '94: 825, 826).

6. Constipation, malabsorption and diarrhea

Feces are three-quarters water. Around 3 ½ ounces (100 milliliters) of fluid are lost everyday. During a passage though the digestive system, some 10 quarts (9.8 liters) are reabsorbed. Whatever fluid is left in the feces belongs there. This optimal water content makes feces soft enough to ensure metabolic waste products can be transported out of the body safely. A third of the solid components are bacteria, that have died or otherwise are exiting the digestive system. Another third is made up of indigestible vegetable fiber. The more fruit and vegetables eaten, the more feces excreted per bowel movement. Increasing the proportion of that food group can raise the weight of a bowel movement from the average 3 ½ to 7 ounces (100 to 200 grams) to as much as 178 or 18 ounces (500 grams) per day. The remaining third is made up of substances the body wants to get rid of, such as the remains of medicines, food coloring or cholesterol (Enders '15: 70, 71). Depending on the individual and the type of food they have eaten, digestion — from mouth to bathroom — takes 24–72 hours. Poop or **feces i**s the remains of food that could not be absorbed by the small intestine that has been rotted down by bacteria in the large intestine. It contains bacteria, and some small amounts of metabolic waste products, such as bile and bilirubin (from the breakdown of blood). Feces can vary in color widely and can be different consistencies, from watery to solid (Newman '18).

The natural color of human feces ranges from brown to yellowish-brown, even when not eating anything of these colors. The same is true of urine, it always tends towards yellow. This is due to freshly manufactured blood. The body creates about 2.4 million new blood corpuscles a day. But the same number are broken down every day too. In that process, the red pigment they contain is first turned green, then yellow. The same process occurs during the various stages of

bruise on the skin. A small portion of this yellow pigment is excreted in the urine. Most of it, though, passes through the liver and into the gut. There, bacteria change its color once again – this time turning it brown. Light brown to yellow feces can be the result of a harmless disorder, affecting about 8 percent of the world's population, called Gilbert's syndrome (or Gilbert-Meulengracht syndrome). In this condition, of the enzymes involved in the breakdown of blood works at only 30 percent of its normal efficiency. This means less pigment finds its way to the gut. This enzyme defect is not harmful. The only effect is a reduced tolerance for acetaminophen, that should be avoided. Another possible cause of yellowish feces is problems with bacteria in the gut. If they are not working as they should, the familiar brown pigment will not be produced. Antibiotics or diarrhea can cause such an alteration in fecal color. Light brown to gray feces can result if the connection between the liver and the gut is blocked by a kink in the tubes or by pressure (usually behind the gall bladder), no blood pigment an make it into the feces. Blocked connections are never good, and those who notice a gray tint to their fees should consult their doctor. Black or red feces is caused by black congealed blood or red fresh blood. The color is not caused by the pigment, but by the presence of entire blood corpuscles. For those with hemorrhoids, a small amount of bright red blood in the stool is not reason to worry. However, anything darker in color than fresh, bright red blood should be checked by a doctor, unless the reddish color is caused by eating a large amount of beetroot (Enders '15: 71-73).

Transit through the small bowel takes 4-5 hours but on average it takes a further 12-18 hours for feces to travel from caecum to rectum, about 24 hours in total. About 1.5 liters of liquid chime passes through the ileocaecal valve each 24 hours, but only about 100-200 grams of stool is evacuated, of which 60-80% is water. Whereas peristaltic activity is more-or-less constant in the small bowel, two separate types of movement can be distinguished in the colon. Segmentation produces mixing of the contents, whereas propulsion is a mass movement which on three or four occasions in the day (generally after a meal) propels feces down the colon. On a typical western diet a daily stool weight in excess of 300 g would be considered pathological unless exceptional quantities of dietary fibre were being eaten. Only 1 in 100 Western citizens have fewer than three bowel movements a week or more than three per day (Jones et al '85: 301). Constipation is discomforting but is not considered life-threatening and is easily treated with enema; diarrhea on the other hand can be deadly, cholera untreated with Oral Rehydration Salts (ORS) has a 50% fatality rate. Diarrhea is perceived as the body’s production of more than 4/5 cups (0.2 L) of stool a day. Low-volume, painful, bloody diarrhea is known as dysentery (Crawford ’94: 790).

The Bristol stool scale was first published in 1997 by Dr. Ken Heaton at the University of Bristol in the United Kingdom. The scale classifies the consistency of feces into seven groups. A healthy digestive system, producing fees with the optimum water content, will produce types 3 or 4. The other types are less than ideal. Type 1 separate hard lumps, like nuts (hard to pass. Type 2 sausage shaped, but lumpy. Type 3 Like a sausage but with cracks on its surface. Type 4 like a sausage or snake, smooth and soft. Type 5 Soft blobs with clear-cut edges (passed easily). Type 6 fluffy pieces with ragged edges, a mushy stool. Type 7 watery, no solid pieces, entirely liquid. The type a person's feces belong to can be an indication of how long indigestible particles take to pass through their gut. Type 1 digestive remains take around one hundred ours t pass through the system (constipation). In Type 7 they pass through in just ten hours (diarrhea). Type 4 is considered ideal, because it has the optimum ratio between fluid and solid content. Those who find types 3 or 4 may also want to observe how quickly their feces sink in water. Ideally, they should not plummet straight to the bottom, as this would indicate the possibility that they still contain nutrients that have not been digested properly. Feces that sink slowly contain bubbles of gas that keep them afloat in water. These gas bubbles are produced by gut bacteria

that mostly perform useful services, so this is a good sign, as long as it is not accompanied by flatulence (Enders '15: 73-75).

Between 10 and 20 percent of the people in the United States are **constipated**, with bowel movements less than three times a week, particularly hard stool a quarter of the time, often in pellet form, which is difficult to pass without medicine or tricks. Dietary fiber is not digested in the small intestine and stimulates the large intestine. The best results are produced by psyllium seed husks and plum. Both contain fiber and agents that draw extra fluids into the gut. It can take two or three days before their effect is felt. One ounce (30 grams) is an appropriate daily dose of dietary fiber. There are two kinds of fiber, water-soluble and insoluble. The latter is better at stimulating movement through the digestive system, but can cause stomachaches. Water-soluble fiber does not provide quite such a powerful push, but it makes the contents of the gut softer and easier to deal with. It is important to drink enough fluids. Probiotics and prebiotics can help. A rocking squat on the toilet can help to evacuate stool. Osmotic laxatives contain certain salts, such as sodium sulfate (Glauber's salt) sugars or tiny molecular chains that travel to the large intestine, gathering all the water they can take along the way. Diarrhea is sure sign of taking too many laxatives. The most widely used laxative is lactulose, that has the double effect of retaining water I the large intestine and feeding the gut flora, but can cause cramps and flatulence. There is a three day rule regarding laxatives. The large intestine has three sections: the ascending, transverse and descending. Usually defecation empties only the last section. By the next day, it has filled up again and it is time to defecate again. Taking a strong laxative may cause the entire large intestine, all three sections, to be emptied. It can then take three days before the large intestine is full again and the patient must not panic and take more laxatives (Enders '15: 108-121). **Angiodysplasias** are torturous dilations of submucosal and mucosal blood vessels are seen most often in the cecum or right colon usually only after the sixth decade of life. Such lesions account for 20% of significant lower intestinal bleeding; intestinal hemorrhage may be chromic and intermittent or acute and massive. Hemorrhoids are variceal dilations of the anal and perianal venous plexuses. These extremely common lesions affect about 5% of the general population and develop in the setting of persistent elevated venous pressure within the hemorrhoidal plexus. The most frequent predisposing influences are constipation with straining at stool (Crawford ’94: 787, 789).

Assuming constipation is ruled out due to narcotic drugs or other pharmaceuticals, or to a neurological problem (like Parkinson’s disease) or to an endocrinological issue (like thyroid disease or diabetes) the causes of constipation can be divided into three categories: slow-transit, dyssynergic, and idiopathic (unknown). In slow-transit constipation things move very slowly through the bowel, the patient produces produce very few bowel movements and none spontaneously. Chronic constipation does not become cancer, ulcerative colitis, Crohn’s disease, or diverticulitis. IBS and chronic constipation may be associated with other syndromes, but they don’t evolve into something more dangerous or life-threatening. Toward the end of the nineteenth century, patients were bombarded by information from health professionals and advertisements form the medical industry about how dangerous it was to be constipated. The dire consequences of being constipated terrified the public and millions of dollars were made flogging drugs for constipation, despite the fact that almost no one has ever died of constipation. In the early years of the twentieth century a prominent British surgeon with an office on prestigious Harley Street in London performed colectomy operations (bowel removal surgery on constipated young women. The only available anesthetic was ether, and antibiotics had not yet been invented. These young women were facing an astoundingly high mortality rate of about 10% to undergo this major surgery for no good reason. To administer an enema fill the enema bag with 8 cups of warm tap water and suspend it from a hook or holder that is 5 feet (1.5 m) off

the ground. Lubricate the tip of the hose and insert it carefully into the rectum while lying on the left side. The fluid should run in for about 10 to 15 minutes. Wait another 15 minutes, then proceed to the toilet and defecate (Newman '11: 47, 48, 168, 160). Constipation is now known to be a Western condition due to high levels of consumption of animal product and processed food whereas the vegetarian diet produces looser stools that becomes diarrheal due to nutritional deficiency after body fat has been depleted.

Malabsorption involves the passage of abnormally bulky, frothy, greasy, yellow or gray stools, accompanied by weight loss, anorexia, abdominal distention, borborygmi (rumbling noise) and muscle wasting. The mal-absorptive disorders most commonly encountered in the United States are celiac sprue, chronic pancreatitis and Crohn's disease. Malabsorption can affect many organ systems (1) Alimentary tract causing diarrhea both from nutrient malabsorption and from excessive intestinal secretions, flatus, abdominal pain, weight loss and mucositis resulting from vitamin deficiencies. (2) Hematopoietic system caused by anemia from iron, pyridoxine, folate or vitamin B_{12} and bleeding from vitamin K deficiency. (3) Musculoskeletal system as osteopenia and tetany from calcium, magnesium, vitamin D and protein malabsorption. (4) Endocrine system causing amenorrhea, impotence, infertility form generalized malnutrition, and hyperparathyroidism from protracted calcium and vitamin D deficiency. (5) Skin causing purpura and petechiae from vitamin D deficiency, edema from protein deficiency, and dermatitis and hyperkeratosis from deficiencies of vitamin A, zinc, essential fatty acids, and niacin. (6) Nervous system causing peripheral neuropathy from vitamin A and B_{12} deficiencies.

Malabsorption is characterized by suboptimal absorption of fats, fat-soluble and other vitamins, proteins, carbohydrates, electrolytes and minerals and water, that results from the disturbance of at least one of the following digestive functions: (1) intraluminal digestion, in which proteins, carbohydrates, and fats are broken down into assimilable forms. The process begins in the mouth with saliva, received a major boost from gastric peptic digestion, and continues in the small intestine, assisted by the emulsive action of bile salts. (2) Terminal digestion, which involves the hydrolysis of carbohydrates and peptides by disaccharidases and peptidases in the brush border of the small intestinal mucosa. (3) Transepithelial transport, in which nutrients, fluid and electrolytes are transported across the epithelium of the small intestine for delivery to the intestinal vasculature. Absorbed fatty acids are converted to triglycerides and with cholesterol are assembled into chylomicrons for delivery to the intestinal lymphatic system. (Crawford '94: 796-797).

Disorders of the small bowel usually present because of poor intraluminal digestion of food substances as well as malabsorption and diarrhea. Relatively common causes are celiac disease (gluten-sensitive enteropathy) and Crohn's disease and less commonly, pancreatic insufficiency. The common clinical presentation of malabsorption are diarrhea and abdominal discomfort, anemia, other nutritional deficiencies, water and electrolyte depletion. When steatorrhoea is present the patient complains of pale, bulky offensive, frothy stools that often float and also characteristically stick to the lavatory pan. Frequent stools are not a common complaint. Abdominal discomfort usually is a bloated, distended felling but occasionally may mimic peptic ulcer disease or irritable bowel syndrome. Severe or prolonged steatorrhoea may also produce symptoms caused by loss of fat-soluble vitamins. Anemia may take the form of a microcytic hypochromic anemia due to iron deficiency, or a macrocytic anaemia due to folic acid or vitamin B_{12} deficiency. The bone pain of osteomalacia (due to calcium and vitamin D deficiency) is not an unusual presentation, especially in the elderly with long-standing malabsorption. In more acute situations (e.g. after small bowel resection), deficiency of calcium and vitamin D may present as tetany. Vitamin K deficiency may manifest itself with deficient clotting ability;

protein loss with edema of the legs and weight loss with muscle wasting. Water depletion may lead to marked dehydration and loss of potassium in particular may lead to generalized weakness and malaise. In infants malabsorption may manifest in response to the introduction of carbohydrate into the infant's diet at around 3 months. Irritability, loss of interest in feeding, and diarrhea with pale bulky stools are soon followed by weight loss and general failure to thrive. Because absorption of drugs takes place largely in the upper small intestine, disease in this area may affect the bioavailability of orally administered drugs, resulting in treatment failure. Specific treatment is only available for some causes of malabsorption, e.g. coeliac disease. Nutritional supplements (e.g. iron, folic acid, vitamin C, calcium, vitamin D) may be given by mouth, whilst others (e.g. vitamins B_{12}) must be given parenterally and may have to given for life. In many patients with mucosal destruction a secondary alactasia develops, and while the lesion is healing a lactose-free diet may alleviate the symptoms. Medium-chain triglycerides can be absorbed without bile salts, pancreatic enzymes, chylomicron formation or lymphatic transport, and therefore provide a valuable additional nutritional support in those conditions for which there is no specific therapy (Jones et al '85: 126-129, 132).

Impaired motility is caused by bacterial overgrowth. Anatomical causes of impaired motility include surgical blind loops, diverticulosis of small bowel, fistulae and obstruction, and defective motility such as occurs in systemic sclerosis, in the syndrome of pseudo-obstruction, when there is defective immunity and bacterial overgrowth of the small intestine occurs, producing malabsorption. The proximal small intestine normally has a sparse population of streptococci, lactobacilli, some yeasts, staphylococci and a few coliforms. The latter organisms are normally more profuse in the ileum and colon, where the predominant microflora is anaerobic and includes bacteroides, coliforms, lactobacilli, and clostridia. In disease states the distal flora ascends the intestine and produces a number of direct and indirect adverse effects. Bacteria have an adverse effect on bile salts, lypolyses, and intraluminal carbohydrate. The contaminating bacteria also produce hydroxyfatty acids which, like unconjugated bile salts, impair colonic uptake of water and electrolytes. Bacterial contamination causes a mild enteropathy by direct damage to the intestinal mucosa. Vitamin B_{12} nutrition may also be compromised because bacterial utilize the dietary vitamin and prevent its absorption' folate deficiency is rare. Lesions will require intermittent courses of broad-spectrum antibiotics especially metronidazole which is especially active against anaerobes such as bacteroides. Nutritional supplements and probiotics are often needed (Jones et al '85: 138, `139). **Whipple's disease** is a rare, systemic condition, which may involve any organ of the body but principally affects the intestine, central nervous system and joints. Whipple's disease is principally encountered in whites in the fourth to fifth decades of life, with a strong male predominance of 10:1. It usually presents as a form of malabsorption with diarrhea and weight loss, sometimes of years duration. Atypical presentations, with polyarthritis, obscure central nervous system complaints and other symptom complexes, are common. Lymphadenopathy and hyperpigmentation are present in more than half of patients. The diagnosis rests on the discovery of gram-positive actinomycete, named *Tropheryma whippelii*. Some patients have a protracted course and relapses occur (Crawford '94: 799).

Consideration should first be given to the conditions known as diarrhea and dysentery. **Dysentery** is the presence of blood in the feces and although it can be caused by over 60 causes is indicative of some sort of bleeding in the intestinal tract or rectum. A typical adult human in the United States imbibes 2 liters of fluid per day, to which is added 1 liter of saliva; 2 liters of gastric juice; 1 liter of bile; 2 liters of pancreatic juice; and 1 liter of intestinal secretions. Of these 9 liters of fluid presented to the intestine, less than 200 gm of stool are excreted per day, of which 65 to 85% is water and one-third is intestinal bacterial flora. Jejunal absorption of water

amounts to 3 to 5 liters/ day, ileal absorption 2 to 4 liters/day. The colon normally absorbs 1 to 2 liters/day but is capable of absorbing almost 6 liters/day. An increase in stool mass, stool frequency or stool fluidity is perceived as diarrhea by most patients. For many individual this consist of daily stool production in excess of 250 gm, containing 70 to 95% water. More than 14 liters of fluid may be lost per day in severe cases of diarrhea, equivalent to the circulating blood volume. Diarrhea is often accompanies by pain, urgency, perianal discomfort and incontinence. Low-volume, painful, bloody diarrhea is known as dysentery (Crawford '94: 790). Diarrhea is perceived as the body's production of more than 4/5 cups (0.2 L) of stool a day. We perceive constipation when the body produces fewer than three movements a week or when the stools are very hard, often described as rabbit-like or as scybala. Almost no one dies from constipation but many people die from diarrhea. Massive diarrhea is spontaneous in origin can be extremely worrisome, with highly significant fluid losses and the development of dehydration and low potassium levels in the blood, a very dangerous situation, indeed. Often it begins after an intestinal infection caused by a bacteria. The bowel is upset and does not fully recover. Small doses of anti-diarrheals, such as loperamide (Imodium) can fully reverse the problem. However, for a substantial number of patients, the symptoms remain and are annoying and debilitating (Newman '11: 30, 32, 33).

There are many disease states which cause **diarrhea**, including bacterial infections for example, *E. coli*, Salmonella, Shigella, or Campylobacter and viruses such as rotavirus in children and Norwalk virus in adults. We all have *Candida albicans* in our gut, and this yeast can cause a spectrum of diseases, some of which are potentially life-threatening. Blood poisoning with candida organisms is often fatal. But in general, the immune-compromised patient is more likely to have an illness caused by this yeast. Many patients on chemotherapy for various malignancies get a yeast esophagitis that makes swallowing extremely painful. There are also mal-absorptive, endocrine, neoplastic and pharmaceutical causes of diarrhea. Diarrheal diseases are among the leading causes of infant and child mortality in the Third world. In Western society, fatal diarrhea is more a major concern in the infirm and elderly, particularly in hospitalized patients and vegans. This has emerged as a significant problem and is usually related to prior profligate use of antibiotics (Newman '11: 42, 43, 41) and a vegan diet. Diarrheal disorders are categorized as follows: (1) secretory diarrhea occurs when net intestinal fluid secretion leads to the output of greater than 500 ml of fluid stool per day, which is isotonic with plasma and persists during fasting. (2) Osmotic diarrhea occurs when excessive osmotic forces exerted by luminal solutes lead to output of more than 500 ml of stool per day, which abates on fasting. Stool exhibits an osmotic gap (stool osmolality exceeds electrolyte concentration by 50 mOsm or more). (3) Exudative diseases are purulent, bloody stools which persist during fasting; stools are frequent but may be small or large volume. (4) Deranged motility is a highly variable features regarding stool volume and consistency; other forms of diarrhea must be excluded. (5) malabsorption involves long-term weight loss; voluminous, bulky stools with increased osmolarity owing to unabsorbed nutrients and excess fat (steatorrhea); usually abates on fasting (Crawford '94: 790).

There are many major causes of diarrheal illnesses**.** Particles in the water require treatment. **Secretory Diarrhea** can be caused by (1) infectious: viral damage to surface of epithelium caused by rotavirus, norovirus or enteric adenoviruses; (2) Infectious enterotoxin-mediated *Vibrio cholera*, *Escherichia coli*, *Bacillus cereus* and *Clostridium perfringes*; (3) Neoplastic tumor elaboration of secretogogues such as (a) Thyroid medullary carcinoma (calcitonin, prostaglandin); (b) Pancreatic cholera syndrome (vasoactive intestinal polypeptide(VIP), others); (c) Ganglioneuroma, ganglioneuroblastoma, neurofibroma (VIP, prostaglandins); (d) Villous adenoma in distal colon (nonhomrone-mediated); (4) Excess laxative use; (5) Defects in intraluminal digestion and absorption regarding bill salt malabsorption and excess delivery of

free fatty acids to colon. **Osmotic diarrhea** can be caused by (1) Disccharidase deficiencies; (2) Lactulose therapy (for hepatic encephalopathy, constipation); (3) Prescribed gut lavage ($NaSO_4$), polyethylene glycol); (4) Antacids ($MgSO_4$ and other magnesium salts; (5) Mannitol, sorbitol ingestion (as from chewing gum) and (6) Generalized malabsorption. **Exudative diseases** are caused by indiopathic inflammatory bowel disease and infectious diarrhea caused by Shigella, Salmonella, Campylobacter and *Entamoeba histolytica*. **Deranged Motility** results from (1) Decreased intestinal transit time caused by (a) Pyloroplasty or hemigrastrectomy; (b) Short-gut syndrome (following bypass or resection); (c) Irritable bowel syndrome; (d) Colonic resection, ileococal valve resection; (e) Hyperthyroidism; (f) Diabetic neuropathy; (g) Carcinoid syndrome or (h) bowel irritation during active inflammation.

Necrotizing enterocolitis (NEC) is an acute, necrotizing inflammation of the small and large intestine that is the most common acquired gastrointestinal emergency of neonates, particularly those who are premature or of low birth weight. It may occur at any time in the first 3 months of life, but its peak incidence is around the time when infants are started on oral foods (two to four days old). The higher prevalence of NEC in formula-fed infants relative to breast-fed, suggests that the absence from commercial formulas of immunoprotective factors normally present in human breast milk may play a role. Typically the patient has abdominal distention, tenderness, ileus, and diarrhea with occult or frank blood (Crawford ’94: 794). **Post-cholecystectomy diarrhea** (diarrhea after the gallbladder is removed) and cholerrheic diarrhea due to bile acids may occur after some surgical procedures. Bile acids are made in the liver and help absorb dietary fats in the upper gut. The bile acids themselves are reabsorbed in the lower portion of the small intestine and returned to the liver and then recycled. It they are not recycled, then they act as stimulants to bowel secretion and cause diarrhea (Newman ’11: 42, 43, 41). Imodium (Loperamide) is categorized as a synthetic piperidine derivative and is the standard for treating conditions of diarrhea occurring due to gastroenteritis. Diarrhea patients must take care to filter the water they use for drinking and cooking or use bottled water.

7. Infectious diarrhea

Intestinal diseases of microbial origin are marked principally by diarrhea and sometimes ulcero-inflammatory changes in the small or large intestine (or both). **Infectious enterocolitis** is a global problem of staggering proportions, causing more than 12,000 deaths per day among children in developing countries and constituting one-half of all deaths before age 5 worldwide. Although far less prevalent in industrialized nations, in the these populations attack rates for enterocolitis still approach one to two illnesses per person per year, second only to the common cold in frequency. An estimated 40% of the population, 99 million people, suffer acute cases of either vomiting or diarrhea per year in the United States. Among the most common offenders are rotavirus and norovirus as well as enterotoxigenic *Escherichia coli*. Many pathogens, however, can cause diarrhea, and in 40 to 50% of cases, the specific agent cannot be isolated. While viruses and bacteria are the predominant enteric pathogens in the United States parasitic disease and protozoal infections collectively affect more than one-half of the world’s population on a chronic or recurrent basis. Diarrheal diseases of the bowel are often caused by microbiologic agents; others arise in the setting of malabsorptive disorders, iron deficiency and idiopathic inflammatory bowel disease (Crawford ’94: 791) often due to unclean water. It is estimated that diarrheal illnesses due to the ingestion of contaminated food and water cause the death of some 20 million children around the world each year. Some 200 million individuals suffer from schistosomiasis, 400 million from hook work and no less than 1 billion from round worm infestation. The annual death rate from cholera in India still runs into many thousands.

Most of these diseases are preventable with clean water and a functioning sewage system (Jones et al '85: 329).

The proximal small bowel may be colonized by an abnormally large population of both aerobic and anaerobic organisms qualitatively similar to those present in the colon. Although the small bowel lumen is not normally sterile, its bacterial population is held in check by the continuous peristaltic activity of the gut, normal gastric acidity, and the presence of the immune-globulins secreted into the lumen by the mucosal cells. Accordingly bacterial overgrowth can be expected to occur in patients with intestinal lesions that predispose to (1) luminal stasis – strictures, fistulas, diverticula, blind loops or pouches, reduplications, motility disorders, long afferent bowel loops following surgical reconstruction and surgical denervation of bowel (2) hypochlorhydria or achlorhydria – gastric mucosal atrophy, antacid therapy, and (3) immune deficiencies or impaired mucosal immunity. A wide spectrum of absorptive defects, including malabsorption of proteins, fats carbohydrates, vitamins, water and electrolytes ensues. Treatment with appropriate antibiotics, namely metronidazole (Flagyl ER) for bacterial overgrowth in the gut and liver, ulcers and antibiotic associated colitis, and Traveler's diarrhea caused by *E. coli*, usually yields prompt clinical improvement (Crawford '94: 779).

Infections originating in the alimentary tract may be (a) endogenous, where they are due to the normal gut commensals escaping into the body, e.g. in perforated appendicitis with peritonitis, or (b) exogenous, where the gut is the portal of entry to the body for pathogens, which have usually been ingested in contaminated water or food. The response to these infections depends on the general health and nutrition of the patient, the integrity of the immune defenses and the virulence and dose of the infecting organisms. The acid medium of the normal stomach inhibits bacterial growth, and many ingested pathogens are killed in the stomach. In health, the duodenum and jejunum contain low concentrations of aerobes (10^1-10^4 per ml), mainly streptococci and lactobacilli: coliforms and anaerobes are unusual. In the ileum, the bacterial counts are higher (10^3-10^8 per ml) and coliform become progressively commoner. The ileococal valve separates the flora of the distal gut into two main types: on the ileal side, both gram-positive and coliform aerobes predominate; beyond the ileococal valve, anaerobes greatly outnumber aerobes (10^8-10^{12} organisms per ml) – largely bacteroides, coliforms and lactobacilli and clostridia. This huge bacterial population constitutes one-third of the solid bulk of feces, with anaerobes outnumbering anaerobes by at least 90 to 1 (Jones et al '85: 327).

Infectious diarrhea, **gastroenteritis** is an inflammation of the stomach and intestines, characterized by abdominal distress, nausea, vomiting and diarrhea. Enteropathogenic strains of *Escherichia coli* are associated with infantile diarrhea and *Vibrio parahemolyticus* (Japanese raw-fish enteritis). One of the major causes of food poisoning is *Clostridium perfringens* and its toxins, *C. perfringens*, strain type F can produce a rare but more fatal type, *enteritis necroticans*. Other outbreaks of food poisoning have implicated Bacillus cereus and species of *Proteus*, *Klebsiella, Providencia* (Paracolon), *Citrobacter*, *Pseudomonas*, *Enterobacter*, and *Actinomyces*. When there is suppression of gut flora due to antibiotic therapy, overgrowth of organisms, such as *Staphylococcus aureus*, or C*andida albicans*, *Streptococcus faecalis*, *Pseudomonas aeroginosa*, and *Proteus mirabilis*, can result in enterocolitis or infection of the bowel wall. Enterocolitis may also be a manifestation of *Salmonella*, cholera, and *Shigella* infections. Bacterial enterotoxins are polypeptides that cause diarrhea. Symptoms usually occur within a matter of hours from ingesting bacterial toxins. Traveler's diarrhea (*E. coli*) usually occurs following ingestion of fecal contaminated food or water; it begins abruptly and subsides within 2 to 3 days, but can lead to chronic infection.

Major Causes of Bacterial Enterocolitis

Organism	Pathogenic Mechanism	Source	Clinical Feature
Escherichia coli	Toxic or invasive	Food, water or person-to-person	
Enterotoxigenic (ETEC) *E.coli*	Cholera-like toxin, no invasion	Food, water	Traveler's diarrhea and inability to eat green leafy vegetables
Enterohemorrhagic (EHEC) *E. coli*	Shiga-like toxin, no invasion	Undercooked beef products	Hemorrhagic colitis, hemolytic uremic syndrome
Enteropathogenic E. coli (EPEC)	Attachment, enterocyte effacement, no invasion	Weaning foods, water	Watery diarrhea, infants and toddlers
Enteroinvasive (EIEC) *E. coli*	Invasion, local spread	Person-to-person	Fever, pain, diarrhea, dysentery
Salmonella	Invasion, translocation, lymphoid inflammation, dissemination	Milk, beef, eggs, poultry	Fever, pain, diarrhea, dysentery
Shigella	Invasion, local spread	Person-to-person, low inoculum	Fever, pain, diarrhea, dysentery, epidemic spread
Campylobacter	Toxic or invasive	Milk, poultry, animal contact	Fever, pain, diarrhea, dysentery, food sources, animal reservoirs
Yersinia enterocolitica	Invasion, translocation, lymphoid inflammation, dissemination	Milk, pork	Fever, pain, diarrhea, mesenteric adenitis, extraintestinal infection, food sources
Vibrio cholera, other Vibrios	Enterotoxin, no invasion	Water, shellfish, person-to-person spread	Watery diarrhea, cholera, pandemic spread
Clostridium difficile	Cotyotoxin, local invasion	Nosocomial environment	Fever, pain, bloody diarrhea, following antibiotic use, nosocomial acquisition
Clostridium perfringens	Enterotoxin, no invasion	Meat, poultry, fish	Watery diarrhea, food sources
Staphyloccus aureus	Nosocomial	Unwashed hands	Methicillin resistant skin lesions, can infect organs and spine.
Mycobacterium tuberculosis	Invasion, mural inflammatory foci	Contaminate mil, swallowing of	Chronic abdominal pain, complications of

	with necrosis and scarring	coughed-up organism	malabsorption, stricture, perforation, fistuals, hemorrhage

Source: Crawford ’94: Table 17-8; 792

Clostridium botulinum can survive much boiling and, if processing is inadequate, can survive in vegetables (especially beans) where the spores produce a neurotoxin. The toxin is destroyed by boiling for 10 minutes. If toxin is ingested, 12-36 hours later a flaccid paralysis comes on with prolonged respiratory failure. **Botulism** is rare but nearly always fatal. *Bacillus cereus* is most often found in fried rice, it survives boiling, multiplies at room temperatures, and may not be killed by rapid frying. Ingestion of the preformed enterotoxin induces vomiting in one to six hours. *Vibrio parahaemolyticus* contaminate raw fish and is ingested with seafood. An enterotoxin produces vomiting, pain and diarrhea within 12-24 hours (Jones et al '85: 347, 348). **Cholera**, a nonexudative form of acute diarrheal disease, is characterized by severe bloody diarrhea and dehydration due to the choleragen endotoxin associated with the etiologic agent, *Vibrio cholera*. This endotoxin, stimulates a prolonged increase in capillary permeability, inducing a basic lesion in the jejunal microcirculation with striking water and ion fluxes. Prognosis is excellent with current electrolyte replacement therapy, which involves infusing the patient with an alkaline saline solution in order to rehydrate him and to correct his acidosis. Once hydration has been achieved, tetracycline is used to reduce the number of organisms shed in the stool. Homeostasis is maintained by infusing solutions at a rate to match the measured stool volume (Lewis and Elvin-Lewis ’77: 288). In order to produce disease, ingested organisms must adhere to the mucosa; otherwise they will be swept away by the fluid stream. Adherence of enterotoxigenic organisms such as *E. coli* and *Vibrio cholera* is mediated by plasmid-coded adhesins. Adherence causes effacement of the apical enterocyte membrane, with destruction of the microvillus brush border and changes in the underlying cell cytoplasm. *Vibrio vulnificus* is a bacteria found in warm salt water that causes a serious infection. It's in the same family of bacterium that causes cholera. In 2013 31 people across Florida have been infected by the severe strain of vibrio, and 10 have died. In fresh water, the *Naegleria fowleri* amoeba usually feeds on bacteria in the sediment of warm lakes and rivers. If it gets high up in the nose, it can get into the brain. Fatalities have been reported in Louisiana, Arkansas and in Florida, including the August death of a boy in the southwestern part of the state who contracted the amoeba while knee boarding in a water-filled ditch (Lush '13).

Infections with *Campylobacter jejuni* have recently been recognized as a common cause of diarrhea. Large outbreaks have followed milk-borne infections, and infection has also been transmitted directly from chickens and dogs. The organisms invades the mucosa and may elaborate an enterotoxin. Following an incubation period of 3-5 days, the illness is heralded by rigors, headache and myalgia. Abdominal pain may be so severe as to precipitate admission to a surgical unit. Diarrhea may occur one or two days later and may contain blood. The diagnosis is made by stool culture and serology. Treatment is by fluid replacement and erythromycin may be indicated if the symptoms are severe. Relapses occur in approximately 10% of cases (Jones et al '85: 334). **Salmonella** infections may be due to pathogens exclusive to humans (e.g. *S. typhi* and *S. paratyphi*) which are associated with the syndrome of enteric fever and pathogens which primarily affect animals (e.g. *S. typhimurium*, S. *enteritidis* and *S. Heidelberg*) that produce a form of food poisoning which, when contaminated food or water is ingested, is gastroenteritis confined to the bowel mucosa. Typhoid and paratyphoid fevers are caused by *Salmonella typhi* and *S. paratyphi.* The only reservoir for these bacteria are humans and patients can only contrat the infection from human excreta containing the salmonellae. Outbreaks may be water borne. Although a systemic disease the most serious complications are in the gut. Typhoid bacilli

multiply in the small bowel and penetrate the lymphoid tissue (Peyer's patches) in the submucosa, where they multiply. Blood-borne dissemination then occurs, reaching the reticuloendothelial cells of liver and spleen. At the end of the incubation period of 10-14 days (sometimes up to 21 days), the organisms reemerge into the blood stream, and there is heavy recolonization of the gut via infected bile. This leads to severe ulceration of the surface of Peyer's patches, especially in the lower ileum, and it is this deep ulceration which can cause severe melaena or free perforation of ileum into the peritoneal cavity. The patient complains of headache, malasise, anorexia, cough and fever and tends to be constipated. Untreated, the severely affected patient sinks further into a stupor, runs a high fever, and may pass loose green stools. Hemorrhage and perforation are major risks in the third week. Blood culture is usually positive during the first week, and feces and urine cultures are positive during the second and third weeks. Chloramphenicol is the antibiotic of choice, 500 mg four-hourly until defervescence and then 500 mg 6-hourly for a total of 10 days. Some resistant strains of *S. typhi* have emerged, and co-trimoxazole is then helpful. Stool cultures should become negative before the end of 3 months. If persistently positive, the carrier state must be treated, using amoxicillin and mecillinam, or co-trimoxazole. Chloramphnicol is not then helpful. Continuation of the carrier state may need treatment by cholecystectomy, because infection can lie dormant in gall-bladder mucosa for years, especially if gallstones are present (Jones et al '85: 336, 337). 2019 deaths from Salmonella contamination of beef products in the United States and Mexico, after the deportation of slaughterhouse workers, require prescription for metronidazole. The prescription of antibiotics other than metronidazole to treat intestinal infection is always an error because antibiotics other than metronidazole invariably cause antibiotic associated colitis.

Giardiasis is a protozoal infection that is usually acquired by ingestion of contaminated food or water, it is the most common waterborne pathogen in the North America, but may also be transmitted by male homosexuals. The *Giardia lamblia* trophozite inhabits the proximal small intestine where it multiplies and forms cysts. The infection is frequently asymptomatic but some people develop diarrhea with associate nausea and abdominal pain. Rarely there is an associated malabsorption of fat. The diagnosis is made by identifying cysts in the stool or trophozoites in the fresh duodenal spirate. Metronidazole in a single daily dose of 2 g for 3 days, or tinidazole in a single dose of 2 g are effective treatment. Amoebiasis caused by infestation with *Entamoeba histolytica* appears to be confined to man and is of world-wide distribution though much commoner is warm climates with poor sanitation. It is said to affect 5% of non-travelled residents of the USA. Infection occurs by swallowing mature cysts in contaminated water or food. Boiling the water kills cysts, but acceptable levels of chlorination do not. In the distal ileum or colon the cyst develops into the trophozoite – a four- nucleated amoeba – which divides into four single-nucleated entamoebae. If the patient has diarrhea, these amoebae, containing ingested red cells, can be seen in the stool, but if there is no diarrhea there is time for the amoebae to encyst and it is these mature cysts in the feces which are the infective form of *E. histolytica*. As the amoebae develop they penetrate the colonic mucosa and, by a process of invasion and destruction ,produce typically flask-shaped ulcers, which may or may not penetrate the muscularis mucosae. The secondary infection which accompanies repeated ulceration can lead to oedema, granulation tissue and fibrosis, forming an inflammatory mass – an amoeboma that may be found anywhere in the colon, more often in the proximal part. Metastatic spread can occur, especially to the liver and may be facilitated by inappropriate corticosteroid therapy. Typically amoebiasis precipitates dysentery-like illness of days or weeks which, if untreated, is followed by a quiescent period during which the patient tends to be constipated. If an amoeboma forms, this gives a palpable mass which is very difficult to distinguish from a carcinoma or Crohn's disease. Treatment with a combination of metronidazole, 400 mg 8 hourly for 5 days,

with diloxanide furoate, 500 mg 8-hourly for 10 days, gives the best results (Jones et al '85: 339-341).

Metronidazole (Flagyl ER) is the most effective antibiotic for all gastrointestinal infections and does not tend to cause a vitamin B_{12} deficiency, but it is reversibly carcinogenic. Diarrhea is a significant complication of acquired immunodeficiency syndrome (AIDS) enteropathy attributable to the direct mucosal damage by HIV infection. Diarrhea is also a complication of graft-versus-host disease, bone marrow transplantation and may be caused by exposure to radiation or chemotherapy (Crawford ’94: 795). Metronidazole (Flagyl ER) is uniquely useful in the treatment of diarrhea and intra-abdominal infections (including ulcers, peritonitis, intra-abdominal abscess, liver abscess), because it is effective against antibiotic resistant *Clostridium difficile* and although it can cause nausea as a side-effect is generally sympathetic to the gastrointestinal tract usually disturbed into malabsorption by antibiotics and NSAIDs. Metronidazole possesses bactericidal, amebicidal, and trichomonacidal action and has direct anti-inflammatory effects and effects on neutrophil motility, lymphocyte transformation, and some aspects of cell-mediated immunity. Spectrum of activity includes most obligately anaerobic bacteria and many protozoa. Inactive against fungi and viruses and most aerobic or facultatively anaerobic bacteria. Gram-positive anaerobes: *Clostridium*, *C. difficile*, *C. perfringens*, *Eubacterium*, *Peptococcus*, and *Peptostreptococcus*. Gram-negative anaerobes: Active against *Bacteroides fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*, *B. ureolyticus*, *Fusobacterium*, *Prevotella bivia*, *P. buccae*, *P. disiens*, *P. intermedia*, *P. melaninogenica*, *P. oralis*, *Porphyromonas*, and *Veillonella*. Active against *Helicobacter pylori*, *Entamoeba histolytica*, *Trichomonas vaginalis*, *Giardia lamblia*, and *Balantidium coli*. Acts principally against the trophozoite forms of *E. histolytica* and has limited activity against the encysted form. Resistance has been reported in some *Bacteroides* and *T. vaginalis*. Giardiasis for the treatment *Giardia lamblia*, the most common waterborne pathogen in North America, is performed with the oral administration of 200-250 mg 3 times daily given for 5–7 days and *Clostridium difficile*-associated Diarrhea and Colitis, resistant to all other antibiotics is effectively treated with 200-250 mg 4 times daily or 400-500 mg 3 times daily given for 10 days of metronidazole (Flagyl ER). **Antibiotic-Associate Colitis** (Pseudomembranous Colitis) is an acute colitis characterized by the formation of an adherent inflammatory “membrane” (pseudomembran) overlying sites of mucosal injury. It is usually caused by toxins of *C. difficile*, a normal gut commensal. This disease occurs most often following a course of broad-spectrum antibiotic therapy. Nearly all antibacterial agents have been implicated, with the exception of Metronidazole (Flagyl ER) that is effective against *C. difficile*. Diagnosis is confirmed by the detection of *C. difficile* cytotoxin in the stool Response to treatment with Metronidazole (Flagyl ER) is usually prompt, but relapse occurs in up to 25% of patients (Crawford ’94: 795). It is essential to filter water from a reliable source or drink and cook with bottled water.

C*ryptosporidium* is a microscopic parasite that causes the diarrheal disease cryptosporidiosis. Many species of *Cryptosporidium* infect humans and animals. The parasite is protected by an outer shell that allows it to survive outside the body for long periods of time and makes it very tolerant to chlorine disinfection. While this parasite can be spread in several different ways, water (drinking water and recreational water) is the most common method of transmission. *Cryptosporidium* is one of the most frequent causes of waterborne disease among humans in the United States. An infected person or animal sheds *Cryptosporidium* parasites in the stool. Contaminated water may include water that has not been boiled or filtered, as well as contaminated recreational water sources. Several community-wide outbreaks of cryptosporidiosis have been linked to drinking municipal water or recreational water contaminated with *Cryptosporidium*. *Cryptosporidium* parasites are found in every region of the

United States and throughout the world. Travelers to developing countries may be at greater risk for infection because of poorer water treatment and food sanitation, but cryptosporidiosis occurs worldwide. In the United States, an estimated 748,000 cases of cryptosporidiosis occur each year. Once infected, people with decreased immunity are most at risk for severe disease. The risk of developing severe disease may differ depending on each person's degree of immune suppression. Most people who have healthy immune systems will recover without treatment. Diarrhea can be managed by drinking plenty of fluids to prevent dehydration. People who are in poor health or who have weakened immune systems are at higher risk for more severe and prolonged illness. Young children and pregnant women may be more susceptible to dehydration resulting from diarrhea and should drink plenty of fluids while ill. Rapid loss of fluids from diarrhea may be especially life threatening to babies. Therefore, parents should talk to their health care providers about fluid replacement therapy options for infants. Anti-diarrheal medicine may help slow down diarrhea, but a health care provider should be consulted before such medicine is taken. Nitazoxanide has been FDA-approved for treatment of diarrhea caused by *Cryptosporidium* in people with healthy immune systems and is available by prescription. However, the effectiveness of nitazoxanide in immunosuppressed individuals is unclear. HIV-positive individuals who suspect they have cryptosporidiosis should contact their health care provider. For those persons with AIDS, anti-retroviral therapy that improves the immune status will also decrease or eliminate symptoms of cryptosporidiosis. However, even if symptoms disappear, cryptosporidiosis is often not curable and the symptoms may return if the immune status worsens (Scallan '11).

Leptospirosis are disease caused by the spirochetes of the complex *Leptospira interrogans*, of which the best known is *L. icterohaemorrhoagiae*, the causative organisms of icteric leptospirosis or Weil's disease. Rats are the best known hosts (*L. icterohaemorrhagiae*), but dogs (*L. canicola*) and other animals can be infected. In all the leptospires survive in the renal tubules of the host and are therefore shed in the urine. Infection can enter through abrasions on the skin, and also through the mucosa of the eyes, nose, mouth and throat. Ninety percent of infections are anicteric and many are subclinical. In these patients, the septicemic phase develops after 7-10 days, with myalgia, pyrexia, abdominal pain and proteinuria. The temperature settles after 3-7 days, but the second immune phase develops 3 days later, with a recurrent temperature. Skin rashes, uveitis and meningitis may develop. In the icteric form (Weil's syndrome) the two phases merge, and these patients are frequently very ill with jaundice, renal failure and circulatory collapse. Organisms can be isolated form blood or cerebrospinal fluid only during the first week of illness. Subsequently the diagnosis depends on serology. Antibiotic therapy in the form of benzyl penicillin or tetracycline is only helpful when administered early in the illness (Jones et al '85: 350).

There are several causes of viral enterocolitis. **Norovirus infection**, well known as "the stomach flu," is one of the most common causes of acute gastrointestinal epidemics (AGE), afflicting nearly 23 million Americans annually. **Rotavirus** is the most common cause of severe diarrhea among infants and children throughout the world and causes the death of about 600,000 children worldwide annually. The incubation period for norovirus-associated gastroenteritis in humans is usually between 24 and 48 hours (median in outbreaks, 33 to 36 hours), but cases can occur within 12 hours of exposure. Norovirus infection usually presents as acute-onset vomiting, watery non-bloody diarrhea with abdominal cramps, and nausea. Low-grade fever also occasionally occurs, and diarrhea is more common than vomiting in children. Symptoms usually last 24 to 72 hours. Dehydration is the most common complication, white rice water is the traditional remedy. Imodium (Loperamide) is available without prescription. 30% of rotavirus cases catch a secondary bacterial infection, for which metronidazole (Flagyl ER) is the preferred

antibiotic. Rotrovirus vaccine Rotarix (GSK) and Rotateq (Merck & Co.) were approved by FDA in 2006; and by 2010 it had reduced the number of babies and young children needing emergency department care or hospitalization for rotavirus disease by 85%.

Common Gastrointestinal Viruses

Virus	Genome	Size (nm)	% US Childhood Hospitalizations	Host age	Mode of Transmission	Prodrome/ Duration of Illness
Rotavirus (group A)	dsRNA	70	35-40	6-24 months	Person-to-person, food, water	2 days/3-8 days
Noroviruses	ssRNA	27	Not applicable	School age; adult	Person-to-person, water, cold foods, raw shellfish	1-2 days/12-60 hours
Enteric adenoviruses	dsDNA	80	5-20	Child <2 years	Person-to-person	3-10 days/7+days
Caliciviruses	ssRNA	35-40	3-5	Child	Person-to-person, water, cold foods, raw shell-fish	1-3 days/4 days
Astroviruses	ssRNA	28	3-5	Child	Person-to-person, water, raw shellfish	24-36 hours/1-4 days

Source: Crawford '94: table 17-7; 792

Rotaviruses and Norwalk (Ohio) virus, are now known as **Noroviruses**. They cause billions of cases of diarrhea, mostly in children, every year and millions of deaths in poor countries. Both viruses were discovered in the early 1970s. Before then the pathogens behind most cases of gastroenteritis and epidemic diarrhea in young children were a mystery, bacteria such as *Escherichia coli* are more prevalent in older children and adults. Noroviruses and rotaviruses pass around through infected feces. Noroviruses are part of the larger *Calicivirus* family, which also includes the genus Sapovirus and was created to classify. Currently, there are five recognized norovirus genogroups, of which three (GI, GII, and GIV) are known to affect humans. More than 25 different genotypes have been identified within these genogroups. Since 2002, variants of the GII.4 genotype have been the most common cause of norovirus outbreaks. Ligocyte trials for a **Intranasal Norovirus VLP Vaccine**, began with an injection in 2007 are entering stage II clinical trials. In 77 adults vaccination decreased the incidence of Acute Gastroenteritis (AGE) due to norovirus from 69.2 percent to 36.8 percent and the incidence of norovirus infection from 82.1 percent to 60.5 percent. The severity of illness was also significantly reduced in those vaccinated within the trial (Sanders'11:3).

Schistosome and soil-transmitted **helminth** (roundworms, hookworms and whipworms) infections are among the most common infections in developing countries and can cause internal

bleeding, leading to anemia. They can also cause malabsorption of nutrients, diarrhea and vomiting, and loss of appetite, further damaging nutritional status. Children infected with soil-transmitted helminths benefit significantly from anthelminthic treatment, in terms of reduction of worm burden and weight and height gain. Preventive chemotherapy (deworming), using annual or biannual single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for all young children (12–23 months of age), preschool (24–59 months of age), school-age children (5–12 years) and non-pregnant women (15-49) living in areas where the baseline prevalence of any soil-transmitted infection is 20% or more among children, in order to reduce the worm burden of soil-transmitted helminths. Albendazole and mebendazole are well tolerated among children over 12 months of age, at appropriate doses, with only minor and transient side-effects reported. The most cost-effective approach to reach infected individuals is to treat the entire group at risk without individual diagnosis. Deliver deworming together with promotion of health and hygiene, to reduce transmission by encouraging healthy behaviors, such as hand-washing, use of footwear and proper disposal of feces. Take extra care and precaution in ensuring that women receiving anthelminthic medicines are not pregnant. Albendazole and mebendazole are well tolerated, with no adverse events in pregnant women and their fetuses when given after the first trimester of pregnancy. Anthelminthic medicines must not be given during the first trimester. Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for pregnant women, after the first trimester, living in areas where both: (i) the baseline prevalence of hookworm and/or *T. trichiura* infection is 20% or higher among pregnant women, and (ii) anemia is a severe public health problem, in order to reduce the worm burden of soil-transmitted helminths (WHO '19).

Parasites

Parasite	Treatment
Nematodes	
Hookworm (*Ancylostoma duodenale* and *Necator americanus*	Mebendazole and ferrous sulphate
Roundworm (*Ascaris lumbricoides*)	Piperazine
Echinococcus granulosus	Mebendazole
Cestodes (tapeworms)	
Threadworm (*Enterobiasis vermicularis*)	Piperazine
Whipworm (*Trichuris trichiuria*)	Mebendazole
Trematodes	
Toxocariasis (*Toxocara anis*)	Pet deworming
Trematodes	
Schistosomiasis (blood flukes) *S. haematobium*, *S. mansoni*, and *S. japonicum; Clonorchiasis* (liver flukes);	Niridazole or praziquantel (active against all species) or oxamniquine, which is the treatment of choice for *S. mansoni* infection

Paragonimiasis (lung flukes)	

Source: Jones et al '85: 341-344, WHO '19

Three categories of **worm infestation** are recognized (1) nematodes (roundworms), (2) cestodes (tapeworms) and (3) trematodes (flukes). **Nematode** infestations by hookworm (*Ancylostoma duodenale* and *Necator americanus*) are estimated to affect up to one quarter of the world's population, and is found in tropical and subtropical regions. Eggs pass out with the stools and, under suitable conditions, hatch into larvae which may penetrate the skin. The larvae are carried in the circulation to the lungs and, after penetration of the alveolar wall, make their way to the small intestine via the trachea, and swallowed sputum. Clinical manifestations include an itch at the site of penetration, transient chest symptoms with radiological opacities, and eosinophilia during the stage of migration. Abdominal discomfort and diarrhea occur during the phase of worm attachment, and ultimately iron deficiency anaemia develops due to blood loss. The diagnosis is established by finding eggs in the stool. Heavy infestations require treatment with mebendazole and ferrous sulphate. Infestation with **Roundworm**, (*Ascaris lumbricoides*) is extremely common throughout the tropics and subtropics. These are larger white worms, males being about 15 cm long and females over 20 cm. Consequently a major infestation can be a serious matter, with the lumen of the small bowel being occupied by a mass of worms, causing some degree of obstruction and malnutrition: they may also migrate into the biliary tree. Infection occurs in poor hygienic conditions from ingestion of ova form the stools of a patient. These ova can survive for a long time, even in dust, so acquisition of infection, especially in children is easy. When the ova are swallowed they develop in the small bowel into larvae, which burrow through the intestinal wall and are carried in the portal blood to the liver and on into the lungs. Cough, dyspnea and eosinophilia may occur at this stage. The larvae migrate though the alveolar wall, up the bronchial tree to reach the pharynx and are swallowed with food and saliva. In the small bowel they develop into adult worms: fertilized eggs form the females pass in the stools and are ready to repeat the cycle in another individual. Piperazine is the treatment of choice. **Threadworm** (*Enterobiasis vermicularis*), otherwise known as pinworms, are extremely common world-wide. These are very small white highly motile worms, about 1 cm long, which can quite often be seen in rectosigmoid at sigmoidoscopy, wriggling over the mucosal surface. The females migrate out onto the perianal skin, where they deposit their ova, and this migration sets up considerable irritation. Patients tend to scratch, contaminate their fingers with ova and readily re-infect themselves. Cross infection through use of family linen and towels can easily occur. Piperazine compounds are non-toxic and effective and often the opportunity is taken to treat the whole family. **Whipworm** (*Trichuris trichiuria*) infestation is very common in tropical countries. Larvae from swallowed eggs attach to the mucosa of the distal small bowel, wher ehtye mature into adult worms, 3-5 cm long. Light infestations are asymptomatic, but heavy infestations may cause diarrhea with bleeding. Diagnosis is confirmed by finding eggs in the stool and mebendazole is the treatment of choice. **Toxocariasis** (*Toxocara anis*) is commonly found in the intestines of dogs, and children are particularly likely to ingest ova. Larvae are liberated in the stomach and may migrate through the body, producing allergic reactions. Granulomata may develop around dead larvae, especially in the eye and the liver. Treatment is unsatisfactory, but prevention by the regular worming of pet animals and careful hygiene is very effective (Jones et al '85: 341-344).

Hydatid disease is caused by the adult worm of *Echinococcus granulosus* that lives in the small intestine of the definitive host. Eggs are passed in the feces and are eaten by the intermediate hosts – sheep and cattle. Hydatid cysts (which are the larval state) develop in the tissues of these herbivores and, if that flesh is eaten by a dog, the cycle is completed with the development of further worms, which will pass ova in the canine feces. When ova from canine feces reach the

small bowel the embryo is liberated, gains access to the bloodstream, and may lodge in liver, lung, brain or other tissues. Each cyst grows slowly, having an inner germinal layer secreted by the cyst with a fibrous capsule developed from the tissues of the host: new cysts develop within the germinal layer. As the cyst grows it causes swelling and pain, but liver function is usually normal. An x-ray may show calcification of the capsule. The Casoni test is sensitive but not very specific and the diagnosis is confirmed by specific complement fixation tests. Careful surgical removal of the cyst may be required to relieve pressure effects, but great care must be exercised because any accidental spillage of cyst fluid into the tissues may cause a fatal anaphylactic reaction and there is also risk of spread of daughter cysts. Specific treatment with mebendazole may prove valuable and diminish the risks of surgery (Jones et al '85: 352).

Many parasites gain access to the body through the intestinal tract. A number with primarily non-intestinal clinical features may sometimes produce alimentary symptoms, including malabsorption, including strongyloidiasis, capillariasis and trichinosis. Cestodes (**tapeworms**) are widely distributed especially in tropical and subtropical countries. Infection is acquired by the patient eating the encysted larva (cysticercus) in the undercooked flesh of beef (*Taenia saginata*) or pork (*T. solium*). In the case of *T. saginata*, the cysticercus is ingested and liberated in the upper small bowel and the head of the worm attaches itself to the mucosa; the adult develops by proliferating thousands of segments, and an measure up to 12 meters. There are few symptoms and the patients usually only realize they have a worm infestation when segments are seen in the faces. If the ova in the feces are ingested by the intermediate host – beef cattle – the embryo is liberated, enters the bloodstream and settles in the animal's tissues and becomes a cysticercus. If eaten, undercooked, by man this completes the cycle of development. The life cycle of *T. solium* has one important difference. Whereas the larval cysticercoid stage usually occurs in the flesh of the pig, it can also occur in the tissues of the sufferer because, if man y swallows the eggs of a gravid segment of a worm (either his own by the fecal –oral route, or by the liberation of many eggs within the intestine, or from another worm) the larvae liberated from these eggs in the small bowel can penetrate the bowel wall and circulate to encyst in the tissues. When the cysticerci settle in connective tissue or voluntary muscle they gradually calcify and can be seen on plain radiographs. However, in the other site of lodgment, the central nervous system, the cisticerci tend to swell as they age and can give rise to pressure effects, e.g. epileptic fits. The prognosis of this complication is severe. Infection with the fish tapeworm, *Diphyllobothrium latum*, may cause a macrocytic anaemia due to vitamin B_{12} deficiency. The smallest tapeworm of importance is *Echinococcus granulosus*, for which man is one of the intermediate hosts as a carrier of hydatid cysts (Jones et al '85: 344).

Trematode infestations include schistosomiasis (blood flukes), clonorchiasis (liver flukes) and paragonimiasis (lung flukes). There are estimated to be 200 million sufferers of schistosomiasis, which is found in parts of Africa, South America and the Far East. The three main species are *S. haematobium*, *S. mansoni*, and *S. japonicum*. Infection is acquired when the skin is penetrated by cercarieae, or by drinking water contaminated with cercariae. These lose their tails and migrate to the liver, where they develop over three months in the portal venous system into adult worms. The worms then migrate to their final habitat: *S. haematobium* to the bladder and uterine plexus; *S. mansoni* to the tributaries of the inferior mesenteric veins; and S. japonicum to the superior and inferior mesenteric veins. Numerous eggs are laid, and some reach the exterior via the urine (*S. haemoatobium*) or stool (*S. mansoni* and *S. japonica*), and hatch in water to liberate miracidia. These penetrate the intermediate host, a snail, in which cercariae develop. Many eggs remain in the tissues and provoke a fibrotic reaction in the bladder or intestinal wall and some are swept up the portal vein and provoke periportal hepatic fibrosis. The consequent presinusoidal hypertension results in portal systemic shunting, which is how some eggs are

carried into the lungs and other organs. Three clinical phases are recognized. Pruritis at the site of penetration may be followed by a systemic illness, with fever and eosinophilia, which corresponds to the onset of egg-laying and finally chronic schistosomiasis ensues, in which symptoms relate to egg deposition in different organs. Diagnosis depends on the identification of eggs in the stool or terminal urine. Mucosal biopsy at sigmoidoscopy (or cystoscopy) is a more reliable diagnostic technique. Treatment with niridazole is appropriate for urinary and uncomplicated intestinal disease, but sever neurophsychiatric reactions preclude its use in the presence of portal hypertension or hypoalbuminaemia. Under these circumstances there is a choice of praziquantel (active against all species) or oxamniquine, which is the treatment of choice for *S. mansoni* infection (Jones et al '85: 344, 345).

8. Food allergies, gluten, lactose and fructose intolerance and post-infectious diarrhea

Apart from general overconsumption, antibiotics, high stress levels, or gastrointestinal infections, can trigger temporary or permanent **allergies** or hypersensitivities to certain foods. When the body has returned to a healthy equilibrium, even a sensitive gut can usually sort itself out. There is no need to impose a life-long ban on certain products, but simply to make sure consumption is limited to quantities the system can cope with. The most common food intolerance in the Western hemisphere is digesting the fruit sugar fructose, with about 40 percent of the population affected. Recent estimates say about 25 percent of people in the United States lose their ability to break down lactose after weaning. The older the person the greater the probability that they will be unable to break down lactose (Enders '15: 61-67). At least 2 to 3 percent of the Caucasian population has celiac disease, and it seems to be most prevalent in Celts (Scots and Irish) and Italians; it is very uncommon in non-Caucasian populations. Although more serious than other allergies, due to gluten latching on to fat molecules and contaminating the lymphatic system, as in too much flour in the rue, Celiac disease is relatively easy to treat by rigidly adhering to a gluten-free diet (Newman ’11: 38). *Aspergillus niger* infections of peanuts, tobacco and other agricultural commodities, best known for its peanut allergy, and suspected of causing lung nodules and cancer if untreated, is cured with topical hydrocortisone crème. Foods that commonly cause reactions in individuals suffering from inflammatory conditions, namely Crohn's Disease, are (1) wheat and sometimes gluten as a constituent of wheat and other grains such as barley and spelt (2) dairy (3) sugar (4) potatoes (5) tomatoes (6) eggplant (7) peppers (8) paprika (9) cayenne (10) tobacco. Smoking may not cause the disease but can certainly aggravate symptoms (Black ’10: 62, 65). The **dietary elimination strategies** shown to alleviate symptoms of irritable bowel syndrome (IBS) and functional dyspepsia (FD) are (1) eliminate gluten from wheat, rye and barley grains (2) avoid lactose from milk and dairy products (3) reduce fructose (4) reduce saturated fats (5) reduce protein (6) reduce insoluble fiber (7) avoid caffeine and alcohol in favor of water and (8) eat frequent small meals (grazing) (Newman ’11: 134).

Although the human **immune response** occurs at the cellular level the human eye can only notice the mucus that is excreted out of the rectum as feces and out of the mouth and nostrils as coughs and sneezes. The digestive system is attributed with being responsible for as much 60-80% of the body’s immune response and the urinary tract only about 5%. **Chronic diarrhea**, like coughing and sneezing, is more likely to be an inappropriate immune response against allergens, particles in the water known by antibodies. The immune system operates on one fundamental truth: there is “self” and there is “non-self”. Ideally, immune system cells go after only non-self molecules such as bacteria, viruses, fungi, parasites and even tumors, and leave self-cells, such as nerve, muscle and brain cells, alone. The immune system knows which are “good” cells and which are “bad” cells because the surface of every sell in your body sports

special proteins called human leukocyte antigens, HLAs. The cells doing the detect-and-destroy work are white blood cells. Millions of them circulate in blood and tissues, there are five main types: Lymphocytes, macrophages, neutrophils, eosinophils and basophils. Lymphocytes, found mostly in the lymphatic system, search your body for cells that don't belong there and alert other cells to their presence (Berger '04: 23).

There are two types of **lymphocytes**: T lymphocytes, or T cells, secrete potent substances to attract the immune system cells that do the actual work. They also attack and destroy diseased cells. B lymphocytes, or B cells, are immune cells that actually produce antibodies, specialized fighter proteins that help immune cells do their job. B cells that long memories for their enemies and may remain in the body for years, ready at any time to turn into little antibody factories whenever an antigen they recognize appears. This is how a vaccination works: a tiny bit of a (usually) killed virus, or antigen, such as polio, measles, or flu, is injected into the blood-stream, provoking B cells to produce antibodies. Then, if ever encountering the fully functional form of the virus, your body can quickly marshal its defenses and produce millions of the required antibodies without delay. If the B cells had never met up with that particular antigen before, the antibody response would be much slower, and the intruder could gain the upper hand. Macrophages engulf and destroy large cells, such as bacteria or yeast, as well as the debris from natural cell formation in a growing body. Neutrophils, are the most common type of white blood cells in the bloodstream, they are first to appear at the site of an injury. Their job is to consume unwelcome cells. Eosinophils make up 4 percent or less of active white blood cells. They attack larger cells, in part by secreting toxins that trigger inflammation. Basophils release granules of germ-killing toxins and histamine, a substance that triggers inflammation when they encounter damaged tissue (Berger '04: 23, 24).

Human blood contains more than 1 trillion **antibodies**. Antibodies are made up of chains of molecules that form a Y shape. The sections that make up the tips of the Y's arms vary greatly from one antibody to another; this is called the variable region. It develops a unique shape based on the antigen it was created to react to, so it can "lock" onto that antigen just like a key fitting into a lock. Sometimes this locking neutralizes the antigen on its own, rendering it harmless; sometimes it ruptures the cells of the foreign body; and sometimes it forces antigens to clump together, creating sitting-duck target for other immune cells to attack. There are five classes of antibodies, each with a slightly different function and operating method. Scientists call them immunoglobulins, or Igs for short. Of the five, IgE is the one we could call the "allergy antibody", since IgE antibodies are the main culprits contributing to allergies. Normally, they are present in tiny quantities in the body and are produced in response to relatively large invaders, such as parasites like ringworm and fluke. However, it never gets a chance to do its job, it begins to act out like a bored teenager. Instead of attacking parasites as it's supposed to do, it begins attacking proteins and molecules it should recognize as perfectly harmless, such as dust and peanuts and pollen. When that happens, the IgE binds the allergen molecule either to basophils, or to cells called mast cells found in the mucous linings of tissues throughout the body, such as the throat, nose, lungs, skin or stomach lining. This binding triggers the mast cells or basophils to release inflammatory chemicals, such as histamine, prostaglandins, and leukotrienes. The inflammatory process begins, with swelling, creation of mucus, reddening, heat and vessel constriction – an allergic reaction (Berger '04: 27, 28, 30).

One theory about the origin of allergies is that if the metabolism fails to break down a protein into its constituent amino acids, bits of it will remain, and enter the lymphatic system, where embedded in fat droplets, attract the attention of immune cells, who attack it as a foreign body. The next time the immune cells encounter a peanut, or other particle they recognize, they attack

it aggressively. The result is increasingly severe allergic reactions, such as extreme swelling of the face and tongue. This applies to allergies caused by foods that are both fatty and rich in protein, such as milk, and most commonly peanuts. Another theory about allergies is that the wall of the gut an become temporarily more porous, allowing food remnants to enter the tissue of the gut and the bloodstream. This theory is best applied to gluten, a protein found in wheat and related grains. In humans, gluten can pass into the cells of the gut in a partially undigested state. There, it an slacken the connections between individual cells. This allows wheat proteins to enter areas they have no business being in, and this triggers an immune response. One person in a hundred has a genetic intolerance to gluten (celiac disease), but many more suffer from gluten sensitivity. In patients with celiac disease, easting wheat can cause serious infections or damage to the villi of the gut wall; it can also damage the central nervous system. Celiac disease can cause diarrhea and failure to thrive in children, who may show reduced growth or winter pallor. Those with more subtle forms of celiac disease may live with the symptoms for years without realizing the cause of their occasional stomachache or anemia during routine blood tests. The most effective treatment for celiac disease is a life-long gluten free diet. Gluten sensitivity is not a sentence to a life of gluten avoidance. Those with this condition can eat wheat without risking serious damage to their small intestine, but they should enjoy wheat products in moderation. Many people notice their sensitivity when they swear off gluten for a week or two and see an improvement in their general well-being. Symptoms improve when a gluten-free diet is introduced, although tests for celiac disease show negative. The villi are not inflamed or damaged but eating too much bread still appears to have an unpleasant effect on the immune system. The gut can also become porous for a short time after a course of antibiotics, after a heavy bout of drinking alcohol, or as a result of stress. Sensitivity to gluten resulting from these temporary causes can sometimes look the same as the symptoms of true glucose intolerance. Alongside, the familiar blood groups A, B, AB, and O, there are many other indicators for categorizing human blood, including what doctors call DQ markers. Those who do not belong to group DQ2 or DQ8 are extremely unlikely to have celiac disease (Enders '15: 58-61).

Celiac disease is a condition in which a wheat protein – gluten – causes damage to the intestinal lining. In addition to wheat, the celiac patient is also intolerant to rye, barley, and possibly oats. This intestinal damage may result in malabsorption of fats, certain vitamins, and iron and is accompanied by abdominal pain and bloating. At least 2% to 3% of the Caucasian population has celiac disease, and it seems to be most prevalent in Celts (Scots and Irish) and Italians; it is very uncommon in non-Caucasian populations. Celiac disease is relatively easy to treat by rigidly adhering to a gluten-free diet (Newman ’11: 38). Celiac sprue is a chronic disease, in which there is a characteristic mucosal lesion of the small intestine and impaired nutrient absorption, which improves on withdrawal of wheat gliadins and related grain proteins from the diet (wheat, oat, barley and rye). Celiac sprue occurs largely in whites and is rare or nonexistent among native Africans, Japanese and Chinese. Its prevalence in the United States is not known accurately, the prevalence in Europe is in the range of 1: 2000 or 3000. Biopsy specimens demonstrate a diffuse enteritis, with marked atrophy or total loss of villi. Clinical diagnosis (1) documentation of malabsorption, (2) demonstration of the intestinal lesion by small bowel bipsy, and (3) unequivocal improvement in both symptoms and mucosal histology on gluten withdrawal form the diet. Most patients with celiac sprue who adhere to a gluten-free diet remain well indefinitely and ultimately die of unrelated causes. There is however a long-term risk of malignant disease, such as intestinal lymphomas, particularly T-cell lymphomas, gastrointestinal and breast carcinomas (Crawford ’94: 798).

Celiac disease results from a hyperplastic enteropathy induced in a susceptible person by exposure of the small intestinal mucosa to a component of the protein, gluten, which is found in

wheat, barley, rye and oats. Cow's milk sensitivity in children and tropical sprue, may be associated with a temporary sensitivity to gluten, but in celiac disease the sensitivity is thought to be life-long. Incidence in the UK is 1 in 2,000-6,000, but in the west of Eire it is as high as 1 in 300. Patients with coeliac disease may present with predominantly abdominal symptoms (distension, discomfort, diarrhea), nutritional deficiencies (especially iron or folate), general malaise, or any combination. The diagnosis of celiac disease must be confirmed by jejunal biopsy carried out on at least two separate occasions. The first must show a compatible mucosal lesion and the second a morphological response to gluten withdrawal from the diet. Once celiac disease is suspected form the jejunal biopsy, a trial of a strict gluten-free diet is mandatory. This has to be strictly supervised by the gastroenterologist with the close help of a dietician. The aim is to exclude gluten completely from the diet and this means total life-long exclusion of the protein content of wheat, rye, barley and oats. Rice and maize can be used as substitutes, and soya flour and maize flour can be used in baking. The Coeliac Society handbook contained updated lists of safe proprietary foods. Many convenience store foods contain flour that may not be declared on the label. Gluten may be contained in some items, not usually considered as foods, such as sweets, ice cream, some antacids and communion wafers. Symptomatic response to a gluten-free diet is quite dramatic in some patients, with many cures of mental illness. Failure to respond to a gluten-free diet is usually due to failure to keep strictly to the diet, but secondary pancreatic insufficiency (causing fat, starch and/or protein intolerance), secondary lactase deficiency, intestinal ulceration, lymphoma or bacterial overgrowth may be causative (Jones et al '85: 132).

Lactose intolerance is not an allergy or real intolerance, it is a deficiency resulting from a failure to break down certain nutrients completely into their component parts. Lactose is found in milk. It is derived from two sugar molecules that linked together by chemical bonds. They body requires a digestive enzyme to break that bond, but, unlike other enzymes, this one does not come from the papilla. The cells of the small intestine secrete it themselves from the tips of their tiny little villi. Lactose breaks down when it comes into contact with the enzyme on the gut wall, and the resulting simple sugars can be absorbed. If the enzyme is missing, bellyache, diarrhea and flatulence can occur. Unlike celiac disease, however, no undigested lactose particles pass through the gut wall, they simply move on down the line, into the large intestine, where they become food for the gas-producing bacteria there. Lactose intolerance is far less harmful to health than celiac disease. In extremely rare cases, problems with lactose digestion occur from birth. Such newborns are unable to digest their mother's milk and drinking it causes severe diarrhea. In 75 percent of the world's population, the gene for digesting lactose, slowly begins to switch off as they get older and are no longer reliant on mother's milk, or formula, for nourishment. Outside of Western Europe and the United States, adults who are tolerant to dairy products are a rarity. Recent estimates say about 25% of people in the United States lose their ability to break down lactose after weaning. The older the person the greater the probability that they will be unable to break down lactose (Enders '15: 61, 62). All babies are born with the ability to digest milk. Some, especially those of northern European ancestry, keep this trait for life. Most children, though, gradually lose this ability as their bodies stop making an enzyme called lactase that breaks down milk sugar (lactose). In fact, only about a quarter of the world's adults can digest milk. In the United States, as many as fifty million Americans aren't equipped to digest milk. Half of Hispanic Americans, 75 percent of African Americans, and more than 90 percent of Asian Americans can't tolerate a lot of lactose. A glass of milk can have unpleasant consequences (Willet '01: 131, 132). Cheese aged over 60 days, medium cheddar or older, contains no lactose because it has been completely converted to lactic acid.

Lactose is a sugar found in dairy products, appearing in high levels in cow's milk, cream, yogurt, and ice cream and in much lower concentrations in cheese. Lactose can be absorbed only if the cells of the intestinal lining possess an enzyme called lactase, which breaks down the lactose into glucose and galactose. These simpler sugars can be absorbed readily. However, it is undeniable that a lactose-intolerant person forced to drink 4 cups (1 L) of milk does experience diarrhea and intestinal distress. Lactose, or milk sugar, is a 12-carbon sugar composed of two slightly different 6-carbon sugars – glucose and galactose. Lactose cannot be absorbed by the human intestine, it must be broken down into glucose and galactose, and then these simpler sugars are absorbed. Fructose is also a 6-carbon sugar, but it looks very different from glucose and galactose and it is much less well absorbed (Newman '11: 34, 35, 138). Lactose intolerance is the result of a disaccharidase deficiency. The disaccharidases are located in the apical cell membrane of the villous absorptive epithelial cells. Congenital lactase deficiency is a rare condition, but acquired lactase deficiency is common, particularly among North American blacks. Incomplete breakdown of the disaccharide lactose into its monosaccharides, glucose and galactose, leads to osmotic diarrhea from the unabsorbed lactose. Bacterial fermentation of the unabsorbed sugars lead to increased hydrogen production, which is readily measured in exhaled air by gas chromatography. When inherited as an enzyme deficiency, malabsorption becomes evident with the initiation of milk feeding. Infants develop explosive, watery, frothy stools and abdominal distention. Malabsorption is promptly corrected when exposure to milk and milk products is terminated. In the adult, lactase insufficiency may become apparent during viral and bacterial enteric infections (Crawford '94: 800).

The most common food intolerance in the Western hemisphere is digesting the fruit sugar fructose, with about 40 percent of the population affected. **Fructose intolerance** can be the result of a severe hereditary inability to metabolize fruit sugar, which causes the patients' digestive system to react to even the slightest amounts of the substance. Most people affected by fructose intolerance actually have a condition more accurately described as fructose malabsorption, and they experience problems only when they are exposed to large amounts of the sugar. Fructose is described on food packages as "fruit sugar" and consumers assume it is a healthier more natural option. Some types of tomato are specially bred to contain large amounts of this sugar. Globalization and air transport mean that we are now exposed to an overabundance of fruit. The mechanism behind fructose intolerance is different from the digestion of gluten or lactose. The cells of people with hereditary fructose intolerance contain fewer fructose processing enzymes. That means fructose may gather in their cells, where it can interfere with other processes. Fructose intolerance that appears later in life is though to be caused by a reduced ability of the gut to absorb fruit sugars. Such patients often have fewer transporters (GLUT5 transporters) in their gut wall. Their limited transporters are overwhelmed by small amounts of fructose, and the sugar ends up feeding the gut flora of the large intestine, resulting in unpleasant symptoms, of colitis, flatulence and diarrhea. This can also happen to people who consume large amounts of fructose. Fructose intolerance may affect mood. Sugar helps the body absorb many other nutrients into the bloodstream. The amino avid tryptophan likes to latch on to fructose during digestion, for example. When there is so much sugar that it cannot be absorbed into the blood and the sugar is lost to the large intestine, the tryptophan attached to the sugar molecule is also lost. Tryptophan is needed by the body to produce serotonin, a neurotransmitter needed to prevent depression. For more than 50 percent of people, eating 2 ounces (50 grams) of fructose or more per day (equivalent to five pears, eight bananas, or six apples) will overtax their natural transporters. Eating more than that can lead to health problems such as diarrhea, stomachaches, and flatulence and over longer periods, depressive disorders. The current fructose intake of the average American is lose to 3 ounces (80 grams) a day, while the previous generation took in no more than 1/1 to 1 ounce (16 to 24 grams) a day.

High fructose corn syrup can suppress leptin, the hormone that makes us feel full, even in people who are not fructose intolerant. A salad containing the same amount of calories but with a homemade vinaigrette dressing will feel full for longer (Enders '15: 64-65).

Tropical sprue (**post-infectious diarrhea**) is named because this celiac-like disease occurs almost exclusively in people living in or visiting the tropics. Bacterial overgrowth by enterotoxigenic *E. coli* has been implicated in tropical sprue. Post-infectious diarrhea is very typical amongst people who have been treated for diarrheal illness with antibiotics, causing damage to their gut flora and immune system. Furthermore, the initial and continuing diarrhea evacuate and continue to eliminate necessary vitamins and minerals stored in the bowel causing certain deficiencies, such as iron and vitamin B_{12}, that perpetuate the nutrition wasting diarrhea (Crawford '94: 798-799). Partly as the result of tissue damage caused by the infection and partly the result of not being able to consume green leafy vegetables wherefore patients, particularly vegans who eat no animal products, frequently have folate or vitamin B_{12} deficiency leading to markedly atypical enlargement of the nuclei of epithelial cells (megaloblastic change) reminiscent of changes seen in pernicious anemia. Malabsorption usually becomes apparent in visitors to endemic locales within days or a few week of an acute diarrheal enteric infection and may persist if untreated (Crawford '94: 798-799). Most vitamin B_{12} deficiency symptoms are actually folate deficiency symptoms, since they include all the effects of pernicious anemia and megaloblastosis, which are due to poor synthesis of DNA when the body does not have a proper supply of folic acid for the production of thymine. When sufficient folic acid is available, all known B_{12} related deficiency syndromes normalize, save those narrowly connected with the vitamin B_{12}-dependent enzymes Methylmalonyl Coenzyme A mutase, and 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), also known as methionine synthase; and the buildup of their respective substrates (methylmalonic acid, MMA) and homocysteine. B_{12} supplementation, in a multivitamin with adequate folate, is necessary for the treatment of post-infectious diarrhea. In people with bacterial overgrowth of the small bowel, antibiotics such as metronidazole (Flagyl) can actually improve vitamin B_{12} status.

Iron deficiency anemia is the most common cause of diarrhea worldwide. In normal subjects, daily iron loss amounts to 1–2 mg and this requires a similar amount to be taken up from the diet. Dietary iron occurs in two forms: heme (from myoglobin in animal products such as dairy, meat, poultry, and fish) and non-heme (mostly from dark green leafy plants). **Fortification of maize flour and corn meal with iron** is recommended to prevent iron deficiency in populations, particularly vulnerable groups such as children and women. Fortification of maize our and corn meal with folic acid is recommended to reduce the risk of occurrence of births with neural tube defects. Evidence on fortification of maize flour with folic acid or iron shows a positive effect on health outcomes in the general population. Fortification of maize flour with iron, in combination with other micronutrients, reduces the risk of iron deficiency but has no effect on anaemia in children. Addition of folic acid to wheat and maize flour in the United States of America (USA) and other countries has had a significant impact on multiple measures, including folate intake, blood folate concentrations and the prevalence of neural tube defects. The choice of iron compound is a compromise between cost, bioavailability, micronutrient interactions and the acceptance of texture, taste, smell and/or color. Nixtamalized flour (lime treated), commonly used in the Americas, is more reactive to ferrous compounds. The use of electrolytic iron does not appear to be effective in fortification of nixtamalized maize flour. Since some of the B-complex vitamins naturally present in the maize grain are removed during milling and degerming, the restoration of niacin, riboflavin and thiamine in maize flour should remain a regular practice in fortification, especially niacin for non-nixtamalized maize flour. This strategy has contributed to the virtual elimination of beriberi and pellagra in many countries. The

addition of vitamin C and the removal of phytates in maize flour and corn meal could increase the bioavailability of iron (WHO '19: 29-30).

Fortification of rice with iron is recommended as a public health strategy to improve the iron status of populations, in settings where rice is a staple food. Fortification of rice with vitamin A may be used as a public health strategy to improve the iron status and vitamin A nutrition of populations. Fortification of rice with folic acid may be used as a public health strategy to improve the folate nutritional status of populations. Provision of rice fortified with vitamins and minerals including iron, when compared with unfortified rice, probably improves iron status by reducing the risk of iron deficiency by 35% and increasing the average concentration of hemoglobin by almost 2 g/L, but may not make a difference to the risk of anaemia in the general population of those aged over 2 years. When the fortification of rice includes vitamin A, it may reduce both iron deficiency and vitamin A deficiency. When fortification includes folic acid, fortified rice may slightly increase serum folate concentrations. Rice milling results in the loss of a significant proportion of B vitamins and minerals that are found predominately in the outer germ and bran layers. Nutrient losses during milling can be minimized by a process called parboiling, in which raw rice is soaked in water and partially steamed before drying and milling, resulting in some of the B vitamins migrating further into the grain. Since some of the fat- and micronutrient-rich bran layers are removed during rice milling, the restoration of thiamine, niacin, riboflavin and vitamin B_6 (pyridoxine) in the fortification profile should remain a regular practice in fortification. The prevalence of depletion and deficiency of vitamin B_{12} (cobalamin) is high in all age groups, reaching 50% in some countries. The inclusion of vitamin B_{12} is recommended when staples are fortified with folic acid, to avoid the masking effect of folic acid on vitamin B_{12} deficiency. Fortification of rice with iron has been a challenge, since most of the bioavailable iron powders used in food fortification are colored, which produces changes in the aspect of fortified kernels compared to unfortified ones. Rice fortification on a national scale requires a large, cost-effective and sustainable supply of fortified kernels. In malaria-endemic areas, the provision of iron through rice fortification, as a public health strategy, should be done in conjunction with public health measures to prevent, diagnose and treat malaria (WHO '19: 30-31).

Approximately 600 million preschool and school-age children have anemia and roughly half of anaemia cases are estimated to be due to iron deficiency. **Iron deficiency anaemia** in children has been linked to increased children morbidity and impaired cognitive development and school performance. Children are particularly vulnerable to iron deficiency anaemia because of their increased iron requirements in the periods of rapid growth, especially in the first 5 years of life. Daily iron supplementation for children aged 24–59 months is associated with increased ferritin (an indicator of iron stores) and hemoglobin levels, and lower risk of anaemia, iron deficiency and iron deficiency anaemia in children aged 5–12 years. Daily iron supplementation is recommended as a public health intervention for preschool children (24–59 months) and school-age children (5–12 years), living in settings where the prevalence of anaemia in these age groups is 40% or higher, for increasing hemoglobin concentrations, improving iron status and preventing iron deficiency and anaemia. Preschool-age children (24–59 months) should receive 30 mg of elemental iron. School-age children (5–12 years) should receive 30–60 mg of elemental iron. 30–60 mg of elemental iron equals 150–300 mg of ferrous sulfate heptahydrate, 90–180 mg of ferrous fumarate, or 250–500 mg of ferrous gluconate. In settings where the prevalence of anaemia in preschool (24–59 months) or school-age (5–12 years) children is 20% or higher, intermittent iron supplementation is recommended as a public health intervention for preschool and school-age children, to improve iron status and reduce the risk of anaemia. Preschool-age children (24–59 months) should receive 25 mg of elemental iron, 25 mg of

elemental iron equals 75 mg of ferrous fumarate, 125 mg of ferrous sulfate heptahydrate or 210 mg of ferrous gluconate. School-age children (5–12 years) should receive 45 mg of elemental iron 45 mg of elemental iron equals 135 mg of ferrous fumarate, 225 mg of ferrous sulfate heptahydrate or 375 mg of ferrous gluconate. Where infection with hookworm is endemic (prevalence 20% or greater), it may be more effective to combine iron supplementation with anthelminthic treatment in children aged over 5 years. Universal anthelminthic treatment, irrespective of infection status, is recommended at least annually in these areas (WHO '19: 71-74).

9. Irritable bowel disease, Crohn's disease and ulcerative colitis

In most Western countries, about 20% of the population suffers from a chronic functional gastrointestinal disorder lasting more than 6 months, known collectively as **idiopathic bowel disease**. Of those one in five people who suffer from one or several problems with the digestive system, only about half seek medical help. One recent estimate placed the direct annual cost of IBS treatment in North America at a billion and a half dollars. That figure is more than the combined costs of treating ulcerative colitis, Crohn's disease, colorectal cancer, peptic ulcers, pancreatitis, and diverticular disease. Most patients with IBS are women, but men do get IBS, and they are more likely to have diarrhea. Women with IBS are more likely to report pain, bloating and constipation. Younger women often relate their bowel symptoms to their menstrual cycle, with more pain before menstruation and with more diarrhea during menstrual periods (Newman '11: 21). Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are gastrointestinal (GI) illnesses. They are not organic diseases, meaning that they are not connected to one specific organ such as the stomach or colon; rather, they are functional illnesses, with many symptoms affecting various organs systems, a condition known as a syndrome, which means things that go together. Irritable bowel syndrome and functional dyspepsia are the two most common functional GI syndromes among the more than 25 GI syndromes categorized in ROME III: The Functional Gastrointestinal Disorders, the most authoritative publication in this field. A worldwide association of gastroenterologists has met three time in Rome, Italy. The book comprising a thousand pages classifies these disorders into 28 different functional GI syndromes for adults over the age of 16. However instead of 28 syndromes, there are in practice fewer syndromes, the most common being IBS and FD (Newman '11: 13, 23).

There are three **idiopathic disorders affecting the bowel** (1) Irritable bowel syndrome (IBS), (2) Crohn's disease (CD) and (3) Ulcerative colitis (UC). Diagnosis is difficult and unrewarding, because it is an idiopathic disorder without known etiology or cure, however the basic distinction is that in IBS only the mucosa is affected, in CD the mucosa and submucosa are affected and in UC there is ulceration of all three layers and bleeding of the muscularis propria. Irritable bowel syndrome (IBS) is a disorder of the lower intestinal tract that can cause cramping, diarrhea, bloating and pain. The cause of IBS is also unknown but symptoms are more closely linked to the brain and emotional stress resulting in alternating diarrhea and constipation largely driven by emotional factors. Crohn's disease (named for Dr. Crohn who was part of study circa 1932) is an inflammation of the transmural wall of the intestines, usually of the small interesting but inflammation may involve any part of the GI tract. Ulcerative colitis (UC) is characterized by mucosal ulceration in the colon where it causes inflammation and ulcers in the top layer of the lining of the large intestine. In contrast, for those with Crohn's disease, all layers of the intestine may be involved, and normal healthy bowel can be found between sections of diseased bowel. All inflammatory bowel diseases, including Crohn's disease and UC, are immunologic-response or autoimmune diseases, defined by an abnormal response of the immune system. In the case of

Crohn's and UC, an immune response or defense mechanism is triggered as a result of something such as an environmentally-related cause. Suddenly, the immune system becomes overactive and damage to the body results. For individuals with Crohn's and UC a variety of health issues can result. A compromised immune system, resulting in inflammatory bowel disease, can lead to ancillary disorders of the eyes, liver, gallbladder, muscles and joints, kidneys and skin. In some cases, a fistula (an abnormal connection between two organs, characteristic of Crohn's disease but not ulcerative colitis) can form aberrant passages from your bowels to your anus, vagina, or skin surface (Black '10: 6, 7, 8).

Estimated Number of North Americans Affected Digestive Disorders

IBS	5,000,000
Gastroesophageal reflux disease (GERD)	5,000,000
Stomach ulcer	1,300,000
Pancreatitis	1,000,000
Duodenal ulcer	850,000
Barrett's esophagus	800,000
Celiac disease	300,000
Inflammatory bowel disease	250,000
Diverticular disease	130,000
Colorectal cancer	93,000

Source: Canadian Digestive Health Foundation; Newman '11: 21

Idiopathic inflammatory bowel diseases (IBD) are diseases without known etiology causing mucosal damage and architectural distortion – blunting of the villus and crypt destruction. Two such inflammatory disorders are Crohn's disease (CD) and ulcerative colitis (UC). They are known collectively as inflammatory bowel disease (IBD). Both CD and UC are chronic, relapsing inflammatory disorders of obscure origin. CD is a granulomatous disease that may affect any portion of the gastrointestinal tract from mouth to anus but most often involves the small intestine and colon. UC is a non-granulomatous disease limited to colonic involvement. The normal intestine is usually in a steady state of physiologic inflammation, representing a dynamic balance between (1) factors that activate the host immune system (.e.g. luminal microbes, dietary antigens, endogenous inflammatory stimuli) and (2) host defenses that maintain the integrity of the mucosa and down-regulate inflammation. There is a ten-fold increased risk for first-degree relatives, and concordance among twins for CD. The fact that marked clinical improvement follows immunosuppressive therapy such as corticosteroids points toward an immune-mediated process. Both the clinical manifestations of IBD and the diagnostic pathology are ultimately the result of activation of inflammatory cells whose products cause tissue injury (Crawford '94: 801).

Chronic diarrhea in the elderly is a debilitating problem. The specific protocol for screening the elderly is: First, test the stool for the presence of blood. Second, ask if the patient had imaging studies performed on the colon. If a good-quality colonoscopy has been conducted within the previous 5 years, it is highly unlikely that a full colonoscopy will be a high yield test. Third, perform a sigmoidscopy with biopsies of the lining of the colon to test for miscroscopic colitis, which is a disease of the older patient, usually older women. Medical conditions that are associated with IBS and FD are Celiac disease, Fibromyalgia, Chronic fatigue, Interstitial cystitis and painful bladder syndrome, dyspareunia, temporomandibular joint (TMJ) syndrome, migraine headaches, and pelvic pain syndromes. Fibromyalgia is a chronic condition, overwhelmingly more common in women, involving constant, dull aching pain in joints, tendons and muscles,

and it is associated with depression and extreme fatigue. Despite being fatigued, these patients suffer from significant disabling insomnia. Usually the pain occurs on both sides of the body and in both the upper body and the lower body. There are specific painful points that can be identified by the examining physician. These include the back of the head, the front sides of the neck, the top of the shoulders, between the shoulder blades, the upper chest, the outer elbows, the hips and the sides of the knees (Newman '11: 33, 107).

Chronic fatigue syndrome (CFS) is an "old" disease that has been around for centuries under different names. In the eighteenth century, it was called febricula; in the mid-nineteenth century, it was Da Costa's syndrome; and by the end of the nineteenth century, it was neurasthenia. In the twentieth century, it was chronic brucellosis, and then it was chronic mononucleosis, chronic Lyme disease, multiple chemical sensitivities, and chronic candidiasis. None of these causes or etiologies has been proven, and several have been emphatically disproved. What remains is a common disorder affecting young, middle-class-to-affluent people. More women than men suffer from CFS, becoming fatigued and incapable of functioning at their previously high level. Most patients with chronic fatigue readily fulfill the criteria for depression or generalized anxiety disorder (GAD), but there is little acceptance of the idea that this is manifestation of a primary psychiatric disorder, and this is tragic because GAD and depression are highly treatable. In CFS, the symptoms must last longer than 6 months, and physical activity must be reduced by at least half (Newman '11: 105, 107).

There are a number of ways that **fibromyalgia** is associated with IBS: (1) Both are chronic diseases that occur predominantly in women (2) Neither has a reproducibly abnormal blood test or biopsy finding (3) Neither goes on to become another disease and (4) Neither responds particularly well to medication. Another two diseases frequently associated with IBS are interstitial cystitis and painful bladder syndrome, maddening bladder conditions in which sufferers urinate frequently, unpleasantly, and painfully, resembling what is found in urinary trat infections but in a bladder that is not infected. The bladder wall is inflamed and stiff so that it does not distend comfortably and patients have to urinate frequently. Antibiotics are useless. Pentosan polysulfate (El;miron) is marketed specifically for this. Some patients gain relief from tricyclic antidepressants used in very low doses. This is a condition found almost exclusively in women and is extremely debilitating. Painful bladder syndrome, fibromyalgia and IBS often occur simultaneously in patients. Dyspareunia refers to painful intercourse. It is seen almost exclusively in women, and it is often found in conjunction with endometriosis and interstitial cystitis, and therefore with fibromyalgia and IBS (Newman '11: 108, 109).

Endometriosis is the most common gynecological explanation for pelvic pain and accounts for about 30% of cases. Endometriosis is a disease of young women (just like IBS) and it is characterized by the deposition of piece of endometrium, the lining layer of the uterus, in places where they were never meant to be. The illness is painful and is associated with dysmenorrhea (painful periods) and dyspareunia (painful intercourse) although there is a rare painless variety of endometriosis too. Endometriosis is a leading cause of fertility problems and chronic pelvic pain. Treatment consists of analgesics and hormones, either as birth control pills, other estrogens and/or progesterone products, danazol (which is a testosterone-like drug). Chronic pelvic pain (CPP) refers to pain that lasts at least 6 months and it accounts for approximately 10% of all ambulatory referrals to a gynecologist. Some surveys indicate that 15% of women report chronic pelvic pain. A more usual figure for this pain is 4%. The patient may have endometriosis, interstitial cystitis, and emotional stress. Farting is not a disease, nor is farting a sign of disease. In most cases, it should be ignored (Newman '11: 111, 112, 64).

Patients with irritable bowel disease suffers from diarrhea and pain, as do some patients with irritable bowel syndrome, but IBD patients have inflammatory disease of one or more parts of the digestive symptom, and IBS patients do not. Having both IBD and IBS is not rare. A minor amount of ulcerative colitis confined to the rectum or a few inches of Crohn's disease of the ileum is not a good explanation for the presence of the severe symptoms of IBS constipation, IBS diarrhea, or functional abdominal pain syndrome (FAPS). Most of the time distinguishing IBS from IBD is not difficult. Clinical examination, laboratory blood and stool tests, and imaging studies using x-rays, and scopes can readily distinguish these conditions. There is not evidence that IBS develops into either Crohn's disease or ulcerative colitis. In order to be diagnosed with Irritable Bowel syndrome (IBS), patients need to meet the **Rome III criteria**: Recurrent abdominal pain or discomfort has occurred at least 3 days a month in the past 3 months, and symptoms began at least 6 months prior to diagnosis and is associated with two or more of the following: (1) Improvement with defecation (bowel movement), (2) Onset of pain associated with a change in frequency of stool (3) onset associated with a change in form (appearance of stool). IBS typically begins with abdominal pain. Despite the intensity, severity and duration of the pain, it improves with defecation; in fact, it often disappears entirely with the passage of a bowel movement. Pain almost never occurs while the patient is asleep. During the painful episodes, the stools look different but there is never blood in the bowel movements (Newman '11: 15, 24, 25).

Some scientists have postulated that often the cause of IBS-D is a low-grade bacterial infection in the intestinal tract. Most parasites tested for in stool do not cause IBS. IBS is not easily confused with amebic dysentery, hookworm, roundworm, pinworm, or schistosominasis. However there are two parasites worth mentioning: *Dientamoeba fragilis* and *Blastocystis hominis*. *Dientamoeba fragilis* (*D. fragilis*) parasite may be responsible for mild diarrhea, pain, fatigue and loss of appetite. It this protozoan is found in stools it should be eradicated by means of a one week course of antibiotics. Closely related to *D. fragilis* are three other chronic diarrhea-causing parasites, all protozoans, cyclospora, cryptosporidia and isispora. The latter two are most often found in immune-compromised patients, such as those with HIV/A IDS. Cyclospora has been found in people with normal immune systems after they have eaten raspberries imported from Central America. *Blastocystis hominis* (*B. hominis*) parasite is frequently found in stools and may be responsible for disease, but this is highly uncertain. With remarkable regularity, tests for the presence of *Blastocystis* species in stool specimens come back with positive results. We know that blastocystis is present in the human gut, but we do not yet known whether it is a pathogen that causes disease. It is not very likely that you have a parasite unless the particular illness incriminates a parasite. Most of the time, the pursuit of parasites is a time and resource wasting, futile exercise. The parasite most likely to cause IBS-like symptoms is a one-celled organism called *Giardia lamblia*, and the illness provoked by *Giardia* is called, giardiasis. There have been epidemics of giardiasis from St. Petersburg in Russia to Aspen, Colorado. Because beavers may become infected with giardia, inveterate campers who share the wild, their urinals, and their drinking water with beavers are at risk of acquiring the parasite by drinking improperly treated lake water. This is why giardiasis is often called beaver fever (Newman '11: 30, 31, 32). Giardia is treated with a three day course of metronidazole (Flagyl ER) 400 mg 2 x day.

Drug treatment of irritable bowel disease (IBD) employs corticosteroids, sulphasalazine (Salazopyrin) and azathioprine (Imuran). Oral prednisone is generally the preferred corticosteroid, although hydrocortisone and ACTH may be given intravenously in severe attacks. Corticosteroids can also be given through the anal canal. In localized proctitis, prednisone suppositories are very useful, and in proctosigmoiditis prednisone 21-phosphate in water can be

given as a retention enema, or administered as a foaming preparation. This local treatment can be used over quite long periods and side-effects are generally slight. Over the space of 20 years, about 20% of patients will show gradual proximal extension of the inflammation. Suphasalazine (Salazopyrin) is a compound of sulphapyridine and 5- amino salicylic acid, which is split into its two components by bacterial action in the colon. It is now accepted that 5-amino salicylic acid is the active component. The drug is the mainstay of maintenance therapy in ulcerative colitis and many patients take it prophylactically over years. Unfortunately it is not so effective at preventing relapse in Crohn's disease. Side-effects are common, especially nausea and vomiting, but they are lessened with enteric-coated tablets. Other side-effects include skin rashes, headaches and rarely, blood dyscrasia. Oligospermia occurs, but is reversed if the drug continues. Azathiprine (Imuran) is of value in maintaining remission in chronic active CD. Some believe that it promotes the healing of fistulae. Side-effects, especially on haemopoiesis, can be severe, and it should only be used when other treatments are ineffective. Regular blood counts must be made. If colitis is active it is a serious mistake to give constipating drugs such as codeine phosphate or loperamide whereas there is a strong suspicion that they may precipitate toxic megacolon. However, after disease have been excised by right hemicolectomy, or colectomy and ileorectal anastomosis, these drugs are very helpful. After terminal ileal resection, cholestyramine may be useful. Sometimes lower abdominal pain is a feature of relapse and may be helped by antispasmodics such as mebeverine or propantheline (Jones et al '85: 234, 245, 240).

Drugs Used in Managing IBS

Anti-diarrheals	Diphenoxylate (Lomotil) Loperamide (Imodium) Octerotide (Sandostatin)
Laxatives	Lubricants, Mineral Oil, Secretory laxatives, Senna, Cascara, Bisacodyl, Osmotic laxatives, Lactulose, Magnesium slats (Milk of Magnesia, Citromag), Polyethylene glycol (Miralax)
Others	Lubiprostone (not in Canada) Prucalopride (not on the market)
Antispasmodics	Dicyclomine (Benylol) Hyoscine (Buscopan) Pinaverium (Dicetel)
Tranquilizers	Benzodiazepines: Valium, Ativan, Xanax
Anti-depressants	Tricylclics: desipramine, nortriptyline, amitriptyline, clomipramine (Anafranil) Selective serotonin reuptake inhibitors (SSRIs): fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa) Serotonin and norepinephrine reuptake inhibitors (SNRIs): bupropion (Wellbutrin), mirtazapine (Remeron), venlafaxine (Effexor), duloxetine (Cymbalta) Atypical antipsychotics: quetiapine (Seroquel)

Source: Newman ’11: 159

Many IBS sufferers claim that smoking two joints a day is the most effective pharmacological treatment for their IBS. Octreotide (Sandostatin) is a polypeptide (with sort protein molecules) hormone that serves as an anti-secretory molecule. Because it is a polypeptide, it must be given by subcutaneous injection a few times a day. Octreotide stops the secretion of many other hormones and has been useful in some diarrheal disease, such as severe IBS-D, carcinoid syndrome and other rare tumors. The acid suppression induced by the histamine receptor antagonists (H2RAs) such as ranitidine (Zantac) and famotidine (Pepcid) is less than that caused by the proton pump inhibitors (PPIs) such as omeprazole (Lozec or Prilosec) and lansoprazxole (Prevacid). Studies of the H2RAs show a modest perhaps 30% reduction in epigastric pain when compared to placebo. The more vigorous acid suppression induced by PPIs might increase the number of "responders" about 35% of the time. The response to placebos in these studies was around 20% to 25% (Newman '11: 160, 182). There is no maintenance drug for IBS and whatever agent is used should be used for a finite, brief period of time. Guiding principles: 1. Narcotics have no role to play in this disease. 2. Long term use of antinausea drugs, such as dimenhudrinate (Gravol or Dramamine) is not a successful therapeutic approach. 3. Antidiarrheal agents, such as diphenoxylate (Lomotil) or loperamide (Imodium) are quite safe and may be used chronically in those patients who respond to them. 4. Patients who don't respond to these antidiarreals may need to be treated under close supervision with 5-HT3 antagonists. 5. No drug yet produced can displace the relationship between patient and doctor. 6. Osmotic laxatives (magnesium salts, sulfates, PEG containing laxatives, or lactulose) are the preferred agents for chronic constipation and should be used first when a laxative is required. 7. Stimulant laxatives (senna preparations or bisacodyl) have too many deleterious features to be recommended to fuse on a regular basis. 8. Tranquilizers in the benzodiazepine family (Valium, Ativan, Xanax) should be used only at times of panic and acute stress, and never used as maintenance medications. 9. A percentage of patients will respond with improved symptoms when they are on low-dose antidepressnats, but such therapy should probably be used only for several months and not longer (Newman '11: 178).

Crohn's disease is an inflammatory condition of the digestive system that can affect almost any part of the gut, although it most often affects the last part of the small intestine (the terminal ileum) and the first part of the colon. The bowel become inflamed and scarred, a symptom that can readily be seen on barium x-ray or a CAT scan, or with a colonoscope. The inflammation in Crohn's disease is quite deep and involves the two inner layers of the bowel. Biopsies of the affected areas are abnormal. The disease is characterized by diarrhea, cramping, pain and ill health. Other frequent manifestations of Crohn's disease include skin tags or fistulas around the anus, canker sores in the mouth, swollen joints, and severe backaches. Crohn's disease can cause bowel obstructions: severe pain and vomiting and a characteristic abdominal x-ray showing a pattern of obstruction. (Newman '11: 14). Crohn's Disease occurs through the world but primarily in Western developed populations. Its annual incidence in the United States, United Kingdom and Scandinavia is 1 to 3 per 100,000 which is slightly less frequent than UC. It occurs at any age, from young childhood to advanced age, but peak ages of detection are the second and third decades of life with a minor peak in the sixth and seventh decades. Females are affected slightly more often than males. Whites appear to develop the disease two to five times more often than do non-whites. In the United States, CD occurs three to five times more often among Jews than among non-Jews (Crawford '94: 801-803).

In CD there is gross involvement of the small intestine alone in about 40% of cases, of small intestine and colon in 30% and of the colon alone in about 30%. In diseased bowel segments the serosa is granular and dull gray and often the mesenteric fat wraps around the bowel surface and

is sometimes fibrotic. A characteristic sign of early disease is focal mucosal ulcers resembling canker sores (aphthous ulcers), edema and loss of the normal mucosal texture. With progressive disease, mucosal ulcers coalesce into long, serpentine "linear ulcers" which tend to be oriented along the axis of the bowel. Fissures develop between the folds of the mucosa, often penetrating deeply through the bowel wall and leading to bowel adhesions. As the disease becomes more established neutrophils infiltrate isolated crypts and crypt abscesses form usually resulting in ultimate destruction of the crypt. When first described in 1932, Crohn's disease was thought to be limited to the terminal ileum. When fully developed, CD is characterized pathologically by (1) sharply delimited and typically transmural involvement of the bowel by an inflammatory process with mucosal damage, (2) the presence of noncaseating granulomas, (3) fissuring and formation of fistulas, and (4) systemic manifestation in some patients (Crawford '94: 801-803).

CD usually begins with intermittent attacks of relatively mild diarrhea, fever and abdominal pain, spaced by asymptomatic periods lasting for weeks to many months. The course of the disease includes bouts of diarrhea, with fluid and electrolyte losses, weight loss and weakness. Extensive involvement of the small bowel including the terminal ileum, may cause marked loss of albumin (protein-losing enteropathy), generalized malabsorption, specific malabsorption of vitamin B_{12} (with consequent pernicious anemia) or malabsorption of bile salts, leading to steatorrhea. Extraintestinal manifestations of this disease include migratory polyarthritis, sacroiliitis, ankylosing spondylitis, erythema nodosum, or clubbing of the fingertips. Pernicious anemia is a type of vitamin B_{12} anemia. The body needs vitamin B_{12} to make red blood cells. You get this vitamin from eating foods such as meat, poultry, shellfish, eggs, and dairy products. A special protein, called intrinsic factor, helps your intestines absorb vitamin B_{12}. This protein is released by cells in the stomach. When the stomach does not make enough intrinsic factor, the intestine cannot properly absorb vitamin B_{12}. Common causes of pernicious anemia include weakened stomach lining (atrophic gastritis) or an autoimmune condition in which the body's immune system attacks intrinsic factor protein or the cells that make it. Very rarely, pernicious anemia is passed down through families. This is called congenital pernicious anemia. Babies with this type of anemia do not make enough intrinsic factor or cannot properly absorb vitamin 12 in the small intestine. In adults, symptoms of pernicious anemia are usually not seen until after age 30. The average age of diagnosis is age 60. You are more likely to get this disease if you are Scandinavian or Northern European or have a family history of the condition. There is an increased incidence of cancer of the gastrointestinal tract in patients with long-standing progressive CD, representing a fivefold to sixfold increased risk over age-matched populations. The risk of cancer however, appears to be considerably less than that in chronic UC (Crawford '94: 803, 804).

Crohn's disease is hard to diagnose. Most physicians will use a combination of blood tests, endoscopies, X-rays, CAT scans or ultrasounds, and biopsies to help get a clear picture of the disease. Most conventional treatment focus on relieving symptoms with anti-inflammatory drugs or surgically removing the affected part of het intestine. Drugs that suppress the entire immune system are typically used to treat UC. Drug therapies typically include Aminosalicylates (Sulfasalazine and 5-ASA), corticosteroids (prednisone), immunomodulators (6MP) and other suppressive drugs similar to the drugs given to patients with Crohn's disease. New research has shown a genetic link to Crohn's disease and colitis through a gene called the interleukin-23 (IL-23) receptor. Because interleukin-23 is a major cytokine in controlling gut inflammation, this information stresses the importance of reducing inflammation in the gut through controllable factors such as food choices, reducing stress, and promoting proper digestion (Black '10: 28, 29).

Approximately 75% of Crohn's disease patients who have disease on the small bowel will have surgery in the first 10 years after diagnosis. Unfortunately, if no other treatment is done, nearly 50% of those who have surgery will still have a reoccurrence of disease symptoms.
Some absolute indications for surgery in Crohn's disease are (1) perforation with generalized peritonitis, generalized peritonitis is inflammation of the peritoneum, the tissue that lines par to the abdominal cavity and other internal organs of the body such as the liver and intestines (2) massive hemorrhage: hemorrhage is when severe bleeding occurs, leading to risk of fatality (3) carcinoma, carcinoma is a form of cancerous growth of tissue (4) fulminant or unresponsive acute severe colitis: fulminant colitis is any colitis that has rapidly become progressively worse. Some absolute indications for surgery in ulcerative colitis are (1) toxic megacolon: toxic megacolon occurs when a life-threatening widening of the colon occurs rapidly in any intestinal disease (2) perforation: perforation is a hold in the intestine that causes potentially life threatening effects (3) hemorrhage (4) severe colitis failing to respond to medical treatment (Black '10: 108). Crohn's disease has been effectively treated with 400 mg twice daily or 1 g daily of metronidazole (Flagyl ER).

Ulcerative colitis is an inflammatory disease of the colon and involves the innermost layer of the bowel. It always begins just inside the anus and extends upward to a variable extent. Patients with ulcerative colitis pass bloody diarrhea. The diagnosis of ulcerative colitis is easy to establish: the linings of the rectum and the colon above are obviously inflamed, as can be readily seen with a sigmoidscope or a colonoscope, and from biopsies, which are simple to obtain. In ulcerative colitis, the inner lining of the colon is literally weeping bloody mucus, several times a day. Patients with ulcerative colitis often have back problems and may suffer from other join issues. Although the rectum is inflame, the skin surrounding the anus is not affected. Patients with IBD and especially those with ulcerative colitis, have nocturnal symptoms and do not sleep well (Newman '11: 14). Ulcerative colitis (UC) is an ulcero-inflammatory disease limited to the colon and affecting only the mucosa and submucosa except in the most severe cases. UC extends in a continuous fashion proximally from the rectum. Well-formed granulomas are absent. UC is a systemic disorder associated in some patients with migratory polyarthritis, sacroiliitis, ankylosing spondylitis, uveitis, hepatic involvement (pericholongitis) and primary sclerosing cholangitis, and skin lesions. In the United States, United Kingdom and Scandinavia the incidence of UC is about 4 to 6 per 100,000 population, which is slightly greater than UC. As with CD, the incidence of this condition has risen in recent decades. In the United States, it is more common among whites than blacks, and females are affected more often than males. The onset of disease peaks between the ages of 20 and 25 years, but the condition may arise in both younger and considerably older individuals. With healed disease, fibrosis is evident in the submucosa, and the muscularis mucosa. Particularly significant in UC is the spectrum of epithelial changes signifying dysplasia and the progression to frank carcinomas (Crawford '94: 805).

UC typically presents as a relapsing disorder marked by attack of bloody mucoid diarrhea that may persist for days, weeks or months and then subside, only to recur after an asymptomatic interval of months, years or decades. Bloody diarrhea containing stringy mucus, accompanied by lower abdominal pain and cramps usually relieved by defecation, is the first manifestation of the disease. Flare-ups when they occur, may be precipitated by emotional or physical stress and rarely concurrent intraluminal growth of enterotoxin-forming *C. dificile*. The outlook for patients with UC depends on two factors (1) the severity of active disease and (2) its duration. About 60% of patients have clinically mild disease, but almost all patients (97%) have at least one relapse during a10-year period. About 30% of patients undergo colectomy within the first 3 years of onset owing to uncontrollable disease. Historically the risk of cancer is highest in

patients with pancolitis of 10 or more years' duration, in whom it exceeds by 20-fold to 30-fold that in a control population, equivalent to an absolute risk of colorectal cancer 35 years after diagnosis of 30%. Screening programs indicated the progression of UC to dysplasia and carcinoma is in fact quite low (Crawford '94: 806).

Treatment for mild to moderate ulcerative colitis often begins with sulfasalazine (Azulfidine). Sulfasalazine (Azulfidine) works 40% to 80% of the time to make ulcerative colitis symptoms better or keep them from coming back. But it cannot be used by people who are allergic to or cannot tolerate sulfa drugs. Mesalamine (Asacol, Canasa, Rowasa), olsalazine (Dipentum), and balsalazide (Colazal) do not contain sulfa. So they may be used to treat mild to moderate ulcerative colitis if you cannot take sulfasalazine. Mesalamine enemas are effective in treating symptoms of mild to moderate distal (left-sided) ulcerative colitis and in maintaining remission. Mesalamine suppositories are preferred for people who have proctitis. The combination of a mesalamine pill (oral) and a mesalamine enema, foam, or suppository (topical) works better to treat left-sided colitis than either oral or topical mesalamine by itself (Friedman and Liechtenstein '6: 803-817). Patients with diverticular disease may respond to a high-fibre diet, the most popular way being to give wheat bran in one of its forms. Anti-cholinergic such as propantheline, or smooth muscle relaxants such as mebeverine, may be of value. If the pain is severe, analgesics may be required, but opiates (including codeine) should be avoided since these drugs increase intracolonic pressure and theoretically expose the patient to the risk of perforation of a diverticulum. Hospital treatment of infection, diverticulitis, involves intravenous gentamycin and metronidazole and analgesia for pain. When perforated diverticulum of the sigmoid colon have caused peritonitis, the patient complains of severe abdominal pain. Treatment consists of urgent resuscitation of the patient with a view to laparotomy. If pus is present in the peritoneal cavity, and the inflamed area in the colon is reasonably well sealed, drainage of the abomen with lavage of the peritoneal cavity with antibiotic solution and administration of intravenous antibiotics may be all that is required. If there is faecal contamination of the peritoneal cavity, most surgeons advocate exision of the perforated area of the colon with formation of a colostomy above the resected area. The rectal stump can be oversewn (Hartmann's resection) but if the perforation is high in the sigmoid colon, the affected area should be excised as a double-barrelled colostomy. The bowel is re-anastomosed six months later. If an abscess which has formed around the colon discharges into a structure adjacent to it, a fistula may be formed into the vagina, bladder, small bowel, or very occasionally, on to the skin. Bleeding is an uncommon but serious complication of diverticular disease. If surgery is necessary then resection of the appropriate area of colon is the method of choice, if the site of bleeding is uncertain, total colectomy with ileorectal anastomosis may occasionally be required. Toxic megacolon occurs when the ulceration of the colon involves the muscle layers. The reported mortality associated with toxic megacolon has been as high as 30% but in most centres it is now nearer 10% (Jones et al '85: 216-218, 232).

The elective operation for ulcerative colitis is the **proctocolectomy**. All large-bowel mucosa is removed, so that the disease cannot recur, and the patient can therefore be offered complete relief at the cost of living with a permanent ileostomy. The whole colon is removed, from the ileocaecal valve. The rectum must be carefully removed so that the pelvic autonomic nerves are not disturbed and there should be no interference with bladder or sexual functions. An ileostomy is fashioned in the right iliac fossa by bringing the cut end of the ileum through a carefully sited circular hole cut in the abdominal wall of the right iliac fossa. The ileum is turned bak to form a spout and the edge of the ileum sutured to the skin edge. An ileostomy bag is immediately applied which fits snugly around the ileostomy and received the ileal effluent. Ileostomy can be avoided in three ways: (1) total colectomy with ileo-rectal anastomosis for patients under 45 with

no sepsis and little rectal ulceration in whom 50-60% of patients report highly satisfactory results. (2) Kock's ileostomy involves making an S-shaped pouch of ileum containing a valve which prevents the contents reaching the stoma at skin level. The pouch is emptied by intermittent catheterization and the patient wears only a small flat dressing over the stoma instead of a bag, but there are high complication rates and is not suited to patients with Crohn's disease. (3) perineal reservoir is a recent development where the whole colon and the upper half of the rectum are removed. Then the lower rectum is denuded of mucosa down to the dentate line. An S-shaped pouch of ileum is fashioned, to act as a reservoir, and the efferent limb is brought down and sutured to the upper end of the anal canal and many patients achieve normal defection. The main surgical principle in Crohn's disease is to relieve the complications whilst removing as little normal tissue as possible. There is no evidence that removing enlarged lymph nodes or lengths of normal-looking bowel on either side of diseased segments does anything to improve prognosis (Jones et al '85: 236-240).

10. Intestinal Neoplasm

Virtually 98% of all cancers in the large intestine are adenocarcinomas. **Adenocarcinomas** constitute the vast majority of colorectal cancers and represent 70% of all malignancies arising in the gastrointestinal tract. The colon (including the rectum) is one of the most common hosts of primary neoplasms in the body. Overall, colon cancer ranks second only to bronchogenic carcinoma among the cancer killers. With an estimated 150,000 new cases per year and about 58,000 deaths this disease accounts for nearly 15% of all cancer-related deaths in the United States. There is a slight preponderance of benign tumors. The annual U.S. death rate is only about 1% of gastrointestinal malignancies. Any segment of the GI may be secondarily involved by systemic dissemination of non-Hodgkin‘s lymphoma. Up to 40% of lymphomas, however, arise in sites other than lymph nodes, and the gut is the most common location. Primary gastrointestinal tumors occur more frequently in certain patient populations, chronic sprue-like malabsorption syndromes, natives of Mediterranean region, congenital immunodeficiency states, infection with HIV and following organ transplantation with immunosuppression. Gastrointestinal lymphoma usually affects adults, lacks a sex predilection and may arise anywhere in the gut: stomach (55 to 60% of cases), small intestine (25 to 30%), proximal colon (10 to 15%) and distal colon (up to 10%) (Crawford ’94: 817, 820).There is persuasive evidence that non-steroidal anti-inflammatory drugs can reduce the incidence of precursor lesions in the colon and lower the risk of colon cancer, perhaps by 50 percent (Greaves '00: 253).

Tumors of the small and large intestines are: (1) non-neoplastic polyps (a) hyperplastic polyps, (b) hamartomatous polyps (i) juvenile polyps, (ii). Peutz-Jegher polyps, (c) inflammatory polyps and (d) lymphoid polyps; (2) Neoplastic epithelial lesions can be (a) benign polyps (i) Tubular adenoma, (ii) Tubulovillous adenoma and (ii) Villous adenoma or (b) malignant lesions (i) adenocarcinoma, (ii) carcinoid tumor or (ii) anal zone carcinoma; (3) Mesenchymal lesions can be (a) benign lesions, (i) Leiomyoma, (ii) Lipoma, (iii) Lipoma, (iv) Neuroma, or (v) Angioma or (b) malignant lesions (i) Leiomyosarcoma, (ii) Liposarcoma, (iii) Malignant spindle cell tumor, or (iv) Kaposi’s sarcoma or (4) Lymphoma (malignant) (Crawford ’94: 809 Table 17-13). Sarcomas, lymphomas, carcinoid tumors and rarely adenocarcinomas of the small bowel occur. **Gastroinstestinal (GI) sarcomas** are generaly leimyosarcomas that present with pain and bleeding. Obstruction, intussusception, perforation or fistula formations are rare. GI sarcomas arise in the stomach (62%), small intestine (29%), or colon (10%). Liver, lung and intraperitoneal seeding are the most frequent metastatic sites. The 5-year survival is 35% to 50%. Subtotal excision results in a poor prognosis. Response rates to chemotherapy appear equivalent to that of soft tissue sarcomas in other locations. Single agent doxorubicin, 70 mg/m^2

has a response rate of 15% to 35%. DTIC 1 g. m^2 every 3 weeks has a single agent response rate of 17%. Response rates improved in combination doxorubicin, 70 mg/m^2 and DTIC 1 g. m^2 every 3 weeks but nausea and vomiting increased. Trials of ifostfamide in previously untreated patients yield response rates of 20% to 40%. A study of a combination doxorubicin, ifostfamide, and DTIC with mesna uroprotection yielded a response rate of 48% with 13% complete response (Elias & Antman '90: 299-301).

Small bowel carcinomas are recognized as constricting "napkin-ring" lesions. Endoscopy may be useful if the lesion is duodenal, to the ligament of Treitz. Complete blood count and liver function tests are useful to rule out disseminated disease. There is not established staging system, the most important prognostic factor is resectability. Overall 5-years survival rates after surgery vary from 10% to 20%. Curative therapy of small bowel cancer is limited to surgery. Resection of the tumor encompasses mesentery and nodal drainage of the involved area of the small bowel whenever possible. Radiation therapy may provide significant palliation for patients with pain and high-grade obstruction who cannot undergo surgery. However, no studies suggest it is curative. The bowel tolerates radiation very poorly. 5-FU is the most commonly used chemotherapeutic agent. Combinations of irradiation and 5-FU may be useful in treating locally advanced small bowel carcinoma. FAM (5-FU, doxorubicin, mitomycin-C) might be more effective than a single agent (Macdonald '90: 231, 232).

Any segment of the GI may be secondarily involved by systemic dissemination of non-Hodgkin‘s lymphoma. Up to 40% of lymphomas, however, arise in sites other than lymph nodes, and the gut is the most common location (Crawford ’94: 817). The gut may be affected by **lymphoma**, nearly always non-Hodgkin's type. In addition there are two special type of primary lymphoma of the gut – Mediterranean lymphoma and α-chain disease. Patient usually present with a short history of weight loss, abdominal pain, fever, finger clubbing and easily palpable abdominal masses. Gastrointestinal ulceration with bleeding and perforation may occur. Mediterranean lymphoma occurs in many parts of the world, and involves the small bowel diffusely. α-chain disease is a rare variant where the lesion consists of excess plasmacytoid cells and excessive production of the heavy (α) chain, portion of the IgA molecules detectable in body fluids or tissues by immunological techniques. Usually confined to bowel, this condition sometimes terminates as disseminated malignancy. Curative resection is usually attempted. However, both radiotherapy or chemotherapy and corticosteroids have also been used (Jones et al '85: 137) with an 80% cure rate.

Colorectal carcinoma is one of the most common and serious of visceral malignancies in the United States, about 1 out of every 20 Americans will develop the disease. Approximately 95% of colorectal cancers develop in patients 50 years of age or older. Diets high in fat and red meat and relatively low in vegetable fiber are associated with higher risks of colorectal cancer. Ulverative colitis involving the total colon and persisting fr more than 10 years is associated with a colon cancer risk of about 4% per year. Familial polyposis syndromes are associated with a 100% development of carcinoma of the colon, if they do not undergo prophylactic colectomy. All patients who manifest the phenotype of multiple polyposis in their late teens or twenties will develop colorectal cancer by their early forties if prophylactic intervention has not occurred. Approximately 20% to 25% of patients who develop colorectal cancer after the age of 50 years will have siblings or parents who develop the disease at approximately the same stage of life. Over 75% of colorectal cancer patients have absolutely no family history. Colorectal cancer is more common in patients who have had occasional adenomatous ployps of villous adenomas. Adenopatous polyps are less likely to contain malignancy than villous adenomas and polyps less than 1 cm in size rarely contain malignancy, whereas at least one third of polyps 3 cm in size

contain malignancy. Larger polyps should definitely be removed. Diagnosis can be made by flexible sigmoidoscopy or cheaper digital rectal examination. Laboratory evaluation should include a complete blood count, a microcytic hypchromicanemia suggests chronic blood loss. Liver function test may reflect the presence of liver metastases. A complete urinalysis helps exlclude local extension to the bladder. Abdominal CT scan can help. Patients with elevated CEA (2.5 ng/ml) have a higher likelihood of metastastatic disease (Macdonald '90: 233, 234).

Colon Cancer Staging

Staging	% 5 Year Survival
Initial Extension	
A Mucosa only	95
B1 Within wall	85-90
B2(m) Microscopically through wall	60-70
B2(g) Grossly though wall	50
B3 Involves adjacent structures	30
Lymph Nodes	
C1 Within wall	40-50
C2(m) Microscopically through wall	40-50
C2(g) Grossly through wall	15-25
C3 Involves adjacent structures	10-20
D Distant metastases	5

Source: Macdonald '90: Table 29-9; Pg. 234

Systemic **chemotherapy of colorectal cancer** has been disappointing. The 1 g/m2/day infusion schedule of 5-FU may be given generally for 7 to 10 days, is limited by stomatitis rather than myelosuppression and has a response rate of 31%. Combination chemotherapy has not been proven to be more effective than 5-FU. Studies of 5-FU plus methyl-CCNU and 5-FU, methyl-CCNU, streptozo in and vincristine demonstrated partial response rates as high as 40%, but this was not confirmed. Sequential methotrexate followed by 5-FU and 5-FU and leucovorin have produced response rates as high as 41%. There is no evidence in favor of chemotherapy adjuvant to surgery. A significant decrease in relapse rates has been noted with the use of combined-modality therapy (combined 5-FU and methyl-CCNU, and radiation therapy) compared to surgery alone (relapse rates of 55% versus 30%) (Macdonald '0: 237, 238).

The primary therapy of colorectal cancer is **surgical resection**. The overriding principle in surgical management is to resect an adequate segment of bowel containing the area of malignancy and the adjacent mesentery with its lymph nodes. For other than rectal carcinomas, the procedure are variations of rights, left, or transverse colectomies. For rectal cancer, an anterior resection may be performed if the tumor is located proximally enough to allow resection and low rectal anastomosis. If a rectal cancer is so far distal that anastomosis is impossible, then a variation of the Miles procedure, abdominal-perineal resection, must be performed, this procedure sacrifices the rectum, and patients have a permanent colostomy. Since more than 50% of patients with colon cancer develop recurrence, the treatment of advanced colorectal cancer is important. The most common sites of dissemination for colorectal cancer are the liver and the abdominal cavity, with local or disseminated intra-abdominal carcinomatosis. Survival is possible with as little as 25 cm of surviving bowel following resection, as the result of hypertrophy and elongation of the existing villi in adaptation (Jones et al '85: 113-116). Extensive resection of the small bowel, especially if involving the lower ileum, leads to severe malabsorption. The most common reasons for massive resection of the small bowel are Crohn's

disease, mesenteric vascular occlusion with resultant infarction of bowel, volvulus of the small bowel and, occasionally, incarceration and strangulation of a large section of small bowl in a hernia. The consequence of bowel resection will depend on the extent of the resection. The ileum is capable of adaptive changes and compensation for loss of jejunal absorptive capacity. The jejunum adapts less well and cannot take over the specific ileal absorption of vitamin B_{12} and bile salts. Resection of the terminal ileum thus removes the conservation of bile salts, and their deficiency is the mot important cause of malabsorption. Unabsorbed bile salts and fatty acids pass into the colon, inhibiting fluid and electrolyte absorption and causing a watery diarrhea, that is often worse in the morning. Colonic absorption of is increased and this may lead to the formation of urinary oxalate stones and the risk of gallstones increases. Loss of a substantial portion of small bowel mucosa is said to reduce inactivation of gastrin. In approximately 50% of patients with massive small bowel resection there is resultant hypersecretion of acid, leading to peptic ulceration. This is usually transient and settles within a year, and further surgery for peptic ulceration should be avoided. In the early postoperative period, fluid and electrolyte replacement is important. After several months, the remaining small bowel attempts to compensate by dilating and by developing marked hyperplasia of the remaining mucosa. Villi may increase in length by a factor of three or four. Continuing nutrient supplementation and symptomatic measures will be necessary in some patients for life. After extensive distal resection, a low-fat diet and medium-chain triglycerides are usually necessary. Life long vitamin B_{12} treatment will required. If only a small part of ileum has been resected (one meter or less), the resulting diarrhea is usually due to colonic irritation and this will normally respond to cholestyramine. Diarrhea following larger resections of small bowel is due to steatorrhoea, and further depletion of the bile salt pool by giving cholestyramine will merely serve to increase steatorrhoea. Antacids or H_2- receptor antagonists may help. Small frequent feeds of a lactose-free diet and short-term parenteral feeding may help (Jones et al '85: 135-137).

Anal carcinoma comprise between 2% and 4% of all tumors of the distal alimentary tract. Cancers of the anal margin are more common in men, while women have a higher incidence of carcinomas of the anal canal. Conditions resulting in chronic irritation of the anal canal or perinanal area, including hemorrhoids, chronic dermatitis, fissures, condylomata, abscesses, and fistulas, may be predisposing factors to the development of carcinoma. Anal carcinoma is more common in male homosexuals. These tumors have been called cloacogenic, basaloid, basal cell, keratinizing and nonkeratinizing squamous cell carcinomas and squamous cell carcinomas of the anal skin. In general, it is reasonable to divide the carcinomas of the anus into nonkeratinizing and keratinizing malignancies deriving from transitional or squamous epitheliu. The keratinizing tumors have a somewhat better prognosis. Anal carcinoma spreads with initial infiltration of the anal canal and the anal sphincter, subsequently,t he prostate and vagina may be involved by direct extension. The other major mode of dissemination is nodal lymphatics. For lesions of both the anal canal and margin the most common site of nodal metastases is the inguinal area. Fewer than 5% of patients have dissemination to the liver or lung (Macdonald '90: 238, 239).

Staging for Anal Cancer

Stage	% 5 Year Survival
A Invasion to mucosa and submucosa	100%
B Sphincter muscle involved	100%
B1 Invasion to internal sphincter	77%
B2 Invasion to external sphincter	77%
B3 Invasion beyond sphincter into adjacent tissue	48%
	48%

C Lymph node involvement	

Source: Macdonald '90: 238, 239

In the past, the only appropriate therapy for aggressive anal canal carcinoma was abdominoperineal resection (APR). 5 year survival rates were from 70% to 90%, however, APR results in considerable morbidity and requires a permanent colostomy. In the 1980s, the treatment of carcinoma of the anal region was revolutionized by the application of combined modality therapy (CMT) that do not utilize radical surgery – 5-FU 1000 mg/m2 per day, as continuous infusion on days 1 to 4, repeat on days 28 to 31; Mitomycin-C, 15 mg/m2 IV bolus on day 1 only; external radiation therapy, 3000 cGy, to primary tumor, pelvic and inguinal nodes on days 1 to 21 at 200 cGy per day, 5 days a week. Tumor response is universal, with at least 80% compete response. Treatment may be associated with anal mucositis, oral mucosits and myelosuppression. However, anal-stricture or persistent anal ulcers requiring surgical intervention have been seen with radiation alone in high doses (Macdonald '90: 239, 240).

11. Hepatitis and cirrhosis

Hepatobiliary disorders are very common. It is estimated that 200 million worldwide carry the hepatitis B virus; about 200 million suffer from hepatic schistosomiasis, primary liver cancer is the one of the commonest tumors in the world; 20% of all Britons have gall stones; cirrhosis is now the fourth commonest cause of death in the males in the USA. Subsequent to the dissolution of the Soviet Union, in Russia the average male life expectancy has declined from nearly 70 to 50 due to **alcoholic liver disease**. The liver is remarkable in three respect, which affect its response to insult. Firstly, it has enormous reserve functional capacity. It can be largely replaced by tumor and yet function adequately. Advanced but compensated **cirrhosis** may be accompanied by few if any clinical signs or biochemical abnormalities. **Prolonged extra-hepatic obstruction**, usually obstruction of the gallbladder by stones or other cause primary,, may be tolerated for weeks before liver failure occurs. Secondly, the liver has the greatest powers of **regeneration** of any body tissue. Surgical removal of a lobe is followed by rapid return to normal structure. Regeneration is the hallmark of the end-state injury, i.e. cirrhosis. Thirdly, the liver's function is more diverse than that of any other organ. **Liver failure** is expressed primarily as jaundice, fluid retention and ascites, bleeding or encephalopathy, or any combination of these (Jones et al '85: 141).

Alcoholic liver disease is the most prevalent form of liver disease in most Western countries. In the U.S. more than 10 million Americans are alcoholics, alcohol causes more than 200,000 deaths annually, the fifth leading cause of death and 25 to 30% of hospitalized patients have problems related to alcohol abuse. Chronic alcohol consumption causes three distinct, albeit overlapping, forms of alcoholic liver disease (1) hepatic steatosis (fatty liver); (2) alcoholic hepatitis and (3) cirrhosis. Following even moderate intake of alcohol, small lipid droplets accumulate in hepatocytes. Short-term ingestion of up to 80 gm of ethanol per day (8 beers or 7 ounces of 80 proof liquor) generally produces mild, reversible hepatic changes, such as fatty liver. Daily ingestion of 160 gm or more of ethanol for 10 to 20 years is associated more consistently with severe injury; chronic intake of 80 to 160 gm/day is considered a borderline risk for severe injury. Only 10 to 15% of alcoholics however develop cirrhosis. Women tend to be more susceptible. Alcoholic hepatitis tends to appear relatively acutely, usually following a bout of heavy drinking. Each bout of hepatitis incurs about a 10 to 20% risk of death. Cirrhosis is likely to appear in about one-third of patients within a few years if there are repeated bouts.

In about 10% of patients, the **alcoholic cirrhosis** is discovered only at autopsy. In the end-stage alcoholic, the immediate causes of death are (1) hepatic coma (2) a massive gastrointestinal variceal hemorrhage (3) an intercurrent infection or (4) hepatorenal syndrome following a bout of alcoholic hepatitis. In about 3 to 6% of cases, death is related to the development of hepatocellular carcinoma (Crawford '94: 857- 861). Alcohol withdrawal must be promptly diagnosed as being an acute cause of anxiety to the patient, because untreated delirium tremors have a mortality of 15%. Commonly detoxification is accomplished with chlordiazeposide at a starting dose of 50 mg orally every 6 hours with extra doses of 25 mg as needed to control symptoms. After an effective total daily dose has been reached, a taper of 10% total dose per day can be instituted. If parenteral administration is required, an equivalent dose of lorazepam can be used. In cases of hepatic dysfunction **oxazepam** is the drug of choice. All suspected alcohol abusers should receive thiamine, 100 mg intramuscularly for 7 days (to help prevent Wernicki-Korsakoff encephalopathy) as well as folate, 1 mg daily, and multivitamins (Massie & Sinsheimer '90: 539). Metronidazole interacts badly with alcohol, but is otherwise the most effective antibiotic for the liver. Treatment of alcoholic liver disease should involve quitting drinking to effect a cure with medicines such as metronidazole.

Drug Induced and Toxin-Induced Hepatic Injury

Tissue Reaction	Examples
Hepatocellular Damage	
Microvesicular fatty change	Tetracycline, salicylates, yellow phosphorus
Macrovesicular fatty change	Ethanol, methotrexate, amio-darone
Centrilobular necrosis	Bromobenzene, CCl_4, acetaminophen, halothane, rifampin
Diffuse or massive necrosis	Halothane, isoniazid, acetaminophen, α-methyldopa, trinitrotoluene, *Amanita phalloides,* (mushroom) toxin
Hepatitis, acute and chronic	α-methyldopa, isoniazid, nitrofurantoin, phenytoin, oxyphenisatin
Fibrosis-cirrhosis	Ethanol, methotrexate, amiodarone, most drugs that cause chronic hepatitis
Granuloma formation	Sulfonamides, α-methyldopa, quinidine, phenylbutazone, hydralazine, allopurinol
Cholestasis (with or without hepatocellular injury)	Chlorpromazine, anabolic steroids, erythromycin estolate, oral contraceptives, organic arsenicals
Vascular Disorders	
Veno-occlusive diesease	Cytotoxic drugs, pyrrolizidine alkaloids (bush tea)
Hepatic or portal vein thrombosis	Estrogens, including oral contraceptives, cytotoxic drugs
Peliosis hepatis	Anabolic steroids, oral contraceptives, danazol
Hyperplasia and Neoplasia	
Adenoma	Oral contraceptives
Hepatocellular carcinoma	Vinyl chloride, aflatoxin, Thorotrast
Cholangiocarcinonoma	Thorotrast
Angiosarcoma	Vinyl chloride, inorganic arsenicals, Thorotrast

Source: Crawford '94: Table 18-6, pg. 857

Hepatic disorders have far-reaching consequences. The liver is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory and neoplastic insults which may cause hepatocyte necrosis. Massive necrosis is most commonly caused by severe chemical and drug toxicity or viral hepatitis. Short of outright necrosis, hepatocytes may take on a swollen, edematous appearance (ballooning degeneration) with irregularly clumped cytoplasm or retained biliary material may impart a diffuse foamy swollen appearance to the hepatocyte (cholestasis). Inflammation is defined as the influx of acute or chronic inflammatory cells into the liver and is termed hepatitis. The liver has enormous reserve and regeneration occurs in all but the most fulminant diseases (Crawford ’94: 833-834). Although numerous insults lead to liver damage, the pathological responses are few but distinctive. Cell damage or necrosis means damage to or death of hepatocytes and may be: (a) scattered or 'spotty' (e.g. mild virus and toxic hepatitis), (b) confluent and massive (e.g. in fulminant viral hepatitis or paracetamol poisoning) and (c) focal (e.g. in centrilobular hypoxaemia in heart failure). Microscopically, cells are swollen (ballooned) and may contain hyaline material. Following injury, fat may be deposited. Severe necrosis is followed by architectural collapse (and the liver is then clinically small). The causes included (1) hypoxaemia due to circulation insufficieny as in trauma or cardiac failure, (2) metabolic disorders notably iron deposition (haemochromatosis) and Wilson's disease, (3) physical injury such as hyperthermia and radiation, (4) biliary obstruction (a relatively late effect), (5) industrial toxins such as trichlhoethylen and carbon tetrachloride, (6) dietary toxins including fungal poisons (such as aflatoxin found in spoiled grain, i.e. grain infected with the fungus *Aspergillus*) and ethyl alcohol, (7) pharmacologic agents such as paracetamol and halothane and (8) infective agents such as hepatitis B (HBV), bacteria such as *E. coli* and protozoa such aa schistosomiasis. If the noxious insult ceases the liver can, because of its remarkable regenerative capacity, recover completely, sometimes leaving scarring of little clinical importance. Prognosis therefore depends primarily upon the patient's survival of the episode of hepatic failure. If injury continues (for example alcohol abuse), important permanent effects may occur, recovery is incomplete, and irreversible histological change (cirrhosis) follows (Jones et al '85: 153-155).

Hepatitis is said to occur where injury stimulates an inflammatory reaction. The reaction may be focal, generalized, or located around the portal tracts. The common cause are: viral infection, alcohol, certain drugs, autoimmune reactions, septicaemia, and ascending biliary infection. Hepatitis may be acute or chronic. Hepatitis may be accompanied by or followed by fibrosis, suggesting early progression to cirrhosis. Cirrhosis is an end-stage and essentially irreversible reaction to necrosis and hepatitis. It is characterized by (1) fibrosis and distortion of the norma liver architecture, (2) regeneration with new nodule formation and (3) disturbance of vascular supply with intrahepatic shunting. The nodules may vary in size; (a) in micronodular cirrhosis they are small and regular and, in general, this is the hallmark of continuing activity, and the liver tends to be clinically enlarged (b) in macronodular cirrhosis they are coarse and irregular and the disease is usually burnt-out. The liver tends to be small and contracted and clinically impalpable, and (c) mixed and intermediate forms may occur. Since portal hypertension is a common accompaniment of cirrhosis, splenomegaly is common. Markers of immunological reaction such as circulating autoantibodies (humoral immunity) and lymphocyte cytoxicity (cell-mediated immunity) are common in forms of chronic liver disease, including chronic active hepatitis, alcoholic hepatitis, and primary biliary cirrhosis. In chronic hepatitis there is also common association with multi-system involvement (renal disease, pulmonary disease, colitis, arthritis). Hepatitis is common in association with many virus infections, including infectious mononucleosis (glandular fever), yellow fever, rubella, herpes simplex and cytomegalovirus. However by convention, the term 'viral hepatitis' is applied to hepatitis viruses A, B, C & D

(Jones et al '85: 155- 157). *Entamoeba histolytic* infections of the liver and gastrointestinal tract are best treated with metronidazole administered at 750 mg 3 times daily given for 5–10 (usually 10) days for intestinal amebiasis or 500–750 mg 3 times daily given for 5–10 (usually 10) days for amebic liver abscess. Alternatively, amebic liver abscess has been treated with 2.4 g once daily given for 1 or 2 days. Follow-up with a luminal amebicide (e.g., iodoquinol, paromomycin) after metronidazole (Flagyl ER), which cannot be taken with alcohol.

Pain arising in the liver is usually felt as a dull ache in the right upper abdomen and over the rib cage. Such pain (which can sometimes be severe) is thought to be produced by rapid distension of the liver capsule, as may occur in viral hepatitis or acute congestive heart failure. Focal disease such as liver abscess or tumour may also produce discomfort. Pain arising in the biliary tract is experienced very much more often than liver pain. The various patterns of pain that stem from the biliary tract are almost all due to the presence of gallstones, but very infrequently, the gall bladder may be responsible for pain in the absence of stones (Jones et al '85: 185-189). Gallstones are easily treated with Stone breaker ™ herbal remedy. In liver disease, abdominal swelling reflects **ascites**, the accumulation of peritoneal fluid, together with the gaseous bowel distension that commonly accompanies it. Tense ascites may be confused with gross bladder enlargement and also with a large ovarian cyst. Salt restriction is the anchor of therapy. Potassium sparing diuretics are valuable, since hypokalemia is common in cirrhosis. Hypokalemia is aggravated by thiazides and frusemide and tends to precipitate encephelopathy. Spironolactone, 100-400 g daily, is the drug of choice but it is expensive, takes 4-5 day delay in action, and tends to produce gynecomastia. Amiloride is an alternative. In the very rare resistant case, ascites may be recycled into the circulation either by intravenous infusion or via a special surgically emplaced shunt (Leveen shunt). Removal is largely for comfort and cosmetic reasons, overall, liver function is not improved and may be worsened (Jones et al '85: 193-195). **Liver enlargement** may be found in patients who present with the associated upper abdominal discomfort or with associated features of general ill health. In infancy, the liver is normally readily palpable. It may be enlarged as a result of rare abnormalities such glycogen storage disease, or primary malignant tumor, hepatoblastoma. In young adults in Western countries the commonest cause of liver enlargement is alcohol abuse. The possibility of primary hepatic cell malignancy (hepatoma) must be considered. In women of child-bearing age, the rare benign conditions of hepatic adenoma and focal nodular hyperplasia may be asymptomatic, or be discovered due to hemorrhage into the liver substrate. In later life, hepatomegaly is commonly due to alcohol and malignant disease. Metastatic disease is much more common than primary malignancy, but the rapid development of liver enlargement in a cirrhotic patient suggests hematoma. Other causes include cardiac failure, leukemia and myelofibrosis (Jones et al '85: 189).

Hepatic bile formation serves two major functions (1) the emulsification of dietary fat in the lumen of the gut through the detergent action of bile salts and (2) elimination of waste products. Bile constitutes the primary pathway for elimination of bilirubin, excess cholesterol and xenobiotics which are insufficiently water-soluble to be excreted in urine. Virtually all bile acids are reabsorbed (especially in the ileum) and returned to the liver for reuptake. Fecal loss of bile acids (0.2 to 0.6 gm/day) is matched by de novo hepatic synthesis of bile acids from cholesterol. The enterohepatic circulation provides an efficient mechanism for maintaining a large endogenous pool of bile acids for digestive and excretory purposes. **Reduced bile flow** related to intestinal malabsorption, may be caused by deficiencies of the fat-soluble vitamins A,D, or K. Post-infectious diarrhea is usually caused by vitamin B12 deficiency (Crawford ’94: 837-838). The liver makes bile salts, which help the body absorb fat from the diet. If liver function is poor or if bile flow is blocked in a condition such as biliary atresia, then fat cannot be absorbed. This

causes the body to malabsorb (lose) fat-soluble vitamins that dissolve in fat. These include **vitamins A, D, E and K**. Vitamin A: Deficiency in vitamin A can cause problems with the eyes and skin. Deficiency of vitamin A is not as common as deficiency in the other fat-soluble vitamins below. Vitamin A can be supplemented orally with a dose of 5,000 to 10,000 IU/day. It is important not to give an excess of vitamin A since this can cause brain swelling.
Vitamin D: A deficiency in vitamin D can lead to very weak bones (a disease called "rickets") or even bone fractures. Vitamin D can be supplemented using one of several vitamin D preparations. Often very large doses of vitamin D are needed in patients with blockage to bile flow (some jaundiced infants, who would normally need 400 IU of vitamin D, require as much as 8,000 IU of vitamin D). A few infants with blockage to bile flow cannot absorb vitamin D given orally and require a vitamin D shot every three months. Too much vitamin D, however, can cause too much calcium to appear in the blood. Vitamin E: Low vitamin E can cause problems with the nervous system as well as with the skin. Vitamin E can be supplemented orally through several forms. The best absorbed is called Liqui-E or TPGS-conjugated vitamin E. This is ideal for use in infants with liver disease. This preparation can even help other fat-soluble vitamins to be absorbed if they are taken together. Vitamin K: Vitamin K is needed for the liver to make the proteins that make the blood clot. Deficiency in vitamin K can cause severe bleeding in the internal organs or even in the brain, causing stroke. Vitamin K is easily supplemented by giving anywhere between 2.5 and 10 mg/day orally. An occasional patient will require monthly vitamin K injections when absorption is especially poor. **Ursodeoxycholic Acid** or URSO (trade name Actigall) is used to promote bile flow. This drug helps water flow in bile ducts, and also makes bile less toxic to the liver when it backs up due to poor bile flow. Actigall has been used to treat a variety of liver diseases including liver disease related to cystic fibrosis, Alagille's syndrome and many other conditions in which bile flow is poor. Actigall has been used in sclerosing cholangitis where it has been shown to make the blood tests better, although has not improved the general course of the disease.

Disruption of bile formation becomes clinically evident as yellow discoloration of the skin and sclerae (**jaundice** of icterus) owing to retention of pigmented bilirubin, and as cholestasis, defined as retention of not only bilirubin but also other solutes eliminated in bile. **Bilirubin** is the end product of heme degradation. The majority of daily production (0.2 to 0.3 gm) is derived from breakdown of senesescent erythrocyte, especially in the spleen, liver and bone marrow. Bilirubin found outside the liver is bound to albumin because bilirubin is virtually insoluble in aqueous solutions at physiologic pH. The brilliant yellow color of bilirubin makes it an easily identified component of hepatic bile formation. Most bilirubin glucuronides are decongjugated by bacterial beta-glucuronidases and degraded to colorless urobilinogens that are largely excreted in the feces. Bilirubin metabolism and excretion, are however, but one cog in the hepatic machinery that secretes 12 to 36 gm of bile acids into bile per day, mostly taurine and glycine conjugates of cholic and chenodeoxycholic acid. **Clinical jaundice** appears when bilirubin is elevated in blood and is deposited in tissues. Cholestasis refers to bile secretory failure which is accompanied by the accumulation in blood of substances normally excreted in bile (bilirubin, bile salts and cholesterol). Normal blood levels of bilirubin are less than 1.2 mg/dl. Jaundice becomes evident when bilirubin levels rise above 2.0 to 2.5 mg/dl; levels as high as 30 to 40mg/dl can occur with severe disease. Jaundice occurs when bilirubin production exceeds hepatic clearance capacity. Extrahepatic biliary obstruction is frequently amenable to surgical alleviation because it is most often produced by impaction of a gallstone in the common bile duct or ampulla of Vater (adults) or by extrahepatic biliary atresia (infants). In contrast, cholestasis resulting from disease of the intrahepatic biliary tree or hepatocellular secretory failure (collectively terms intrahepatic cholestasis) cannot be benefited by surgery (short of transplantation) and the patient’s condition may be worsened by an operative procedure. There

is thus considerable urgency in making a correct diagnosis of the cause of jaundice and cholestasis (Crawford '94: 838-839).

Hemochromatosis is defined as the excessive accumulation of body iron most of which is deposited in the parenchymal cells of various organs, particularly the liver and pancreas. The total body iron pool ranges from 2 to 6 gm in normal adults, about 0.5 gm is stored in the liver. In HHC total iron accumulation may exceed 50 gm. Fully developed cases exhibit (1) micronodular cirrhosis in most patients (2) diabetes mellitus 75 to 80% and (3) skin pigmentation in 75 to 80% of cases. Symptoms usually first appear in the fifth to sixth decade. Males predominate 5 to 7:1. Symptoms typically develop after 20 gm of storage iron has accumulated. Fully developed HHC features hepatomegaly, abdominal pain, skin pigmentation, deranged glucose homeostasis or frank diabetes mellitus, cardiac dysfunction and atypical arthritis. In some patients hypogonadism. The most common cause of death is hepatocellular carcinoma for which the risk is 200 fold greater than the general population. Patients with HHC diagnosed in the pre-cirrhotic stage and treated with phlebotomy and iron chelators have a normal life expectancy.

Wilson's disease, hepato-lenticular degeneration, is an autosomal recessive disorder of copper metabolism marked by the accumulation of toxic levels of copper in many tissues and organs, principally the liver, brain and eye. Wilson's disease has a gene frequency of 1: 200 to 400 and a disease incidence of 1:200,000. When hepatic involvement remains subclinical, the condition comes to attention as a Parkinson-like movement disorder, as a psychiatric disturbance ranging from behavioral disorders to frank psychoses, or because of the ocular changes. Early recognition permits the long-term use of copper chelators (e.g.) penicillamine) to prevent the accumulation of copper and thsue arrest the progression of organ damage. **Penicillamine** is a commonly used medicine for Wilson's disease. This drug chelates or binds with copper and leads to its secretion from the body. Patients on penicillamine are monitored since this drug can sometimes be tough on the kidneys or bone marrow. It can also affect wound healing. It is important to take penicillamine consistently, since patients with Wilson's disease who stop it have developed liver failure. Zinc therapy prevents the body from absorbing copper in Wilson's. Trientine, which removes copper from the body, is a third drug for Wilson's. Fulminant hepatitis and unmanageable cirrhosis necessitate liver transplantation which appears to be curative. **Alpha$_1$Antitrypsin (α_1-AT) deficiency** is an autosomal recessive disorder marked by abnormally low serum levels of protease inhibitor (Pi). The deficiency leads to the development of pulmonary disease (emphysema) and hepatic disease (cholestasis or cirrhosis). Pulmonary emphysema develops owing to a relative lack of antiprotease in the lungs, thus permitting tissue-destructive enzymes to run amok (Crawford '94: 861-864).

When the liver does not work well toxins accumulate which may make the brain function abnormally, e.g cause encephalitis. Patients with liver disease may be confused, agitated or sleepy. One potential cause of this is accumulation of ammonia. **Lactulose** is sometimes used to help the body get rid of ammonia. Lactulose is given until the child has 3 or 4 loose stools per day. If the body gets rid of more ammonia, the child's mental state may improve. **Neomycin** is an oral antibiotic sometimes used to control the growth of ammonia-producing bacteria in the intestine. **NTBC** is a drug used to treat a metabolic liver disease called tyrosinemia. This drug, which was developed in Sweden, can reverse the liver failure that can be seen in infants with tyrosinemia. The drug does cause accumulations of tyrosine in the bloodstream. Patients are kept on a low protein diet so that tyrosine crystals do not accumulate in the eyes. Growth and development must be monitored carefully while on this drug.

A unique, very small subgroup of pregnant patients (0.1%) develops hepatic complications directly attributable to pregnancy. **Preeclampsia** occurs in 7 to 10% of pregnancies and characterized by maternal hypertension, proteinuria, peripheral edema, coagulation abnormalities and varying degrees of disseminated intravascular coagulation. When hyperreflexia and convulsions occur the condition is called eclampsia. Hepatic disease is distressingly common in preeclampsia, usually as part of a syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). In mild cases, patients may be managed conservatively, definitive treatment in severe cases requires termination of the pregnancy. **Acute fatty liver of pregnancy** presents in the latter half of pregnancy, Symptoms may be directly attributable to hepatic failure, including bleeding, nausea, and vomiting, jaundice or coma. In 20 to 40% of cases, the symptoms coexist with preeclampsia. Although it usually runs a mild course patients can progress within days to hepatic failure and death. The primary treatment for **acute fatty liver of pregnancy** is termination of the pregnancy. **Intrahepatic cholestasis** of pregnancy being with pruritis in the third trimester, followed by darkening of the urine and occasionally light stools and jaundice. Although generally a benign condition, the mother is at risk for gallstones and malabsorption and the incidence of fetal distress, stillbirths, and prematurity is modestly increased (Crawford '94: 875-876).

Extrahepatic biliary atresia (EHBA) occurs in 1: 10,000 live births, one-third of infants with neonatal cholestasis. EHBA is defined as a complete obstruction of bile flow owing to destruction or absence of all or part of the extrahepatic bile ducts. It is the single most frequent cause of death from liver disease in early childhood and accounts for 50 to 60% of children referred for liver transplantation, owing to the rapidly progressing secondary biliary cirrhosis. Most infants with EHBA are born with an intact biliary tree, which undergoes progressive inflammatory destruction in the weeks following birth. Without surgical intervention death usually occurs within 2 years of birth. Prolonged conjugated hyperbilirubinemia in the neonate, termed neonatal cholestasis, affects approximately 1 in 2500 live births. **Neonatal cholestasis and hepatitis** are not specific entities, nor are the disorders necessary inflammatory but the diagnosis should bring about a diligent search for recognizable toxic, metabolic and infectious liver diseases. Affected infants have jaundice, dark urine, light or acholic stools and hepatomegaly. 50 to 60% of cases are idiopathic and 20% are due to extrahepatic biliary atresia (EHBA) and 15% to Alpha$_1$Antitrypsin (α_1-AT) deficiency. **Choledochal cysts** are congenital dilations of the common bile duct presenting most often in children before age 10 with the nonspecific symptoms of jaundice or recurrent abdominal pain typical of biliary colic or both. Approximately 20% of patients become symptomatic only in adulthood. The female-to-male ratio is 3 to 4:1 (Crawford '94: 890, 867, 891).

Circulatory disturbances have a considerable impact on liver status because of the enormous flow of blood through the liver. **Liver infarcts** are rare thanks to the double blood supply, nonetheless, thrombosis or compression of an intrahepatic branch may result in a localized infarct that is usually anemic and pale tan. Occlusion of the portal vein results in a sharply demarcated area of red-blue discoloration referred to as an infarct of Zahn. Acute and chronic passive congestion of the liver usually reflects acute or slowly developing cardiac decompensation, most commonly right-sided failure. Left-sided cardiac failure or shock may lead to hepatic hypoperfusion and hypoxia. Necrosis occurs which leads to fibrosis but rarely fulfills the criteria for a diagnosis of cirrhosis although the term cardiac cirrhosis has been applied. Sinusoidal dilation occurs in any condition in which efflux of hepatic blood impeded. Peliosis hepatis is a rare condition in which the dilation is primary. It is most commonly associated with exposure to anabolic steroids and rarely oral contraceptives and danazol. Mottled and blotchy areas develop in the liver, consisting of irregular blood-filled lakes ranging

in size from 0.1 to greater than 1 cm in diameter. Peliotic lesions usually disappear after cessation of drug treatment. Budd-Chiari syndrome was originally described for acute, usually fatal thrombotic occlusion of the hepatic veins. The chronic form of the condition is far less lethal and about half the patients are alive after 5 years. Hepatic vein thrombosis is associated with polycythemia vera, pregnancy, the post-partum state, the use of oral contraceptives, paroxysmal nocturnal hemoglobinuria, and intra-abdominal cancers, particularly hepatocellular carcinoma. About 30% of cases are idiopathic (Crawford '94: 871-874).

Originally described in Jamaican drinkers of pyrrolizidine alkaloid-containing bush tea, **veno-occlusive disease** now occurs primarily in the immediate weeks following bone marrow transplantation. The incidence is 5% in recipients of autologous marrow and up to 25% in allogeneic marrow recipients. Toxicity resulting from induction chemotherapy and radiotherapy appears to be the primary cause, enhanced by such factors as preexisting hepatitis in older patients. A diagnosis of veno-occlusive disease is frequently made on clinical grounds only (tender hepatomegaly, ascites, weight gain, and jaundice) owing to the high risk of liver biopsy in these patients. Treatment of veno-occlusive disease has been largely supportive and has not significantly affected the mortality rates of 30 to 50% (Crawford '94: 874-875). For patients undergoing bone marrow transplantation, the liver may be damaged by toxic drugs or graft-versus-host disease, whereas patients receiving a liver transplant may encounter graft failure or **graft rejection**. The common themes of toxic or immunologically mediated liver damage, infection of immunosuppressed hosts, and recurrent disease are readily apparent. Liver toxicity affects up to one-half of all such patients. And is heralded by weight gain, tender heptomegaly, edema, ascites, hyperbilirubinemia, and a fall in urinary sodium excretion. The onset is typically on the days immediately following donor marrow administration. Although persistent severe liver dysfunction is a harbinger of fatal outcome, the direct cause of death is usually septicemia, pneumonia, bleeding, or multiorgan failure. Liver damage in acute graft-versus-host disease (10 to 50 days after bone marrow transplantation) is dominated by direct attack of donor lymphocytes on epithelial cells of the liver causing bile duct destruction affecting most portal tracts. Acute cellular rejection of implanted livers exhibits features common to all solid organ transplants. Chronic rejection may affect both arteries and bile ducts. Revascularization and perfusion of the donor liver may result in preservation injury, attributable to the generation of oxygen radical in a hypoxic organ with insufficient reserves of oxygen scavengers to prevent damage. The primary event appears to be necrosis and sloughing of the sinusoidal endothelium (Crawford '94: 877, 878).

Hepatitis is a term used to describe liver problems. Many things can inflame the liver, often to the point of causing jaundice, the yellowing of the skin and tissues that is a telltale sign of liver disease, including alcohol, drugs, and other environmental chemicals and microbes. Systemic viral infections that can involve the liver include (1) infectious mononucleosis (Epstein-Barr virus) which may cause a mild hepatitis during the acute phase, (2) cytomegalovirus, particularly in the newborn or immunosuppressed patient, and (3) yellow fever, which has been a major and serious cause of hepatitis in tropical countries. Infrequently the liver can be affected in the course of rubella, adenovirus, herpes, or enterovirus infections. The term viral hepatitis is reserved for infection of the liver by a small group of viruses having a particular affinity for the liver. The hepatitis viruses, are A, B, C, D, and E. Most cases of hepatitis go away by themselves with favorable outcomes, though the illness can drag on for a month or two (Crawford '94: 842, 843, 855). Hepatitis B is the most dangerous. The relatively uncommon hepatitis C virus, is encountered mainly in the context of blood transfusions, drug abuse, and ingestion of contaminated water. It is related to the yellow fever virus and is a leading cause of chronic liver disease and cirrhosis. Incidence of hepatitis C decreased by more than 50 percent

in the US between 1988 and 1993. Hepatitis E travels from host to host via fecal-oral contact and contamination of water rather like hepatitis A is newly recognized. Hepatitis B virus is much more complex and is only found in humans. It can take as long as six months to incubate to the point of producing symptoms of disease, versus six weeks for hepatitis A. It passes from person to person in blood, saliva and semen, which places it among venereal diseases. The virus is extremely stable and can stay dangerous. Because the germ's long term presence in the body often brings on liver cancer, it ranks as the world's most common viral cause of cancer. Between 1985 and 1993 the incidence of hepatitis B fell by 59 percent in the US. Weight loss, no-protein, no-alcohol diet and exercise are important for recovery from hepatitis like any other necrotic infection of the internal organs. Hepatitis D only thrives in cells also infected with hepatitis B, boosting the severity of the disease (Crawford '94: 855).

Chronic viral hepatitis B is treated with Pegylated interferon alfa-2b (Pegasys), Nucleoside/nucleotide analogues (NAs) such as adefovir (Hepsera), entecavir (Baraclude), lamivudine (Epivir-HBV, Heptovir, Heptodin), telbivudine (Tyzeka) and tenofovir (Viread) (Sanders '11: 3). Ribavirin is an oral drug used for treatment of chronic hepatitis C. This drug can cause anemia due to hemolysis, a process in which blood cells break down. Blood counts must be monitored during ribavirin therapy. Most importantly, ribavirin can cause severe damage to the developing fetus. It must not be taken by pregnant women and strict attention must be paid to birth control if a sexually active patient is taking ribavirin. Lamivudine is an oral drug used for treatment of chronic hepatitis B. It has very few side effects. Unfortunately, in a large fraction of treated patients the virus learns to mutate or change to avoid the drug's effects. Interferon injections are used for treatment of both chronic hepatitis B and hepatitis C, in different doses. As summarized in the section on viral hepatitis, interferon causes fevers, chills, and flu-like symptoms, especially with the first few doses. Drops in white blood cell counts can be seen and can require dose adjustment. Depression must be looked for carefully as it can be a serious complication. GI symptoms and weight loss are seen sometimes. Rare complications include autoimmune diseases, hair loss, bleeding into the eyes, heart, lung and neurological problems.

Hepatitis Virus

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Year of Identification	1973	1965	1989	1977	1980
Agent	27 nm Icosahedral capsid, ssRNA	42 nm enveloped dsDNA	30-60 nm enveloped ssRNA	35 nm enveloped ssRNA; replication defective	32-34 nm unenveloped ssRNA
Classification	Picomavirus	Hepadnavirus	Flavivirus/ pestivirus	Unknown	Caliciviridae
Transmission	Fecal-oral	Parenteral; close personal contact	Parenteral; close personal contact	Parenteral; close personal contact	Water-borne
Incubation period (days)	15-45	30-180	20-90	30-50 in super-infection	15-60

Fulminant Hepatitis	0.1-0.4%	1-4%	/Rare	3-4% in co-infection	0.3-3%; 20% in pregnant women
Carrier State	None	0.1-1.0% of blood donors in U.S.	0.2-1.0% of blood donors in U.S.	1-10% of drug addicts and hemophiliacs	Unknown
Chronic Hepatitis	None	5-10% of acute infections	>50%	<5% coinfection, 80% of superinfection	None
Fatality Rate	0.1%				
Hepatocellular Carcinoma	No	Yes	Yes	No increase above HBV	Unlikely
Vaccine	Monovalent Hepatitis A Vaccine (Havrix GSK), (Vaqta Merck), Bivalent Hepatitis A and B Vaccine (TWINRIX GSK)	Bivalent Hepatitis A and B Vaccine (TWINRIX GSK); Monovalent Hepatitis B Vaccine (Engerix-B; GSK), Recombivax-HB; Merck)			
Treatment		Pegylated interferon alfa-2b (Pegasys), Nucleoside/nucleotide analogues (NAs) such as adefovir (Hepsera), entecavir (Baraclude), lamivudine (Epivir-HBV, Heptovir, Heptodin), telbivudine (Tyzeka) and tenofovir (Viread)	Combination of Pegylated interferon alfa-2b (Pegasys) and Ribavirin (Virazole)		

Source: Crawford ’94: Table 18-4; 843

Hepatitis A (HAV), the least dangerous virus, resembles the polio virus and consists of not much more than a bare strand of RNA in an icosahedral (twenty-sided) shell that reproduces only in the liver. Young infected children are almost never jaundiced, but are prime sources of contagion for adults, who usually show all the classic symptoms of nausea, vomiting, dark urine, and yellowish eyes and skin. Hepatitis A (HAV) is a benign, self-limited disease with an incubation period of 14-45 days, does not cause chronic hepatitis or a carrier state and only rarely fulminant hepatitis and so the fatality rate is about 0.1%. HAV is endemic in countries with substandard hygiene. Overall HAV accounts for 25% of clinically evident acute hepatitis worldwide. HAV is spread by ingestion of contaminated water and foods (especially seafood) and is shed in the stool for 2 to 3 weeks before and 1 week after the onset of jaundice (Crawford '94: 843-844). Monovalent Hepatitis A Vaccine (Havrix GSK) or (Vaqta Merck) can be used for the prevention of Hepatitis A, but if already infected wait a few months before being vaccinated. A Bivalent (Combination) Hepatitis A and Hepatitis B Vaccine (TWINRIX GSK) and Monovalent Hepatitis B Vaccine (Engerix-B; GSK) or Recombivax-HB; Merck) are also offered by health care professionals.

Hepatitis B virus (HBV) can produce (1) acute hepatitis (80-95%), (2) chronic nonprogressive hepatitis 10-33%, (3) progressive chronic disease ending in cirrhosis, (4) fulminant hepatitis with massive liver necrosis and (5) asymptomatic carrier state with or without progressive disease (5-10%). Globally liver disease caused by HBV is an enormous problem with an estimated worldwide carrier rate of 300 million, in the U.S. alone there are 300,000 new infections per year. Although blood and body fluids are the primary vehicles of transmission, it may also be spread by contact with body secretions, such as semen, saliva, sweat, tears, breast milk and pathologic effusions. Transfusion, blood products, dialysis, needle-stick accidents among health workers, intravenous drug abuse, and homosexual activity constitute the primary risk categories for HBV infection; in one third of patients, the source of infection is unknown. After exposure to the virus there is a relatively long incubation period averaging 6 to 8 weeks followed by acute disease lasting many weeks to months (Crawford '94: 844-846). HBV is particularly carcinogenic and increases the risk of getting liver cancer 100 times.

Hepatitis C virus (HCV) causes 90-95% of cases of transfusion-associated hepatitis. HCV is major cause of liver disease worldwide and about 150,000 to 170,000 new cases of HCV are estimated to occur annually in the U.S. Major routes of transmission are inoculations and blood transfusions. Seroprevalence in the United States population is 0.2 to 0.6% and is about 8% in homosexuals and in house contacts, with higher levels in hemodialysis patients (8 to 24%), hemophiliacs (55 to 85%) intravenous drug abusers (50 to 90%) and patients with unexplained cirrhosis and hepatocellular carcinoma (>50%). HCV has a higher rate of progression to chronic disease and eventual cirrhosis, exceeding 50%. Thus, although HBV is estimated to caused 30,000 new cases of chronic hepatitis annually in the United States, this figure is 85,000 for HCV. HCV may be the leading cause of chronic liver disease. The incubation period for HCV hepatitis ranges from 2 to 26 weeks, with a mean between 6 and 12 weeks. Persistent infection and chronic hepatitis are the hallmarks of HCV infection, despite the generally asymptomatic nature of the acute illness. Cirrhosis can be present at the time of diagnosis or may develop over 5 to 10 years (Crawford '94: 846-848). Hepatitis C is treated with a combination of Pegylated interferon alfa-2b (Pegasys) and Ribavirin (Virazole), an antibiotic drug for certain viruses. By itself, ribavirin has little effect on HCV, but interferon increases its potency.

Hepatitis D virus (HDV) is replication defective and causes infection only when it is encapsulate by HBV. HDV only arises in two settings (1) acute co-infection following exposure to serum

containing both HDV and HBV or (2) super-infection of a chronic carrier of HBV with a new inoculum of HDV resulting in disease about 30 to 50 days later. Simultaneous coinfection with HBV and HDV increases the risk of fulminant disease by 3 to 4% and chronic progressive disease may develop in 80% of patients, often terminating in cirrhosis. Infection by the HBV is worldwide in the United States it is uncommon and largely restricted to drug addicts and hemophiliacs, who exhibit prevalence rates of 1 to 10%. **Hepatitis E** virus (HEV) is enterically transmitted, water-borne infection occurring primarily in young to middle-aged adults; and is rare in children. A characteristic feature of the infection is the high mortality rate among pregnant women, approaching 20%. In most cases the disease is self-limiting; HEV is not associated with chronic liver disease or persistent viremia. The average incubation period after exposure is 6 weeks (Crawford '94: 848, 849).

A number of **clinical syndromes** may develop after exposure to hepatitis viruses (1) carrier states (a) without clinically apparent disease or (b) with chronic hepatitis; (2) Asymptomatic infection with serologic evidence only; (3) Acute hepatitis (a) anicteric or (b) icteric; (4) chronic hepatitis (a) without or (b) with progression to cirrhosis and (5) fulminant hepatitis causes submassive to massive hepatic necrosis. Other infectious or noninfectious causes can lead to essentially identical syndromes, particularly drugs and toxins. The term "carrier" denotes an individual without manifest symptoms who harbors and can transmit an organism, most typically childhood HBV infection (90-95% of time) whereas adults exposed to HBV only yield a carrier state 1-10% of the time. 0.2 to 0.6% of the U.S. population is a carrier of HCV. The disease is more or less the same and can be divided into four phases (1) an incubation period, (2) a symptomatic preicteric phase, (3) a symptomatic icteric phase and (4) convalescence. Peak infectivity occurs during the last asymptomatic days of the incubation period and the early days of acute symptoms. The preicteric phase is marked by nonspecific, constitutional symptoms. Malaise is the most characteristic initial complaint, followed in a few days by general fatigability, nausea, loss of appetite, and sometimes weight loss. Low-grade fever, headaches, muscle and joint aches, and pains and diarrhea are inconstant symptoms. About 10% of patients with acute hepatitis, most often those with hepatitis B, develop a serum sickness like syndrome consisting of fever, rash and arthralgias. In anicteric cases, the illness may be dismissed as flu-like, unless its true nature is revealed by elevated serum aminotransferase. The icteric phase, if it appears, is caused mainly by conjugated hyperbilirubinemia. It is usual in adults, but not children, with HAV but is absent in about half the cases of HBV and the majority of cases of HCV. In icteric patients, the urine turns darker (conjugated bilirubinuria) and the stools may become lighter owing to cholestasis. Retention of bile acids can cause distressing pruritis. The liver may be mildly enlarged and moderately tender. Curiously, with the onset of the icteric phase, the constitutional symptoms begin to clear, and the patient feels better. In a few weeks to perhaps several months, the jaundice and most of the other systemic symptoms clear as convalescence begins (Crawford '94: 850).

Symptomatic, biochemical or serologic evidence of continuing or relapsing hepatic disease for more than 6 months, optimally with histological documented inflammation and necrosis, is taken to mean **chronic hepatitis**. The likelihood of chronic hepatitis following acute viral infection can be summarized: HAV: extremely rare; HBV: develops in more than 9% of infected neonates and 5% of infected adults, of whom one-fourth progress to cirrhosis; HCV: develops in more than 50% of infected patients, of whom half progress to cirrhosis; HDV: rare in acute HDV/HBV coinfection, more frequently the result of HDV superinfection; HEV does not produce chronic hepatitis. Chronic hepatitis with HBV and apparently with HCV contributes significantly to the development of primary hepatocellular carcinoma. When hepatic insufficiency progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks, it is termed fulminant hepatic

failure. A less rapid course, extending up to 3 months is subfulminant. Both patterns are uncommon and are caused mainly by rampant to fulminant viral hepatitis (50 to 65% of cases) and drug or chemical toxicity (25 to 30%). Some people with chronic Hepatitis B develop a Hepatitis D co-infection, which qualifies them for **liver transplantation**. Depending on the magnitude of insult and the sturdiness of the host, the mortality from fulminant hepatic failure ranges from 25-90% in the absence of liver transplantation. One-year survival following liver transplantation approaches 60%. A single attack of massive hepatic necrosis only infrequently gives rise to post-necrotic cirrhosis because either it is fatal, or regeneration of the liver cells permits survival with little or no residual scarring (Crawford '94: 852, 853, 855).

The liver and lungs share the dubious distinction of being the visceral organs most often involved in the metastatic spread of cancers. Primary carcinomas of the liver are relatively uncommon in North America and Western Europe (2% of all cancers) but represent 20 to 40% of cancers in countries endemic for viral hepatitis. The percentage of liver carcinoma to other carcinomas is one to two per cent in Europe and America while Chinese have 33 percent; Javanese, 36.1 percent; Filipinos, 22.2 percent; Japanese, 7.5 percent; and Southern Africans in the Gold Mines, 86.6 per cent. Liver cancer (**hepatocellular carcinoma**) in the USA has almost doubled in incidence in the 1990s, compared with just 10 to 15 years earlier. The increase was most marked in relatively young men and is most plausible ascribed to increased transmission of hepatitis B and C virus in the late 1960s and 70s via intravenous drug abuse, needle re-use, transfusion of unscreened blood and unsafe sex, a sad parallel to HIV. Rates of infection have recently declined and so, in a delayed reaction, will cancer rates (Greaves '00: 262). Primary carcinoma of the liver is much more common in colored races than in the white race, while malignancies in general are less frequent in colored people. Primary heptomas and 50 percent of primary cholangiomas are associated with cirrhosis. Teratomas of the liver are extremely rare. Primary cancer of the liver occurs much more frequently in the cirrhotic liver as compared with the normal liver that cirrhosis has been referred to as a precancerous lesion. There is no dispute that an adequate diet is essential in the treatment of liver disease. About 1:200 malignant tumors arise primarily in the liver. Most malignancies are metastatic in origin and are derived from the intestinal organs (Gerson '90: 68, 72).

The following medicines are recommended to treat **hepatic itching**. Antihistamines hydroxyzine (Atarax) and diphenhydramine (Benadryl) are often the first drugs that are used. These may help the itching, usually by sedating the patient. Rifampin is an antibiotic which for some reason can also help itching. The patient should be monitored carefully since this drug can be hard on the liver. Ursodeoxycholic acid (Actigall or URSO) may also help itching by promoting bile flow. Questran is a material called a resin. This gritty substance binds bile salts in the stool, stimulating flow of bile from the liver. It should not be taken at the same time as certain other medicines such as URSO. **Prednisone** is a corticosteroid drug which is used to treat autoimmune hepatitis as well as to prevent rejection in liver transplant patients. Corticosteroids are normally made by the body in small amounts. Physicians may give these drugs in large amounts to suppress an overactive immune system. Prednisone causes bones to thin and may sometimes cause severe injury to bone. Prednisone can interfere with normal growth. Prednisone suppresses the immune system, making patients more susceptible to infection. Prednisone cannot be stopped suddenly since the adrenal glands, which normally make corticosteroids, may be suppressed. This can cause the patient to develop life-threatening adrenal insufficiency (the body goes into crisis due to lack of corticosteroids). Prednisone causes cosmetic changes such as weight gain, stretch marks and round, full cheeks. Facial acne may appear. Hypertension and cataracts are seen, mostly in adults, and mostly with prolonged treatment. Efforts are usually made to wean the dose down to the least amount that will keep the disease process under control. **Azathioprine** or

Imuran (or a related drug called 6-MP or 6-mercaptopurine) may also be used to suppress the immune system, commonly in the context of autoimmune hepatitis. These drugs affect the DNA synthesis of rapidly dividing cells. Rarely, these drugs can cause hepatitis or pancreatitis. Low white counts are a more common problem, and blood work is monitored to assess this. An allergic reaction with fevers, rash, joint pains, gastrointestinal symptoms can develop 3 to 4 weeks after starting such a drug. Theoretically, since the drugs affect DNA repair, these drugs could be harmful to a developing infant, or even cause an increased risk of cancer. These are not common complications, although pregnancy should be undertaken with caution in patients on Imuran or 6-MP.

There are two types of **primary carcinoma of the liver** (1) hepatocellular carcinoma (HCC) (90% of primary liver cancers) and (2) cholangiocarcinoma composed of bile duct epithelium. Annual incidence rates of 3 to 7 cases of HCC per 100,000 population in North and South America, Europe and compare with rate of up to 20 per 100,000 in countries bordering the Mediterranean. The greatest numbers of cases are found in Taiwan, Mozambique and Southeast China where annual incidence rates approach 150 per 100,000. Blacks have attack rates approximately fourfold higher than whites. Worldwide there is a clear predominance of males ranging from 8:1 in areas of higher frequency to 2:1 or 3:1 in areas of low frequency. The global distribution of HCC is strongly linked to the prevalence of HBV infection. The HBV carrier state beginning in infancy confers a 200 fold increased risk of HCC by adulthood. In these regions cirrhosis may be absent in up to half of HCC patients and the cancer often occurs between 20 and 40 years of age. In the Western World where HBV is not prevalent cirrhosis is present in 85 to 90% of cases. On a global basis, primary liver cancer constitutes the most common visceral malignant tumor and in some populations is the most common cancer overall. A distinctive variant of HCC is the fibrolamellar carcinoma and has no association with HBV or cirrhosis risk factors and has a better prognosis with 60% of patients alive at 5 years. Cholangiocellular carcinoma is not usually detected until late in its course and the clinical outlook is dismal, with death characteristically ensuing in 6 months. Overall the natural course of primary liver cancer is the enlargement of the primary mass until it encroaches on hepatic function or metastasizes generally first to the lungs and then to other sites. Overall death usually occurs within 6 months of diagnosis from (1) cachexia, (2) gastrointestinal or esophageal variceal bleeding (30 liver failure with hepatic coma or rarely (4) rupture of the tumor with fatal hemorrhage. The hepatoblastoma is a tumor usually of young childhood. The angiosarcoma is usually associated with exposure to vinyl chloride, arsenic, or Thorotrast (once used in radiography as a hepatic contrast medium). The latent period between exposure and appearance of neoplasm may be several decades. (Crawford ’94: 878, 878-883).

Hepatic masses may generate epigastric fullness and discomfort or be detected by routine physical examination. The most common benign lesions are **cavernous hemangiomas**. They appear as discrete red-blue, soft nodules, usually less than 2 cm in diameter, and often directly beneath the capsule. Solitary of multiple benign hepatocellular nodules may develop in the liver, in the absence of cirrhosis. Benign neoplasms may develop from hepatocytes or bile duct epithelial cells. **Liver cell adenomas** tend to occur in young women who have used oral contraceptives and regress on discontinuance of use, they may reach 30 cm in diameter. The liver may undergo postmortem autolysis that becomes evident about 24 hours after death and produces softening, dis-cohesion, and enzymatic disintegration of cells in the complete absence of reactive inflammatory changes. In some instance, gas-forming organisms such as *Clostridium welchii* are borne from the gastrointestinal tract and the growth of these organisms release gas which may produce visible or palpable gaseous bubbles (foamy liver) (Crawford ’94: 878, 883).

When massive hepatocullar necrosis occurs and leaves the connective tissue framework intact, almost perfect restitution can occur. Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver. With continuing fibrosis, the liver is subdivided into nodules of regenerating hepatocytes surrounded by scar tissue, termed cirrhosis. **Cirrhosis** is among the top ten causes of death in the Western world, largely the result of alcohol abuse, chronic hepatitis, biliary disease and iron overload. This end-stage liver disease is defined by three characteristics (1) Fibrosis is present in the form of delicate bands or broad scars replacing multiple adjacent lobules; (2) the parenchymal architecture of the entire liver is disrupted by interconnecting fibrous scars and (3) parenchymal nodules are created by regeneration of hepatocytes. The nodules may vary from micronodule (less than 3mm in diameter) to macronodule (3 mm to several centimeters in diameter. The parenchymal injury and consequent fibrosis are diffuse, extending throughout the liver; focal injury with scarring does not constitute cirrhosis. Progressive fibrosis is the central feature of cirrhosis. The etiology of cirrhosis varies both geographically and socially in the Western world the most **common causes of cirrhosis** are alcoholic liver disease (60-70%), viral hepatitis (10%), biliary diseases (5-10%), primary hemochromatosis (5%), Wilson's disease (rare), $Alpha_1$antitrypsin (AAT) deficiency (rare) and cryptogenic cirrhosis (10-15%). Infrequent types of cirrhosis include (1) the cirrhosis developing in infants and children with galactosemia and tyrosinosis; (2) the desmosplastic reaction incited by a diffusely infiltrative cancer of the liver (carcinomatous cirrhosis); (3) drug-induced cirrhosis, as with alpha-methyldopa; and (4) syphilis (Crawford '94: 834, 835). The ultimate **mechanism of most cirrhotic deaths** is (1) progressive liver failure, (2) a complication related to the portal hypertension or (3) development of hepatocellular carcinoma.

Four major clinical consequences of **portal hypertension** are (1) ascites, (2) the formation of portosystemic venous shunts particularly esophagogastric varices that appear in 65% of patients with advanced cirrhosis and cause death in half, (3) congestive splenomegaly and enlargement of the liver of up to 1000 gm and (4) hepatic encephalopathy. Ascites refers to the collection of excess fluid in the peritoneal cavity. It usually becomes clinically detectable when at least 500 ml has accumulated, but many liters may collect and cause massive abdominal distention. It is generally a serous fluid having less than 3 gm/dl of protein (largely albumin) as well as the same concentration of solutes such glucose, sodium and potassium as in the blood. Thus, withdrawal of large volumes of ascites fluid for relief of symptoms invokes a substantial loss of protein and solutes (Crawford '94: 835-837).These "diuretic" drugs and others like them are used to help rid the body of excess fluid: Spironolactone (Aldactone) opposes a hormone that makes patients with cirrhosis retain fluid. Furosemide (Lasix) is another diuretic which makes the patient urinate extra fluid. It can cause abnormalities in the salts in the blood. **Portal blood-flow** (1500 ml/min) constitutes about 75% of total hepatic blood supply. Rise in portal pressure results from obstruction at one of three sites (1) in the portal vein (prehepatic), usually thrombus due to infection in the neonatal period of secondary to encroachment upon the vein by hepatic tumors, (2) in the liver (hepatic) due to cirrhosis, schistomiasis, hepatic fibrosis, central vein sclerosis (as occurs in acute alcoholic liver disease), the reason for the rise in pressure in this group is not clearly understood, and (3) in the hepatic venous drainage (post-hepatic) hepatic vein occlusion (Budd-Chiari syndrome), (4) constrictive pericarditis, e.g. tuberculosis, and (5) severe right-heart failure, predominantly tricuspid incompetence. As sources of hemorrhage, only the esophago-gastric channels are of clinical significance because they cause severe and continuing bleeding into the alimentary tract. Bleeding from other anastomotic sites is rarely troublesome. The spleen is invariably enlarged (Jones et al '85: 191-193).

Liver function tests are several. Transaminases (aminotransferases) reflect liver and other tissue damage especially in cardiac and skeletal muscle. Alanine transaminase (ALT; serum

glutamic pyruvic transaminase, SGPT) is more specifically related to liver damage, but it is not more sensitive than aspartate transaminase (AST; serum glutamic oxaloacetic transaminase, SGOT) and the latter is more generally used. Very high levels (over 1000 units) are found in hepatic necrosis, e.g. severe hepatitis. Numerous other enzymes e.g. lactic dehydrogenase, ornithine carbamoyl transferase) are not widely applicable. LDH isoenzymes are highly specific Gamma gutamyl transpeptidase (GGT) is an enzyme of induction, it is a sensitive enzyme widely used as a screening test and, in conjunction with alkaline phosphatase, to establish the hepatic origin of the later, with which it rises in concert. Some drugs, and particularly alcohol, cause modest to major rises in GGT (50-500 units). Alkaline phosphatase (AP) is an important duct enzyme of several origins but is normally mostly derived from biliary ductular epithelium. Modest rises (up to twice normal) are common, they often reflect liver damage but may be difficult to interpret. Elevation sin excess of 2-3 times normal occur in biliary tract obstruction. Space-occupying lesions can cause levels of AP in excess of 6 times normal. Mild elevations of bilirubin (up to 4-5 time normal) may reflect increased production (haemolysis), impaired transport of conjugation (e.g. Gilbert's disease) or mild cellular damage. Significant rises reflect a failure of excretion. Almost all will be conjugated bilirubin and will be soluble in water and excreted in urine. High bilirubin levels occur in drug-induced and cholestatic viral hepatitis. In established liver disease high levels of bilirubin and jaundice denote a poor prognosis. Albumin tends to be low where protein synthesis is impaired or protein lost, e.g. cirrhosis, malignant disease or severe infection. Prothrombin time (PT) is a sensitive and useful indicator of hepatic function. In simple obstructive jaundice, prolongation may be rapidly reversed with parenteral vitamin K. In drug damage and hepatitis a lengthening or very prolonged PT suggests a poor prognosis. There are many viral markers but the single most important is hepatitis B surface antigen. A positive alpha-feto-protein test strongly suggests primary hepatoma. Mitochondrial antibodies are useful for primary biliary cirrhosis (positive in 98% cases). Smooth muscle antibodies suggest chronic active hepatitis, but are not specific. Ultimately a histological diagnosis should be made in most cases (with the exception of gallstone disease and the relief of extrahepatic obstruction) (Jones et al '85: 175-178).

Loss of **hepatic functional capacity** must exceed 80 to 90% before hepatic failure ensures. In most cases of severe hepatic dysfunction, liver transplantation is the only hope for survival. Overall, mortality from hepatic failure is 70 to 95%. The major disorder having the potential to cause hepatic failure are divided into three classes (1) Ultrastructural lesions that do not produce overt liver cell necrosis; Reye’s syndrome, tetracycline toxicity; (2) chronic liver disease from relentless chronic hepatitis, cirrhosis, inherited metabolic disorders and (3) massive hepatic necrosis from fulminant viral hepatitis, massive toxic damage as from acetominophen, halothane, monoamine oxidase inhibitors used as antidepressants, industrial chemical agents such as carbon tetrachloride and phosphorus, and mushroom poisoning (e.g. Amanita species). **Hepatic encephalopathy** is a complication of acute and chronic liver failure. Patients exhibit a spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to marked confusion to deep coma and death. Particularly characteristic is asterixis, the nonrhythmic, rapid extension-flexion movements of the head and extremities, best seen when the arms are held in extension with dorsiflexed wrists. Hepatic encephalopathy is regarded as a metabolic disorder of the central nervous system and neuromuscular system but it is caused by (1) the shunting of blood around the liver and (2) severe loss of hepatocellular function. Hepatorenal syndrome refers to the appearance of renal failure in patients with severe liver disease. Kidney function promptly improves if hepatic failure is reversed (Crawford ’94: 841-842).

Fulminant hepatic failure is a devastating and highly mortal disease of rapid onset. The causes include viral hepatitis (mainly HAV and HBV), drugs, e.g. paracetamonl (acetaminophen),

poisoning, e.g. Death cap mushroom, *Amanita phalloides*, acute fatty liver of pregnancy and Reye's syndrome. The liver usually shows widespread necrosis, with collapse of the reticulin framework, and consequently a small liver. Cerebral oedema is common and may be a cause of death. Renal failure, alimentary hemorrhage, and pancreatitis are other potentially fatal complications. Signs of impending encephalopathy may supervene upon an otherwise unremarkable case of acute hepatitis. Vomiting, abdominal pain, drowsiness, confusion and tremor are ominous developments. Renal failure is a common accompaniment of both acute hepatic failure and advanced chronic hepatic decompensation, to which the term 'hepato-renal syndrome' has been applied. A rising urea and creatinine with a falling sodium in an oliguric patient is an ominous sign. Despite measures to improve perfusion (e.g. albumin infusions) and induce diuresis (e.g. mannitol), the prognosis is usually poor. Rarely, the kidney is involved directly in the injurious process damaging the liver, e.g. in carbon tetrachloride poisoning. The first principle of treatment is to eliminate a precipitating cause such as infection, hemorrhage, hypokalemia or alcohol withdrawal syndrome. The second principle of treatment is to reduce the degree of assimilation of nitrogenous compounds by lowering oral protein intake (reducing the diet to 30-40 g protein daily and by clearing the gut of protein (e.g blood from bleeding in the upper alimentary tract) by magnesium sulphate enemas. Nitrogen uptake can further be reduced by regulation of colonic bacterial flora with metronidazole. Lactulose, a non-absorbed sugar, also helps by encouraging overgrowth of saccharolytic bacteria to the exclusion of peptide-splitting bacteria. It also acts as a mild osmotic laxative and is safe for use over long periods of time. The third principle of treatment is the avoidance of aggravating factors such as sedative drugs, fluid overload and electrolyte imbalance (Jones et al '85: 197, 198).

Bleeding is the commonest mode of death in liver failure. A bleeding diathesis is common in liver disease and in prolonged biliary obstruction, although the latter is usually rapidly reversible since it is mainly due vitamin K malabsorption. Coagulation problems may be due to (a) failure to absorb due to deficiencies of vitamin K dependent factors II, VII, IX, X, (b) failure of synthesis of factor V, and K-dependent factors, (c) platelet deficiency, (d) disseminated intravascular coagulation, and (e) increased fibrinolysis. Treatment is with fresh blood, parenteral vitamin K, K-factor concentrates, fresh frozen plasma, platelet concentrates, possibly heparin or EACA. Bleeding may be into the skin (petechiae, ecchymoses) and mucous membranes, or rather rarely) into serosal sacs, joints and brain. There is a strong predilection for bleeding into the alimentary tract, for several reasons, (1) vomiting and retching producing a Mallory-Weiss tear of oesophageal muycosa, (2) gastric erosion, of uncertain causation, are relatively common, (3) bleeding from coexistent peptic ulcer, and (4) portal hypertension with esophageal and gastric varices. Alimentary hemorrhage is a major problem with high mortality. Where bleeding is evident or major a full 'clotting screen' including estimation of hemoglobin, prothrombin time and platelet count provides baseline information. In emergency, the freshest blood possible should be used and 10 mg of vitamin K given slowly intravenously (pure vitamin K deficiency may be corrected within several hours). Factor concentrates and platelet infusions may be required where bleeding continues or where operation or biopsy is necessary in patients with defects. In emergency, two units of fresh frozen plasma may be given. Hypocalcemia is a potential risk in patients requiring large volumes of citrated blood.

12. Choledocholithiasis (gallstones) and biliary disease

Gallstones afflict 10 to 20% of adults in developed countries. Doctors and surgeons need to be informed that gallstones and urinary stones are cured overnight with Stonebreaker (Chanca piedra). It is estimated that more than 20 million persons in the United States have gallstones, totaling some 25 to 50 tons in weight. About 1 million new patients annually are found to have

gallstones, of whom approximately 600,000 undergo cholecystectomy. Nevertheless, the vast majority of gallstones (more than 80%) are "silent" and most individual remain free of biliary pain or stone complication for decades. In the West, about 80% of gallstones are cholesterol stones, containing more than 50% of crystalline cholesterol monohydrate. The remainder are composed predominantly of bilirubin calcium slats and are designated pigment stones. The prevalence of cholesterol gallstones approaches 75% in certain native American population: the Pima, Hopi and Navajo. Gallstones are more prevalent in industrialized societies. The prevalence of gallstones increases with age. In the United States less than 5 to 6% of the population under the age of 40 have stones, in contrast to 25 to 30% of those over age 80. The prevalence in which women is about twice as high as in men. Hyper-secretion of biliary cholesterol appears to play the major role. Obesity and rapid weight loss are strongly associated with increased biliary cholesterol secretion. Infection of the biliary tract, as with *Escherichia coli*, *Ascaris lumbricoides*, or in Asia, by the liver fluke, *Opishtochis sinensis*, induces de-conjugation of excreted bilirubin. It appears that asymptomatic patients convert to symptomatic ones at a rate of 1 to 3% per years (Crawford '94: 884).

Stonebreaker (Chanca piedra) herbal remedy excretes gallstones and urinary stones overnight. Stonebreaker must be incorporated into medical surgery prevention practice. Ingredients of the new formulation of Stone Breaker™: formerly Madden/Hydrangia now includes extracts of: Stonebreaker herb (*Phyllanthus niruri*), Hydrangea root (*Hydrangea arborescens*), Celery seed (*Apium graveolens*), Burdock seed (*Arctium lappa*); and other Ingredients: certified organic grain alcohol & distilled water. At around $10 a bottle and no known side-effects Stonebreaker should definitely be taken before surgery or expensive medical treatment. Caution: Do not take during pregnancy and keep out of reach of children. Shake well before taking 40 drops in a full cup of water, three times per day. For children Clark's rule is to divide the child's weight (in pounds) by 150 to get the fraction of the adult dose to give to the child. Example: For a 50 pound child give 50/150 (or 1/3) of the adult dose. Therefore, if the adult dose is 40 drops taken 3 times per day, the child's dose will be 13.3 drops taken 3 times per day. Some extracts are not suitable for children. Consult your doctor for advice.

Disorders of the biliary tract affect a significant portion of the world's population. Cholesterolosis of the gallbladder refers to focal accumulations of triglycerides and cholesterol-laden macrophages within the tips of mucosal folds directly beneath the columnar epithelium - strawberry gallbladder. More than 95% of biliary tract disease is attributable to cholelithiasis (gallstones). Choledocholithiasis is the presence of stones within the biliary tree, occurring in about 10% of patients with cholelithiasis. In the United States, in 1994, the annual cost of cholelithiasis and its complications was around $6-8 billion, around 1% of the national health care budget. **Cholangitis** is the term used for bacterial infection of the bile ducts. Cholangitis can result from any lesion creating obstruction to bile flow, most commonly choledocholithiasis. Uncommon causes include indwelling stents or catheters; tumors; acute pancreatitis, benign stricture and rarely fungi, viruses or parasites. Bacteria most likely enter the biliary tract through the sphincter of Oddi; infection of intrahepatic biliary radicles is termed ascending cholangitis. The bacteria are usually enteric gram-negative aerobes, such as *E. coli*, Klebsiella, Clostridium, Bacteroides, or Enterobacter, and group D streptococci. Cholangitis usually generates fever, chills, abdominal pain, and jaundice, accompanied by acute inflammation of the wall of the bile ducts with entry of neutrophils into the luminal space. Intermittence of symptoms suggests bouts of partial obstruction. The most severe form of cholangitis is suppurative cholangitis, in which purulent bile fills and distends bile ducts. These infections are prone to extending into the hepatic substance and causing liver abscesses. Because sepsis rather than cholestasis tends to

dominate the picture, prompt diagnosis evaluation and intervention are imperative in these unstable patients (Crawford ’94: 893, 883, 891).

Gallbladder disease (Biliary Colic) caused by gallstones causes gallbladder attacks are quite stereotypical, occurring 2 hours after a meal or in the middle of the night. The attacks last for hours, not days, and then dissipate completely. The gallbladder may be surgically removed. The gallbladder is a small sac tucked under the liver. It delivers bile to the intestinal tract via a system of ducts, starting with the cystic duct. Bile is an interesting mixture of cholesterol, other lipids, and bile pigments, and it is useful in digesting and absorbing dietary fats and in excreting the pigmented part of the hemoglobin. Gallstones form either when there is too much pigment or, more commonly, when there is too much cholesterol in the bile. So long as the stones rattle around in the gallbladder, they are painless and of no particular interest. The trouble arises when a stone gets impacted in a bile duct. Most of the time, this occurs when the stone gets stuck at the neck of the gallbladder where it empties into its duct. The body does not like having its ducts blocked and this becomes quite a painful business. Gallbladder attack is an acute, very painful condition caused by stones in the gallbladder. The attacks occur after a meal or in the middle of the night. A gallbladder attack lasts for several hours and then disappears entirely until the next time (Newman ’11: 77).

A tumor at the lower end of the common bile duct may obstruct the termination of the main pancreatic duct to produce pain from pancreatitis as well as obstructive jaundice, a combination suggestive of gallstone obstruction. **Biliary colic** is one of the most severe types of abdominal pain. It begins fairly abruptly, most often in the epigastrum rather than in the right upper quadrant, radiates through to the tip of the right scapula, builds up to a level of severe steady intensity and usually lasts a matter of hours. It is often associated with nausea, vomiting, sweating and restlessness. Relief often requires a potent analgesic such as pethidine and the patient is left with an aftermath of upper abdominal discomfort during the following day or two. The appearance of bile in the urine, or disturbances of liver function tests in association with biliary colic, strongly suggests a stone in the common bile duct. Continuing impaction of a stone at the lower end of the duct will lead to obstructive jaundice. Operation to remove the stone or stones is usually an elective procedure because such stones may pass on into the duodenum, or they may disimpact upwards. Stones in the gall bladder are most of the time, mobile and relatively asymptomatic, but when an attack of biliary colic occurs, acute cholecystitis may supervene, but it more usually develops as a continuous pain, less intense than that of biliary colic, localized in the right upper quadrant. Cholecystectomy is also an elective operation (Jones et al '85: 185-189). Stone breaker™ herbal treatment is highly effective at dissolving urinary stones overnight

Finding gallstones on **imaging studies** is quite straightforward; they show up easily on abdominal ultrasound. Sometimes the gallbladder looks inflamed on ultrasound; however, most often the gallbladder looks normal but contains stones. The ultrasonographer may run his gadget directly over the gallbladder to see if it is tender, but it is not certain that this finding is really important. Determining if the stones are troublemakers is more difficult. How do we know whether the patient really has symptomatic gallstones rather than innocent-bystander gallstones? Surgery for gallstones is only rarely an emergency. Instead, most doctors will follow the patient after a first attack and see if there are further episodes. Patients who spend a lot of time in places where one would not wish surgery on one’s worst enemy should be referred promptly to an experienced gallbladder laparoscopic surgeon, before the patient leaves town. For the other patients, one relies mainly on one’s clinical judgment. If there is strong suspicion that the patient’s distress is caused by gallstones, the problem is solved by removal of the gallbladder.

Because the operation is comparatively simple, we seem to be calling on our surgical colleagues a bit too quickly in too many cases. However, life without a gallbladder is nor more difficult than life with one, and one's lamentations over the unnecessary cholecystectomy should be short-lived. An attack of symptomatic gallstones, or biliary colic, is about as severe as having a symptomatic kidney stone, in other words, it hurts like hell. The pain is the upper abdomen and sometimes on the right side. It often radiates around the back. It can be ferocious, requiring a narcotic to ease the distress. The accompanying vomiting is equally ferocious. The attack lasts as long as the stone is blocking a duct, usually a matter of hours, not a few seconds and not days or weeks. When the stone is released and plops back from the duct into the gallbladder, the attack is over, the pain is gone, and the patient is probably exhausted (Newman '11: 77).

Prominent among symptoms is **biliary pain**, which tends to be excruciating and constant or colicky (spasmodic). Inflammation of the gallbladder almost always develops in the setting of gallstones. Acute calculous cholecystitis may appear with remarkable suddenness and constitute an acute surgical emergency or may present with mild symptoms that resolve without medical attention. In the absence of medical attention the attack usually subsides over 7 to 10 days and frequently within 24 hours. Up to 25% of patients, however, develop progressively severe symptoms requiring immediate medical intervention. In patients that recover recurrence is common. Surgical removal of the diseased gallbladder is the treatment of choice (5 to 12% of gallbladders removed contain no gallstones). Although overall mortality from this disease is under 1% several thousand deaths occur annually in the United States from this condition (Crawford '94: 885). Surgery for gallstones is quite straightforward and is often done on an out-patient basis with a very short recovery time. Because it is simple to diagnose stones and simple to remove the gallbladder, there has been, globally, a dramatic increase in the number of gallbladders removed compared to 40 years ago. Many of these gallbladders were removed from patients in whom the stones were innocent bystanders. This strategy is doomed to side effects such as post-cholecystectomy diarrhea or biliary dyskinesia, a painful motility disturbance of the bile ducts, from the surgery. Gallbladder surgery should be offered only to patients with symptomatic gallstones and characteristic biliary colic, or to certain very high-risk patients (Newman '11: 182). A home remedy for gallstones is to eat a vegan diet, with a lot of apples for about a week and then imbibe a mixture of Epsom salt and apple juice, whereupon the gallstones are excreted and can be seen in the feces. The procedure can be repeated several times until a thorough cleanse has been achieved. A vegan diet, without the cholesterol and fat found in animal products, is highly recommended to prevent cholesterol stones from forming in the gallbladder.

Major developmental anomalies of the **gallbladder and bile ducts** are rare. The gallbladder may be congenitally absent or there may be gallbladder duplication. A longitudinal or transverse septum may create a bi-lobed gallbladder. Aberrant locations of the gallbladder occur in 5 to 10 % of the population, most commonly partially or completely embedded in the liver. A folded fundus is the most common anomaly, creating the so-called Phrygian cap. Agenesis of all or any portion of the hepatic or common bile ducts and hypo-plastic narrowing of biliary channels (biliary atresia) represent a spectrum of hepatobiliary malformations. As a hollow viscus lying adjacent to the liver, the gallbladder is the occasional recipient of a needle thrust from percutaneous liver biopsy or transhepatic cholangiography. In both instances, subsequent leaks of irritant bile can give rise to chemically induced inflammation of the peritoneum, so called bile peritonitis. Repeated infusion of chemotherapeutic agents into the hepatic artery for metastatic liver disease may cause iatrogenic drug injury. Because the intrahepatic and extrahepatic bile ducts and gallbladder are sustained by branches of this artery, chemically induced arterial obliteration can lead to a sclerosing cholangitis-like picture in the biliary tree with loss of

intrahepatic bile ducts or an acute cholecystitis progressing to chronic fibrosis (Crawford ’94:893-894).

The most common cause of obstruction is an **impacted gallstone in the common bile duct** other conditions include biliary atresia, malignancies of the biliary tree and head of the pancreas and strictures resulting from previous surgical procedures. Periportal fibrosis eventually leads to secondary biliary cirrhosis. Secondary bacterial infections (ascending cholangitis) may contribute to the damage, enteric organisms such as coliforms and enterococci are common culprits. Van Meyenburg complexes are rather common, small clusters of modestly dilated bile ducts that must not be mistaken for metastatic carcinoma, these bile duct microhamartomas contain inspissated bile concrements and may communicate with the biliary tree. Polycystic liver disease contains multiple diffuse cystic lesions, numbering from a scattered few to hundreds. The cysts vary from 0.5 to 3-4 cm in diameter and are lined by cuboidal or flattened biliary epithelium and contain straw-colored fluid. The patient may develop pain on stooping. Congenital hepatic fibrosis involves portal tracts enlarged with irregular and broad bands of collagenous tissue, forming septae and dividing the liver into irregular islands. Variable numbers of abnormally shaped bile ducts are embedded in the fibrous tissue. In Caroli’s disease the larger ducts of the intrahepatic biliary tree are segmentally dilated and may contain inspissated bile. Prolonged obstruction to the extrahepatic biliary tree results in profound alteration of the liver (Crawford ’94: 870, 871, 867).

Distinguishing Features of Disorders Associated with Biliary Cirrhosis

	Secondary Biliary Cirrhosis	Primary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Etiology	Extrahepatic bile duct obstruction from primary biliary cirrhosis or primary sclerosing cholangitis; biliary atresia, gallstones, or carcinoma of pancreatic head	Possibly autoimmune; associated with other autoimmune conditions	Unknown; 50-70% of cases associated with inflammatory bowel disease
Sex Predilection	None	Female-to-male 6:1	Female-to-male 1:2
Symptoms and signs	Pruritis, jaundice, malaise, dark urine, light stools, hepatosplenomegaly	Same as secondary biliary cirrhosis; insidious onset	Same as secondary biliary cirrhosis; insidious onset
Laboratory findings	Conjugated hyperbillirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol	Same as secondary biliary cirrhosis, plus elevated serum IgM, presence of autoantibodies, especially antimitochondrial antibody (AMA), hypercholesterolemia	Same as secondary biliary cirrhosis, plus hypergammaglobuline mia, elevated IgM
Distinctive	Prominent bile stasis	Dense lymphocytic	Periductal fibrosis and

Pathological Findings of Bile Ducts	in interlobular bile ducts, sometimes neutrophils in bile ducts; bile duct proliferation	infiltrate around and in wall of interlobular bile ducts with granuloma formation and bile duct destruction	segmental stenosis of extrahepatic and intrahepatic biliary ducts

Source: Crawford ’94: Table 18-9, 868

Primary biliary cirrhosis (pbc) is a chronic, progressive and often fatal cholestatic liver disease, characterized by the destruction of intrahepatic bileducts, portal inflammation and scarring and the eventual development of cirrhosis and liver failure. The primary feature of this disease is a nonsuppurative, granulomatous destruction of medium-sized intrahepatic bile ducts; cirrhosis appears only later in the course. This is primarily a disease of middle-aged women with a female-to-male predominance of 6:1. The onset is insidious, usually presenting with pruritis. Jaundice develops late in the course. Hepatomegaly is typical. Xanthomas and xanthelasmas arise as a result of cholesterol retention. Antimitochondrial antibodies are found in more than 90% of patients. Extrahepatic manifestations include the sicca complex of dry eyes and mouth (Sjogren’s syndrome), scleroderma, thyroiditis, rheumatoid arthritis, Raynaud’s phenomenon, membranous glomerulonephritis, and celiac disease. The major cause of death is liver failure, followed in order by massive variceal hemorrhage and intercurrent infection (Crawford ’94: 867-869). Primary sclerosing cholangitis (PSC) is characterized by inflammation, obliterative fibrosis and segmental dilation of the intrahepatic and extrahepatic bile ducts. PSC is commonly seen in association with inflammatory bowel disease, particularly chronic ulcerative colitis, which coexists in approximately 70% of patients. Conversely, the prevalence of PSC in ulcerative colitis patients is about 4%. PSC tends to occur in the third through fifth decades of life and males predominate 2:1. The concentric periductal fibrosis around affected ducts is followed by their disappearance leaving behind a solid, cord-like fibrous scar. In between areas of the bile ducts become ecstatic and inflamed. As the disease progresses, the liver becomes markedly cholestatic, culminating in biliary cirrhosis. Asymptomatic patients may come to attention based only on persistent elevation of serum alkaline phosphate. Alternatively, progressive fatigue, pruritis and jaundice may develop. Severely afflicted patients exhibit symptoms associated with chronic liver disease, including weight loss, ascites, variceal bleeding, and encephalopathy. Ten-year survival is on the order of 50 to 75%. Progressive decline is arrested only by liver transplantation (Crawford ’94: 869-870). In children, diagnosis of biliary atresia, and in adults, primary biliary cirrhosis, secondary biliary cirrhosis and primary sclerosing cholangitis are indications for liver transplantation (Dienstag '98: 1721).

Carcinoma of the gallbladder is the fifth most common cancer of the digestive tract. Only rarely is it discovered at a resectable stage, and the mean 5-year survival has remained form ay years at about 1%, despite surgical intervention. Gallstones are present in 60 to 90% of patients but not 100%. Malignancies of the extrahepatic biliary tree that occur near the ampulla of Vater are referred to as perampullary carcinomas. Bile duct carcinoma is uncommon but slightly more frequent in males. Gallstones are present in only 35 to 50% of cases. Choldochal cysts, ulcerative colitis, and chronic biliary infection with *Clonorchis sinensis* and *Giardia lamblia* impart an increased risk for bile duct carcinoma, but only in a minority of patients. Jaundice generally arises due to obstruction. Hepatomegaly is present in about 50% and a palpable gallbladder in about 25%. Mean survival times range from 6 to 18 months, regardless of whether aggressive resections of palliative surgery are performed (Crawford ’94: 891, 893).

Surgical resection is the mainstay of therapy for cancer of the gallbladder or extrahepatic biliary system. When possible, total resection of an early gallbladder cancer (confined to the mucosa) can result in 80% survival at 5 years. The prognosis for apparently localized extrahepatic biliary tumors is worse. Palliation may be achieved by mechanical biliary drainage. Conventional chemotherapy has not been extensively evaluated but is usually of very little value. Patients at risk for developing hepatocellular cancer often have underlying liver disease with deranged metabolic function and may not be suitable candidates for resection. Up to 80% of the liver can be removed (trisegmentectomy), but the mortality and morbidity postoperatively can be substantial. However, properly selected cases can benefit from a partial hepatectomy. With complete resection perhaps 25% of patients can be cured. Unfortunately, this approach is appropriate for only 10% or less of patients. Patients not eligible for complete tumor resection, may benefit from such regional approaches as percutaneous hepatic artery embolization or ligation, which produces ischemic necrosis of the tumor. This may result in dramatic tumor shrinkage, but the response is usually temporary. Side-effects include pleuro-eritonitis, fever, hepatic pain, and laboratory evidence of hepatocellular necrosis. After a few days to weeks of discomforts, patients may experience meaningful palliation. Chemotherapy has generally been disappointing. When given by hepatic intra-arterial infusion, the fluoropyrimidines result in modest effects, but this therapy requires either prolonged hospitalization (percutaneous administration) or surgical placement of a catheter. Many patients are too ill for such treatment. Systemic chemotherapy is likewise only modestly effective. Doxorubicin (40 mg – 80 mg/m2 IV every 3 weeks) results in median survival of only 12 of 20 weeks. Other agents such as 5-FU or mitomycin, are inconsistently effective when given systemically. For patients with an estimated survival of 1 month or more, the use of single-agent doxorubicin is appropriate. External irradiation (300 cGy/day for 7 days) can result in palliation without severe organ toxicity, and up to 20% of patients will experience tumor shrinkage, while more than 50% will have diminished local symptoms (Friedman '90: 244). Stonebreaker (Chanca piedra) herbal remedy excretes gallstones and urinary stones overnight.

13. Liver transplant

Liver transplantation is the replacement of the native, end stage diseased liver by a normal organ (allograft). The preferred and technical most advanced approach is orthotopic transplantation, in which the native organ is removed and the donor organ is inserted int eh same anatomic location. Pioneers in the 1960s by Starzl at the University of Colorado and, later, at the University of Pittsburgh and by Calne in Cambridge, England, liver transplantation is now performed routinely by dozens of centers throughout North America and western Europe. Success and survival have improved from approximately 30 percent in the 1970s to >80 percent today. These improved prospects for prolonged survival, dating back to the early 1980s, resulted from refinements in operative techniques, improvements in organ procurement and preservation, advances in immunosuppressive therapy, and, perhaps most influentially, more enlightened patient selection and timing. Despite the perioperative morbidity and mortality, the technical and

management challenges of the procedure, and its costs, liver transplantation has become the approach of choice for selected patients whose chronic or acute liver disease is progressive, life-threatening, and unresponsive to medial therapy. Based on the current level of success, the number of liver transplants has continued to grow each year; in 1995, as many as 6000 patients in the United States were on a waiting list for a donor liver (Dienstag '98: 1721).

Transplantation should be considered in patient with end-stage liver disease who are experiencing or have experienced a life-threatening complication of hepatic decompensation, whose quality of life has deteriorated to unacceptable levels, or whose liver disease will result predictably in irreversible damage to the central nervous system (CNS). The most common reasons for transplantation in children is biliary atresia, inherited or genetic disorders of metabolism associated with liver failure. Liver transplantation is indicated for end-stage cirrhosis of all causes in adults. In sclerosing cholangitis and Caroli's disease (multiple cystic dilations of the intrahepatic biliary tree, recurrent infection and sepsis associated with inflammatory and fibrotic obstruction of the biliary tree may be an indication for transplantation. Because prior biliary surgery complicates, and is a relative contraindication for, liver transplantation, surgical diversion of the biliary has been all but abandoned for patient with sclerosing cholangitis. In patients who undergo transplantation for hepatic vein thrombosis (Budd-Chiari syndrome), postoperative, anticoagulation is essential; underlying myeloproliferative disorders may have to be treated but are not a contraindication to liver transplantation. If a donor organ can be located quickly, before cerebral edema set in, patients with fulminant hepatitis are candidates for liver transplantation. More controversial as candidates for liver transplantation are patient with alcoholic cirrhosis, chronic viral hepatitis and primary hepatocellular malignancies. Absolute **contraindications for transplantation** include life-threatening systemic diseases, uncontrolled extrahepatic bacterial or fungal infections, preexisting advanced cardiovascular or pulmonary disease, multiple uncorrectable life-threatening congenital anomalies, metastatic malignancy, active drug or alcohol abuse, and human immunodeficiency virus (HIV) infection. Because carefully selected patients in their sixties and seventies have undergone transplantation successfully, advanced age per se is no longer considered an absolute contraindication; however, in older patients, a more thorough preoperative evaluation should be undertaken to exclude ischemic cardiac disease (Dienstag '98: 1721, 1722).

Indication for Liver Transplantation

Children	Adults
Biliary atresia	Primary biliary cirrhosis
Neonatal hepatitis	Secondary biliary cirrhosis
Congenital hepatic fibrosis	Primary sclerosing cholangitis
Alagille's disease	Caroli's disease
Byler's disease	Cryptogenic cirrhosis
α 1 – Antitrypsin deficiency	Cryptogenic cirrhosis
Inherited disorders of the metabolism	Chronic hepatitis with cirrhosis
Wilson's disease	Fulminant hepatitis
Tyrosinemia	Alcoholic cirrhosis
Glycogen storage diseases	Chronic viral hepatitis
Lysosomal storage diseases	Primary hepatocellular malignancies
Protoporphyria	Hepatic adenomas
Familial hypercholesterolemia	

Hereditary oxalosis	
Hemophilia	

Source: Table 301-1 Dienstag '98: 1721

After the patient has been identified as a candidate and a donor organ has been procured, the actual **liver transplantation** surgical procedure can take 8 to 22 hours to complete. The procedure involves five anastomoses between recipient and donor organs, including the following vascular anastomosis sites: suprahepatic inferior vena cava, infrahepatic vena cava, portal vein, hepatic artery and biliary tract. The biliary anastomosis site varies, depending on the patient's extrahepatic biliary tract. Critical issues in the post-transplantation period include the following: hypertension, renal dysfunction, hyperlipidemia and cardiovascular disease, obesity, osteoporosis and increased risk for cancer. Psychological issues are especially prominent and caregivers and family should be alert for signs of depression and anxiety. Many of the anti-rejection medications exacerbate these symptoms. With careful follow-up, OLT recipients can live productive lives for many years after transplantation. Chronic rejection, often in the setting of progressive ductopenia, and recurrence of primary pre-transplantation liver disease tend to cause graft failure with time. Actuarial survival at 5 years is approximately 88% for persons with cholestatic liver disease, 78% for patients with non-cholestatic liver disease who are HCV negative, and 70% for persons with HCV (Sartin '05: 954, 955).

A cornerstone of post-transplantation management is immunosuppression to prevent rejection of the transplant graft. The rejection response after liver transplantation most often occurs between postoperative days 4 and 10. Clinical manifestations of **acute rejection** include tachycardia, fever, right upper quadrant or flank pain, diminished bile flow through the T tube or a change in color of bile, and increasing jaundice. Laboratory findings include elevated serum bilirubin, transaminase and alkaline phosphatase levels and increased prothrombin time. Following the successful os of cyclosporine, a number of immunosuppressive drugs have appeared and provide several choices for improving outcome. **Immunosuppressives** may be broadly categorized into three groups: initial immunosuppression, maintenance immunosuppression, and management of acute cellular rejection. Prednisone is the primary posttransplantation immunosuppressive and is steadily tapered off in favor o maintenance drugs. The calcineurin inhibitors cyclosporine and tacrolimus are begun during induction and represent the mainstays of maintenance therapy. In many centers, tacrolimus has supplanted cyclosporine as the preferred immunosuppressive. Adjunctibe maintenance agents include either mycophenolate mofetil or the older drug aathiprine. Acute rejection is managed with infusion of either muromonab-CD3 (OKT#) or an interleukin-2 receptor blocker (e.g. basiliximab) (Sartin '05: 955). The introduction in 1980 of **cyclosporine** as an immunosuppressive agent contributed substantially to the improvement in survival after liver transplantation. Cyclosporine inhibits early activation of T cells and is specific for T cell functions that result form the interaction of the T cell with its receptor and that involve the calcium0duependent signal transduction pathway, as a result the activity of cyclosporine leads to inhibition of lymphokine gene activation, blocking interleukins 2, 3 and 4, tumor necrosis factor α as well as other lymphokines. Cyclosporine also inhibits B cell functions. This process occurs without affecting rapidly dividing cells in the bone marrow, which may account for the reduced frequency of postransplantation systemic infections. The most common and important side effect of cyclosporine therapy is nephrotoxicity. Cyclosporine causes dose-dependent renal tubular injury and direct renal artery vasospasm. Nephrotoxicity is reversible and can be managed by dose reduction. Other adverse effects of cyclosporine therapy include hypertension, hyperkalemia, tremor, hirsutism, glucose intolerance and gum hyperplasia (Dienstag '98: 1722).

Side effects limit the usefulness of all these drugs and are a main source of morbidity and mortality among transplant recipients. The main nonimmunological side effects of cyclosporine and tacrolimus are hypertension and renal insufficiency. Blood levels must be carefully monitored. Side effects of mycophenolate ofetil and azathioprine include bone marrow suppression with cytopenias. Problems with the acute antirejection infusions include hypersensitivity and cytokine reactions, and a heightened risk of opportunistic infection, especially cytomegalovirus, immediately after use. Among the many side-effects of prednisone are hypertension and hyperglycemia. The main consequence of all these treatment is immune suppression and increased risk for infection. Early infections are generally due to issues surrounding surgical technique and preexisting infection (e.g. cholangitis) and have declined significantly in recent years. They usually represent nosocomially acquired pathogens. Infections in the middle period from 1 to 6 months often represent viral infection or reactivation. Trimthoprim-sulfamethoxazole (Bactrim) is usually prescribed for prophyaxis against bacterial infection and *Pneumocystis carinii* for the first year. Of particular concern and the focus of several prophylactic strategies is cytomegalovirus. Cytomegalovirus occurs at a high rate among seronegative recipients who receive a liver from a seropositive recipient, and reactivation rates are significant as well. In the middle and later periods fungal infection is important, especially *Aspergillus* species, and lymphoproliferative disorder due to Epstein-Barr virus is seen. OLT recipients should be instructed to avoid exposure to environmental or food-borne mold, which could increase their risk for fungal infection. Another important preventive strategy is appropriate vaccinations, particularly annual influenza shots. Live virus vaccinations, such as varicella, yellow fever and so forth, should be avoided) (Sartin '05: 955).

Tacrolimus (originally labeled FK 506) is a macrolide lactone antibiotic isolated from a Japanese soil fungus, *Streptomyces tsukubaensis*. It has the same mechanism of action as cyclosporine but is 10 to 100 times more potent. Initially applied as "rescue" therapy for patients in whom rejection occurred despite the use of cyclosporine, tacrolimus has been shown in two large, multicenter, randomized trials to be associated with a reduced frequency of acute rejection, refractory rejection and chronic rejection. Although patient and graft survival are about the same with these two drugs, the advantage of tacrolimus is in minimizing episodes of rejection, reducing the need for additional glucocorticoid doses ad reducing the likelihood of bacterial and cytomegalovirus infection has simplified he management of patients undergoing liver transplantation. In addition, the oral absorption of tacrolimus is more predictable than that of cyclosporine, especially during the early postoperative period when T-tube drainage interferes with the enterohepatic circulation of cyclosporine. As a result, in most transplantation centers, tacrolimus has now supplanted cyclosporine for primary immunosuppression, and many centers rely on oral, rather than intravenous, administration from the outset. For transplantation centers that prefer cyclosporine, a new, better-absorbed, microemulsion preparation is now available. 1722 Although tacrolimus is more potent than cyclosporine, it is also more toxic and more likely to be discontinued for adverse events. The toxicity of tacrolimus is similar to that of cyclosporine; nephrotoxicity and neurotixicity are the most commonly encountered adverse effects, and neurotoxicity (tremors, seizures, hallucinations, psychoses, coma) is more likely and more severe in tacrolimus-treated patients. Both drugs can cause diabetes mellitus, but tacrolimus does not cause hirsuitism or gingival hyperplasia. Because of overlapping toxicity between cyclosporine and tacrolimus, especially nephrotoxicity and because tacrolimus reduces cyclosporine clearance, these two drugs should not be used together. Because 99 percent of tacrolimus is metabolized by the liver, hepatic dysfunction reduces its clearance; in primary graft non-function (when, for technical reasons or because of ischemic damage prior to its insertion, the allograft is defective and does not function normally form the outset) tacrolimus P450 (e.g. phytoin, phenobarbital, carbamazepine, rifampin) reduce available levels of cyclosporine,

fluconazole, ketoconazole, cltrimazole, itraconazole, verapamil, diltiazem, nicardipine, cimetidine, danazole, metoclopramide, bromocriptine) increase cyclosporine and tacrolimus blood levels. Like azathioprine, cyclosporine and tacrolimus appear to be associated with a risk of lymphoproliferative malignancies, which may occur earlier after cyclosporine and tacrolimus than after azathioprine therapy. Because of these side effects, combinations of cyclosporine or tacrolimus with prednisone and azathioprine – all at reduced doses – are preferable regimes for immunosuppressive therapy (Diesntag '98: 1722, 1723).

In patients with pretransplant **renal dysfunction** or renal deterioration that occurs intraoperatively or immediately postoperatively, tacrolimus or cyclosporine therapy might not be practical. Under these circumstances, induction or maintenance of immunosuppression with monoclonal antibodies to T cells, OKT3, may be appropriate. Therapy with OKT3 has been especially effective in reversing acut rejection in the posttransplant period and is the standard treatment for acute rejection that fails to respond to methylprednisolone boluses. Intravenous infusions of OKT3 may be complicated by transient fever, chills and diarrhea. When this drug is used to induce innunosuppression initially or to provide "rescue" in those who reject despite "conventional" therapy, the incidence of bacterial, fungal and especially cytomegalovirus infections is increased during and after such therapy. In some centers, ganciclovir antiviral therapy is initiated prophylactically as a routine along with OKT 3. Another immunosuppressive drug that is likely to be used in the future for patients undergoing liver transplantation is mycophenolic acid, a nonnucleoside purine metabolism inhibitor derived as a fermentation product form several *Penicillium* species. Mycophenolate has been shown to be better than azathioprine, when used with other standard immunosuppressive drugs, in prefventing rejection after renal transplantation and has ben approved for use in renal transplantation. Rapamycin, an inhibitor of later events in T cell activation is yet another drug undergoing experimental evaluation as an immunosuppressive agent. The most important principle of immunosuppression is that the ideal approach strikes a balance between immunosuppression and immunologic competence. Given sufficient immunosuppression, acute liver allograft rejection is always reversible; however, if the cumulative dose of immunosuppressive therapy is too large, the patient will succumb to opportunistic infection. Therefore, immunosuppressive drugs must be used judiciously , with stricft attention to the infectious consequences of such therapy (Diesntag '98: 1723).

Complications of liver transplantation can be divided into hepatic and nonhepatic categories. In addition, both immediately postoperative and late complications are encountered. Patients who undergo liver transplantation as a rule have been chronically ill for protracted periods and may be malnourished and wasted. The impact of such chronic illness and the multisystem failure that accompanies liver failulre continues to require attention in the postoperative period. Because of the massive fluid losses and fluid shifts that occur during the operatin, patients may remain fluid overloaded during the immediate postoperative period, straining cardiovascular reserve; this effect can be amplified in the face of transient renal dysfunction and pulmonary capillary vacular permeability. Other immediate management issues include renal dysfunction; prerenal azotemia, acute kidney injury associated with hypoperfusion (acute tubular necrosis), and renal toxicity caused by antivbiotics, tacrolumus or cyclosporine are frequently encountered int eh postoperative period, sometimes necessitating dialysis. Occasionally, postoperative intraperitoneal bleeding may be sufficient to increase intraabdominal pressure, which, in turn, many reduce renal blood flow – this effeft is rapidly reversible when abdominal distention is relieved y exploratory laparotomy to identify and ligate the bleeding site and to remove intraperitoneal clot. Anemia also may result from acute upper gastrointestinal bleeding or from

transient hemolytic anemia, which may be autoimmune, especially when blood group O livers are transplanted into blood group A or B recipients (Dienstag'98: 1723).

Bacterial, fungal or viral infections are common and may be life-threatening postoperatively. Early after transplant surgery, common **postoperative infections** predominate – pneumonia, wound infections, infected intraabdominal collections, urinary tract infections, and intravenous line infections – rather than opportunistic infections; these infection may involve the biliary tree and iver a well. Beyond the first postoperative month, the toll of immunosuppression becomes evident, and opportunistic infection – cytomegalovirus, herpes viruses, fungal infections (*Aspergillus, Candida*, cryptococcal disease) mycobacterial infections ,parasitic infections (Pneumocystis, Toxoplasma), bacterial infections (*Nocardia*, *Legionella*, and *Listeria*) predominate. Rarely, in early infections represent those transmitted with the donor liver, either infections present in the donor or infections acquired during procurement processing. De novo viral hepatitis infections acquired from the donor organ or from transfused blood products occur after typical incubation periods of these agents (well beyond the month). Obviously, infections in an immunosuppressed host demand early recognition and prompt management; prophylactic antibiotic therapy is administered routinely in the immediate postoperative period. Use of sulfamethoxazole with trimethoprim reduces the incidence of postoperative *Pneumocystis carinii* pneumonia. **Neuropsychiatric complications** include seizures (commonly associated with cyclosporine and tacrolimus toxicity), encephalopathy, depression and difficult psychosocial adjustment. Rarely, diseases are transmitted by the allograft from the donor to the recipient. In addition to viral and bacterial infections, malignancies of donor origin have occurred. Lymphoproliferative malignancies, especially B cell lymphoma, are a recognized complication associated with immunosuppressive drugs such as azathioprine, tacrolimus and cyclosporine. Epstein-Barr virus has been shown to play a contributory role in some of these tumors, which may regress when immunosuppressive therapy is reduced (Dienstag '98: 1723).

Hepatic dysfunction after liver transplantation is similar to the hepatic complications encountered after major abdominal and cardiothoracic surgery; however, in addition, there may be complications such as primary graft failure, vascular compromise, failure or obstruction of the biliary anastomoses, and rejection. As in non-transplant surgery, postoperative jaundice may result from prehepatic intrahepatic, and posthepatic sources. Prehepatic sources represent the massive hemoglobin pigment load from transfusions, hemolysis, hematomas, ecchymoses, and other collections of blood. Early intrahepatic liver injury includes effects of hepatotoxic drugs and anesthesia; hypoperfusion injury associated with hypotension, sepsis, and shock; and benign postoperative cholestasis. Late intrahepatic sources of liver injury include postransfusion hepatitis and recurrent primary disease. Posthepatic sources of hepatic dysfunction include biliary obstruction and reduced renal clearance of conjugated bilirubin. Hepatic complications unique to liver transplantation include primary graft failure associated with ischemic injury to the organ during harvesting; vascular compromise associated with thrombosis or stenosis of the portal vein or hepatic artery anastomoses; stenosis, obstruction or leakage of the anastomosed common bile duct; and rejection (Dienstag '98: 1723, 1724).

Despite the use of immunosuppressive drugs, **rejection** of the transplanted liver still occurs in a majority of patients, beginning 1 to 2 weeks after surgery. Clinical signs suggesting rejection are fever, right upper quadrant pain, and reduced bile pigment and volume. Leukocytosis may occur, but the most reliable indicators are increases in serum bilirubin and aminotransferase levels. Morphologic features of acute rejection include portal infiltration, bile duct injury and/or endothelial inflammation (endothelialitis), some of these findings are reminiscent of graft-versus-host disease and primary biliary cirrhosis. As soon as transplant rejection is suspected,

treatment consists of intravenous methylprednisolone in repeated boluses; if this fails to abort rejection, many centers use antibodies to lymphocytes, such as OKT3, or polyclonal antilymphocyte globulin. Chronic rejection is a relatively rare outcome that may follow repeated bouts of acute rejection or that occurs unrelated to preceding rejection episodes. Morphologically, chronic rejection is characterized by progressive cholestasis, focal parenchymal necrosis, mononuclear infiltration, vascular lesions (intimal fibrosis, subintimal foam cells, fibrinoid necrosis) and fibrosis. This process may be reflected as ductopenia, the vanishing bile duct syndrome. Reversibility of chronic rejection is limited; in patients with therapy-resistant chronic rejection, re-transplantation has yielded encouraging results (Dienstag '98: 1724).

The **survival rate** for patients undergoing liver transplantation has improved steadily since 1983. One-year survival rates have increased from approximately 70 percent in the early 1980s, to 80 to 90 percent in the mid – 1990s. Currently, the 5-year survival rate approaches 60 percent. Survival after re-transplantation for primary graft non-function is approximately 50 percent. Causes of failure of liver transplantation vary with time. Failures within the first 3 months result primarily from technical complications, postoperative infections and hemorrhage. Transplant failures after the first 3 months are more likely to result from infection, rejection, or recurrent disease (such as malignancy or viral hepatitis). The recurrence of autoimmune hepatitis or primary sclerosing cholangitis has not been reported. There have been reports of recurrent primary biliary cirrhosis after liver transplantation; however the histologic features of primary biliary cirrhosis and acute rejection are virtually indistinguishable and occur as frequently in patients with primary biliary cirrhosis as in patients undergoing transplantation for other reasons. Patients who undergo liver transplantation for chronic hepatitis B plus D have a better survival rate than patients undergoing transplantation for hepatitis B alone. Recurrence of hepatitis C virus (HCV) after liver transplantation can be documented in almost every patient and about 5 to 10 percent of patients have sufficiently severe recurrent hepatitis C to merit antiviral therapy with interferon. Patients who undergo liver transplantation for end-stage alcoholic cirrhosis are at risk of resorting to drinking again after transplantation, a potential source of recurrent alcoholic liver injury. Currently alcoholic liver disease is one of the most common indication for liver transplantation and most transplantation centers screen candidates carefully for predictors of continued abstinence. Recidivism is more likely in patients whose sobriety prior to transplantation was shorter than 6 months. Full rehabilitation is achieved in the majority of patients who survive the early postoperative months and escape chronic rejection or unmanageable infection. Psychosocial maladjustment interferes with medical compliance in a small number of patients, but most manage to adhere to immunosuppressive regimen, which must be continued indefinitely. In one study, 85 percent of patients who survived their transplants returned to gainful activities. In fact, some women have conceived and carried pregnancies to term after transplantation without demonstrable injury to their infants (Dienstag '98: 1724, 1725).

14. Pancreatitis

Inflammation of the pancreas, almost always associated with acinar cell injury, is termed **pancreatitis**. Acute pancreatitis includes a mild, self-limited form and a more serious type, acute hemorrhagic pancreatitis, which exhibits extensive hemorrhagic necrosis of the organ. Chronic pancreatitis is the process of continuous or relapsing inflammation of the pancreas, typically causing pain and leading to irreversible morphologic damage and permanent impairment of function. Acute pancreatitis is defined as an acute condition, typically presenting with abdominal pain and associated with raised levels of pancreatic enzymes (especially amylase and lipase) in the blood or urine. Pancreatic inflammation is usually accompanied by edema and limited necrosis of pancreatic tissue. In its severe form acute hemorrhagic pancreatitis, or "necrotizing pancreatitis" there is extensive fat necrosis in and about the pancreas and in other intra-abdominal fatty depots, and hemorrhage into the parenchyma of the pancreas. About 80% of cases are associated with biliary tract disease and alcoholism. Gallstones are present in 35 to 60% of cases and about 5% of patients with gallstones develop pancreatitis. The percent of acute pancreatitis caused by alcoholism varies from 65% in the United States to 20% in Sweden and 5% or less in southern France and England. The male-to-female ratio is 1:3 in the group with biliary tract disease and 6:1 in those with alcoholism. Acute hemorrhagic pancreatitis represents about 5% of all cases of acute pancreatitis (Crawford and Cotran '94: 899-899).

Acute pancreatitis is a frequent cause of acute abdominal pain. Repeated vomiting is common. In a severe attack excretory duct inflammatory change leads to subsequent inflammation of the pancreatic lobule, leading on to necrosis of adjacent pancreatic parenchyme. Between 30-60% of patients have associated gallstones and 10-50% will recently have drunk an excess of alcohol. More rarely, acute pancreatitis follows an abdominal operation or blunt abdominal trauma and it occasionally complicates hypotension due to septicemia or myocardial infarction. Fat necrosis manifests as multiple small white plaques on the peritoneal surface of organs near the pancreas, may lead to hemorrhage, which is the most serious complication, if there is no secondary infection, erosion of pancreatic tissue may lead to extravasation of secretions into the lesser sac, producing a pancreatic pseudocyst in 5-10% of patients, in half of whose disease spontaneously regresses whilst the remainder require drainage. The diagnosis of acute pancreatitis should be suspected in all patients admitted with acute upper abdominal pain and it is customary to estimate the **serum amylase** in all such patients. The normal level is 70-300 international units/l, and values above 1200 units strongly support the diagnosis. A urinary amylase level in excess of 3000 units/l (normal 300-1500) is a valuable confirmation of the diagnosis. Severe pancreatitis is present if any three of the following measurements are positive: (1) WBC> $15{,}000/mm^3$, (2) glucose > 10 mmol/l (no diabetic history), (3) urea > 16 mmol/l (no improvement on i.v. fluids, (4) PaO^2 < 60 mmHg (8 kPa), (5) calcium < 2.0 mmol/l, (6) albumin < 32 g/l), (7) lactic dehydrogenase > 600 units/l, (8) aspartate transaminase > 200 units/l. The differential diagnosis of sudden severe epigastric pain is acute pancreatitis, spontaneous rupture of the oesophagus, perforated peptic ulcer, acute cholcystitis, high para-colic acute appendicitis, myocardial infarction, pneumonia and pleurisy, traumatic rupture of spleen or liver, or high jejunal strangulating obstruction. In 70% of patients acute pancreatitis runs a benign course. Gradual restoration or diet to normal, the avoidance of alcohol, elimination of gallstones by Stonebreaker (*Chanca piedra*) or early surgical removal of gallstones results in survival of 99% of patients, however a severe attack carries a mortality rate of 20%. Respiratory failure is the major hazard and the cause of 65% of deaths (Jones et al '85: 104-106).

Chronic pancreatitis is generally caused by ductal obstruction by concretions, resulting from (1) alcohol induced alterations in acinar and ductal secretions and in the biosynthesis of lithostathine (pancreatic stone protein) that normally inhibits intraluminal precipitation of calcium carbonates, yet is the main constituent of pancreatic stones or (2) interstitial fat necrosis

and hemorrhage which initiate a sequence of perilobular fibrosis, duct distortion, and altered pancreatic secretion and ductal flow, the "necrosis-fibrosis" hypothesis (Crawford '94: 903). Other less common causes of pancreatitis are (1) rising antibody titers to the mumps and coxsackie viruses and to Mycoplasma pneumonia; (2) the helminth parasits Ascaris lumbricoides and Clonorchis sinensis are capable of occluding pancreatic ducts; (3) acute ischemia may be induced by vascular thrombosis, embolism, vasculitis (polarteritis nodosa, systemic lupus erythematous, Henoch-Shonlein purpura) and shock; (4) many drugs cause abdominal pain and elevated serum amylase levels, implicated in causing pancreatic injury are thiazide, diuretics, azathioprine, estrogens, sulfonamides, furosemide, pantamidine, and procainamide (5) pancreatitis is occasionally associated with hyperlipopreinemia (types I and V) and with hyperparathyroidism and other hypercalcemic states and (6) 10 to 20% of cases have no known cause and must be considered idiopathic. Incomplete fusion of the two pancreatic anlagen as a congenital birth defect creates pancreas divisum and predisposes to recurrent pancreatitis. The pancreas may be totally absent (agenesis), or the exocrine and endocrine elements may be hypoplastic and exist as two separate structures. The head of the pancreas may encircle the duodenum as a collar (annular pancreas). Aberrant or ectopic, displaced pancreatic tissue is found in about 2% of careful routine postmortem examinations, usually in the stomach, duodenum, jejunum, Meckel's diverticulum and the ileum. About 2% of islet cell tumors arise in ectopic pancreatic tissue (Crawford and Cotran '94: 903, 898-899).

The frequency of chronic pancreatitis in a community is proportional to alcohol consumption. **Alcohol** increases the protein content of pancreatic juice, with precipitation of protein plus, leading to obstruction and focal distal dilatation of the small drainage ducts. There may be calcification and sometimes stone formation within the ducts. Ultimately, severe destruction, fibrosis and atrophy lead to gross distortion of the gland, with pain and loss of function. Most patients present with pain, usually in the epigastrium or upper quadrants, radiating to the back. Acute severe attacks may supervene upon more chronic pain, often associated with eating. The combined effects of fear of eating, alcohol abuse and malabsorption lead to weight loss in 90% of patients. **Diabetes** occurs in 75% of patients. Biliary obstruction and cholangitis may be present. Distinction from carcinoma of the pancrease, especially where weight-loss is pronounced, may be difficult. Impaired glucose tolerance indicates severe damage to the gland. Correction of malabsorption is easy. This is managed directly by oral administration of pancreatic extract with antacids, and indirectly by the addition of fat-soluble vitamin supplements and medium-chain triglyceride oil preparations. Analgesics may be required. The surgical treatment of the pain of chronic pancreatitis rests on two approaches, the first is internal drainage of an obstructed main pancreatic duct, often into a loop of jejunum, or a sphincteroplasty on the ampulla of Vater may allow removal of stones from the pancreatic duct. The second approach is resection of the most diseased area of pancreas, ranging from distal pancreatectomy to pancreatico-duodenectomy (Whipple's operation) and rarely to subtotal or total pancreatectomy. Another approach is to block the sensory nerves around the coeliac axis with carefully placed injections of 50% alcohol or phenol, but the beneficial effects rarely last more than a few months (Jones et al '85: 106-109).

Cystic fibrosis (mycovisciododi, fibrocystic disease of pancrease) is by far the common cause of pancreatic disease in childhood and is possibly the commonest lethal single-gene disease. It is transmitted as an autosomal recessive trait and the incidence is of the order of 1 in 1500-1800 live births in the West. Treatment is wholly supportive, and death usually supervenes from the respiratory complications during adolescence or early adulthood. The pancreas is from birth hard and knobbly with fibrosis and cystic dilatation of the ducts. Cirrhosis of the liver is a later feature. The lungs are normal at birth but repeated infection with produces bronchitis,

bronchiectasis, fibrosis, emphysema and cor pulmonale. Almost all patients eventually develop an almost ineradicable pulmonary infection with *Pseudomonas auruginosa* (Jones et al '85: 106-109). **Non-neoplastic cysts** are infrequent, except when following chronic pancreatitis, in which case they are inflammatory pseudocysts. Pancreatic cysts range in size from microscopic lesions to 3 to 5 cm in diameter. The cysts are usually enclosed in a thin, fibrous capsule and are filled with a clear-to-turbid mucoid or serous fluid. In the rare entity von Hippel-Lindau disease angiomas are found in the retina and cerebellum or brain stem in association with cysts in the pancreas, liver and kidney. Pseudocysts produce abdominal pain, hemorrhage and infection with generalized peritonitis. **Cystic tumors** comprise 5% of all pancreatic neoplasms. The only way of distinguishing the entirely benign form (mucinous cystadenoma) from its malignant counterpart (cystadenocarconoma) is by histologic assessment following complete surgical removal, usually by distal pancreatectomy (Crawford and Cotran ’94: 905).

Pancreatic cancer accounts for 5% of all cancer deaths in the United States. There are 28,000 new cases and 26,000 deaths from the disease each year. The rates are higher in blacks than whites, males than females, diabetics and incidence of hereditary pancreatitis. The incidence of pancreatic cancer is threefold that of 60 years ago. The risk is 1.5 times greater in smokers, there is a positive correlation between cancer mortality and consumption of fats and meat and (30 there is a two-to-fivefold long-term increased risk of pancreatic cancer following partial gastrectomy. These lesion may arise anywhere in the pancreas most commonly the head of pancreas (60%), body of pancreas (15 to 20%) and tail of pancreas (5%). In 20% the tumor is diffuse or has spread. Tumors at the head of pancreas impinge on the ampulla of Vater, common bile duct and duodenum and thus cause obstructive biliary symptoms relatively early. Jaundice is present in about 90% of patients with carcinomas of the head and in 10 to 40% of those with cancer of the body or tail. One year survival is less than 20% and 5 year survival only 3% (Crawford and Cotran ’94: 905).

Carcinoma of the pancreas is the third commonest cause of cancer death, taking the lives of an estimated 22,000 each year, and incidence is steadily increasing in Western countries, in conjnnction with an increase in diabetes, and is particularly unresponsive to treatment. Carcinoma of the pancreas is usually a well-differentiated adenocarcinoma arising from duct epithelium and 60-70% arise in the head of the gland. As a consequence, the lower end of the bile duct is usually involved, causing obstruction and jaundice. Spread to adjacent organs, lymph nodes, and the liver is common. Carcinomas in the head are usually silent until the patient becomes jaundiced. When the carcinoma arises in the body or tail, the patient generally presents with persistent deep epigastric pain, and jaundice is rare. Very few carcinomas of head of the pancreas are removable but jaundice can nearly always be relieved by cholecytst-jejunostomy, which allows the distended biliary tree to be decompressed via the cystic duct and gall bladder. Two methods of anastomosis are used. Some carcinomas are already invade in the duodenal loop at the time of laparotomy, and then a gastrojejunostomy must also be done to forestall the development of complete duodenal obstruction. Rarely, and early localized carcinoma of the pancreas can be treated like a carcinoma of the ampulla or lower end of the bile duct by radical pancreatico-duidenectomy (**Whipple's operation**). The prognosis, even with a drainage operation is very limited, usually 6-9 months. Neither chemotherapy nor radiotherapy have proved helpful. Carcinoma of the body and tail are never suitable for radical resection although palliative excision occasionally eases back pain (Jones et al '85: 111, 112). There is believed to be a 30% 5 year survival rate.

Islet cell tumors are rare in comparison to tumors of the exocrine pancreas. Beta-cell tumors are the most common of islet cell tumors and may be responsible for the elaboration of sufficient

insulin to induce clinically significant hypoglycemia. Analysis of pancreatic islet lesions inducing hyperinsulinism indicates that about 70% are solitary adenomas, approximately 10% are multiple adenomas, 10% are metastasizing tumors that must be interpreted as carcinomas, and the remainder are a mixed group of diffuse hyperplasia of the islet and adenomas occurring in ectopic pancreatic tissue. The insulinomas vary in size from minute lesions that are difficult to find on the dissecting table to huge masses of over 1500 gm. Five percent of insulinomas are malignant. **Zollinger-Ellison Syndrome** (Gastrinoma) is classically composed of the triad of recalcitrant peptic ulcer disease, gastric hypersecretion, and pancreatic islet cell tumor. Although most common in the pancreas, 10 to 15% of gastrinomas occur in the duodenum. Serum gastrin levels are elevated and indeed hypergastrinemia can point to the presence of early gastrinomas before the development of disease. Approximately 60% of gastrinomas are malignant and only 40% are benign. Spread to the lymph nodes or metastasis mark the tumors as malignant. Diarrhea is often sufficiently extreme to cause serious problems in fluid and electrolyte control, and many patients develop malabsorption syndromes (Crawford and Cotran '94: 922, 923, 924).

Alpha-cell tumors (glucagonomas) are associated with increased serum levels of glucagon and a syndrome consisting of mild diabetes mellitus, a characteristic migratory necrotizing skin erythema and anemia. They occur most frequently in peri and post-menopausal women and are characterized by extremely high plasma glucagon levels. **Delta cell tumors** (somatostatinomas) are associated with diabetes mellitus, cholelithiasis, steatorrhea, and hypochlorhydria. They are exceeding difficult to detect preoperatively. High plasma somatostatin levels are requires for diagnosis. VIPoma (diarrheogenic islet cell tumor) is an islet cell tumor that induces a characteristic syndrome of watery diarrhea, hypokalemia, and achlorhydria (the WDHA syndrome) caused by release vasoactive intestinal polypeptide (VIP) from the tumor. **Pancreatic carcinoid tumors** producing serotonin and an atypical carcinoid syndrome are exceedingly rare. **Pancreatic polypeptide-secreting islet cell tumors** are endocrinologically asymptomatic, despite the presence of high levels of hormone plasma. Some pancreatic and extra-pancreatic tumors produce two or more hormones, usually simultaneously and occasionally in sequence. In addition to insulin, glucagon, and gastrin, islet cell tumors produce adrenocorticotropic hormone (MSH, vasopressin, norephinephrine, and serotonin. These are called multi-hormonal tumors (Crawford and Cotran '94: 922, 923, 924).

The majority of patients with **carcinoma of the pancreas** present with unresectable (incurable) malignancy. However, up to 20% of carefully screened patents can undergo a laparotomy with the expectation of a radical resection. Of those patients who undergo such a resection, perhaps 20% will be cured, resulting in an overall 4% or 5% cure rate. Of course, radical surgery (such as a Whipple procedure), is associated with an operative mortality of at least 5%, and morbidity. The median survival for all patients treated with radical surgery alone is approximately 11 months. Radiation therapy and 5-fluorouracil (5-FU) may be beneficial. Supervoltage radiation is given in fractions of 200 cGy/ day, five times per week, with a 2-week rest period, before the second 2000 cGy is given for a total dose of 4000 cGy. A 1 month rest period after the completion of radiation is followed by weekly 5-FU (500 mg/m^2) therapy for a total treatment time of 2 years. Patients undergoing this combined modality approach had a median survival of approximately 21 months. The 2 year survival for this combination therapy group is 46%, with about 25% of the patients alive at 5 years with no evidence of disease. Toxicities include malaise, hematotoxicity, mucositis, and diarrhea. For unresectable patients a combination of radiation therapy and chemotherapy for local palliation is used. Conventional external irradiation results in a median survival of approximately 16 weeks. The combination of radiation and chemotherapy yields a median survival of 40 weeks. 5-FU is the most effective chemotherapeutic agent. Investigators have attempted to combine drugs to improved efficacy,

such as 5-FU, mitomycin-C, streptozotocin and doxorubicin. Objective partial response rates range between 5% and 35%, with median survivals ranging from 9 to 26 weeks. Without any demonstrated improvements with combination therapy 5-FU alone is the most appropriate chemotherapy choice for pancreatic cancer (Friedman '90: 243, 244).

Among the most common pancreatic endocrine tumors are **insulinomas** (insulin-producing islet cell tumors). They are usually seen in adults in the fourth to sixth decades of life. The diagnosis of insulinoma is confirmed by the finding of an elevated insulin concentration relative to hypoglycemia. In most patients, this finding will be obtained after a 24-hour fast – levels below 60 mh/dl^2 indicateEighty percent of insulinomas are benign and are cured by surgical resection. If an insulinoma is suspected or proven, measurement of serum alpha-human choirionic gonadotropin (HCG) levels may aid in indicating the presence of a malignant islet cell tumor. An elevated HCG is seen only in malignant disease, but does not rule out carcinoma **Gastrinomas** are gastrin-producing islet cell tumors responsible for the Zollinger-Ellison syndrome which consists of fulminant peptic ulcer disease caused by excessive production of gastrin. Approximately two thirds of the cases sporadic and one third genetic. Most of the sporadic gastrinomas are malignant, while most of the MEN-linked tumors are benign, usually small, and often in multiple locations. The most common site remains the pancrease, but extrapancreatic gastrinomas have been reported. Other primary sites include the duodenal wall, stomach, jejunum and even lymph nodes. For insulinomas, if the tumor is malignant and has metastasized beyond the possibility of surgical cure, medical management includes dietary changes such as smaller, more frequent meals, or increased carbohydrates, hyperglycemia is severe. Diazoxide in doses of 300 mg to 800 mg daily inhibits release of insulin and also has a peripheral hyperglycemic effect, a benzothiadizine diuretic should be given with diazoxide. Propranolol and glucocorticoids have also been used (Kelsen '90: 317, 320).

15. Diabetes mellitus

Diabetes mellitus is a non-communicable disease. The probability of dying from any of the four main non- communicable diseases – cardiovascular diseases, cancers, chronic respiratory diseases and diabetes – between the ages of 30 and 70 was 18 per cent in 2016. The risk remains markedly higher for men globally, at 21.6 per cent, compared with 15 per cent for women (Guterres '19: 10). SDG 3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being. Despite the minute size of the islets of Langerhans the endocrine pancreas is responsible for a disproportionate amount of morbidity and mortality. Diabetes mellitus ranks among the top ten causes of death in Western nations (Porterfield '01: 98, 99). In the United States the number of new cases of Diabetes mellitus has nearly doubled in the fifteen years since the atypical antipsychotic Olanzapine (Zyprexa), known to cause both diabetes and fatal diabetic episodes when mixed with alcohol, was marketed by Eli Lilly, the same company that manufactures insulin (Humulin), in 1994. On some Native American reservations 60% of the population has diabetes. In the United States an estimated 23.6 million children and adults, 7.8% of the population, had diabetes in 2008. While an estimated 17.9 million had been diagnosed with diabetes, 5.7 million people (or nearly one quarter) were unaware that they had the disease and another 57 million have pre-diabetes. An estimated 177 million people are affected by diabetes world-wide, the majority by type 2 diabetes. Two-thirds live in the developing world. The rate of new cases of diabetes has increased by about 90 percent in the United States over the past decade. From 1995 to 1997, newly diagnosed cases of diabetes were at 4.8 per 1,000 annually. Between 2005 and 2007, that number rose to 9.1 per 1,000 people. An estimated 90 percent to 95 percent of the new cases are type 2 diabetes. Diabetes and pre-diabetes have skyrocketed

among the nation's youth, jumping from 9 percent of the adolescent population in 2000 to 23 percent in 2008. An estimated 50 percent of Type 1 juvenile onset diabetics die within 20 years of diagnosis. With an annual toll of more than 144,000 deaths diabetes mellitus was the seventh leading cause of death in the United States in 2010. It is estimated that 2 to 3% of the adult population in the United States had diabetes mellitus in 1994 (Crawford and Cotran '94: 909, 910) rising to 7% in 2010.

To prevent obliteration of Islets of Langerhans it is important that children and adults, except women in the first trimester of pregnancy, definitively treat non-*Staph* bacterial and protozoal pancreatitis with **metronidazole**. Methicillin resistant *Staphylococcus aureus* (MRSA) is treated with doxycycline or clindamycin for children under the age of 8 and pregnant women. Diet and exercise may cure people with pre-diabetes. Diabetic symptoms are treated on a mealtime basis, to avoid coma, gangrene and/or death. Hyperinflation in injectable insulin prices must be redressed by Medicaid. A number of oral anti-diabetic drugs have been developed to treat specific conditions, mostly involving Type II diabetes. Diabetes mellitus is characterized by hypoglycemia, polyuria, polydipsia and polyphagia. **Hypoglycemia**, or high blood glucose concentration, occurs because when the I/G ratio is low, glucose uptake and utilization are decreased, as is liver glucose production. **Polyuria** refers to excessive urine production. As serum glucose levels rise, glucose is presented to the renal tubules (filtered load) at a rate that exceeds the glucose tubular maximum (Tm). **Polydipsia**, or increased thirst, is a result of the dehydration that results from the osmotic diuresis **Polyphagia**, or excessive eating, occurs because the areas of the hypothalamus that regulate appetite (ventrolateral and ventromedial nuclei) have insulin –sensitive transport system. Many diabetic symptoms resemble those associated with starvation. **Ketoacidosis** is caused by excessive ketone body production that is a symptom of IDDM that results from both low serum insulin levels and high (relative to blood glucose) glycagon levels. Net protein loss occurs because insulin is need for normal amino acid uptake into cells and protein synthesis. When insulin is deficient, there is a net shift of potassium from the intracellular compartment to the extracellular compartment and potassium is lost in the urine. Diabetic ketoacidosis is serious consequence of poorly controlled IDDM. It is characterized by elevated blood glucose level, ketonemia, increased serum osmolarity and elevated stress hormone levels. A **nonketotic hyperosmolar coma** can occur with either IDDM or NIDDM. People with nonketotic hyperosmolar coma have extremely high serum hyperosmolarity and glucose due to characteristic extreme dehydration. Administering excessive amounts of **insulin**, known as insulin shock, can lead to hypoglycemia, which can cause confusion, convulsions, loss of consciousness and even death (Porterfield '01: 99-101).

There are two types of diabetes type I and II. **Insulin-dependent diabetes mellitus** (IDDM) also called Type I diabetes, juvenile onset and ketosis-prone diabetes. Juvenile onset diabetes accounts for 10 to 20% of all cases of idiopathic diabetes. Non-insulin dependent diabetes mellitus (NIDDM) also called **type II diabetes** and adult onset diabetes accounts for 80 to 90% of all cases. Type II diabetes is divided into obese and non-obese types and third rare form, known as **maturity-onset diabetes of the young** (MODY) that manifests as a mild hyperglycemia and is transmitted as an autosomal dominant trait. While the two major types of diabetes have different pathologic mechanisms and metabolic characteristics, the chronic, long-term complications in blood vessels, kidneys, eyes, and nerves occur in both types and are the major causes of morbidity and mortality in diabetes. Diabetes can result from excessive amounts of **hormones** antagonistic to insulin. These antagonistic hormones include cortisol, GH, epinephrine, glucagon, oral contraceptives, progesterone, and human placental lactogen (hPL). A diabetic patients requires more insulin during periods of stress because the stress hormones (cortisol, GH, epinephrine, glucagon) are elevated. The **diabetogenicity of pregnancy** is

thought to result from high levels of hPL, estrogen and progesterone. In some instances, abnormal forms of insulin are secreted by the beta cells; in other cases, receptor function is compromised. Diabetes can also be caused by a post-receptor defect that increases insulin response (Porterfield '01: 98, 99).

Type I and II Diabetes

	Type I	Type II
Clinical	Onset <20 years; Normal weight, decreased blood insulin, Islet cell antibodies, Ketoacidosis common	Onset >30 years; Obese; Normal or increased blood insulin; No islet cell antibodies; Ketoacidosis rare
Genetics	50% concordance in twins; HLA-D linked	90-100% concordance in twins; No HLA association
Pathogenesis	Autoimmunity; Immunopathologic mechanisms; Severe insulin deficiency	Insulin resistance; Relative insulin deficiency
Islet cells	Insulitis early; Marked atrophy and fibrosis; Beta-cell depletion	No insulitis; Focal atrophy and amyloid; Mild-beta-cell depletion

Source: Crawford and Cotran ’94: Table 19-3, 909

Type 1 diabetes is a disease that involves many genes. Depending on locus or combination of loci, they can be dominant, recessive, or somewhere in between. The strongest gene, IDDM1, is located in the MHC Class II region on chromosome 6, at staining region 6p21. Certain variants of this gene increase the risk for decreased histocompatibility characteristic of type 1. Such variants include DRB1 0401, DRB1 0402, DRB1 0405, DQA 0301, DQB1 0302 and DQB1 0201, which are common in North Americans of European ancestry and in Europeans. Some variants also appear to be protective. The risk of a child developing type 1 diabetes is about 10% if the father has it, about 10% if a sibling has it, about 4% if the mother has type 1 diabetes and was aged 25 or younger when the child was born, and about 1% if the mother was over 25 years old when the child was born. Environmental factors can influence expression of type 1. For identical twins, when one twin had type 1 diabetes, the other twin only had it 30%–50% of the time. Despite having exactly the same genome, one twin had the disease, whereas the other did not; this suggests environmental factors, in addition to genetic factors, can influence the disease's prevalence. Other indications of environmental influence include the presence of a 10-fold difference in occurrence among Caucasians living in different areas of Europe, and a tendency to acquire the incidence of the disease of the destination country for people who migrate.

Some chemicals and drugs selectively destroy pancreatic cells. Pyrinuron (Vacor, N-3-pyridylmethyl-N'-p-nitrophenyl urea), a rodenticide introduced in the United States in 1976, selectively destroys pancreatic beta cells, resulting in type 1 diabetes after accidental or intentional ingestion. Vacor was withdrawn from the U.S. market in 1979, but is still used in some countries. Zanosar is the trade name for streptozotocin, an antibiotic and antineoplastic agent used in chemotherapy for pancreatic cancer; it kills beta cells, resulting in loss of insulin production. Other pancreatic problems, including trauma, pancreatitis or tumors (either malignant or benign), can also lead to loss of insulin production. One theory proposes that type 1 diabetes is a virus-triggered autoimmune response in which the immune system attacks virus-

infected cells along with the beta cells in the pancreas. The Coxsackie virus family or rubella is implicated, although the evidence is inconclusive. In type 1, pancreatic beta cells in the islets of Langerhans are destroyed, decreasing endogenous insulin production. This distinguishes type 1's origin from type 2. The type of diabetes a patient has is determined only by the cause—fundamentally by whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1). The new theory posited in this work pertaining to the obliteration of the pancreas by an antibiotic resistant bacteria requires vindication with a course of metronidazole (Flagyl ER).

Type I **insulin dependent diabetes mellitus** (IDDM) begins by age 20 years in most patients, it is dominated by signs and symptoms emanating from the disordered metabolism – polyuria, polydipsia, polyphagia and ketoacidosis. The plasma insulin is low or absent and glucagon levels are increased. Glucose intolerance is of the unstable or brittle type and is quite sensitive to administered exogenous insulin, deviations from normal dietary intake, unusual physical activity, infection, or other forms of stress. Inadequate fluid intake or vomiting may lead to disturbances in fluid and electrolyte balance. Thus, these patients are vulnerable, on the one hand, to hypoglycemic episodes and, on the other, to ketoacidosis. Infection may precipitate these conditions and, indeed, may precede the first manifestations of diabetes in some patients. Fortunately, these metabolic hazards are avoidable with proper insulin therapy. IDDM (type I diabetes) results from a severe, absolute lack of insulin caused by a reduction in the beta-cell mass. The pathophysiology in diabetes type 1 is a destruction of beta cells in the pancreas, regardless of which risk factors or causative entities have been present. Patients depend on insulin for survival, without insulin, they develop acute metabolic complications such as ketoacidosis and coma. Three interlocking mechanisms are responsible for the islet cell destruction: genetic susceptibility, autoimmunity and an environmental insult. Among identical twins the concordance rate is only 50% and only 5 to 10% of children of first order relatives with IDDM develop the overt disease. As many as 90% of patients with type I diabetes have circulating islet cell antibodies (ICA) when tested within a year of diagnosis. Approximately 10% of persons who have type I diabetes also have other organ-specific autoimmune disorders, such as Grave's disease, Addison's disease, thyroiditis, and pernicious anemia. There is a great deal of evidence suggesting that environmental factors are involved in triggering diabetes. Finnish children have a 60 to 70 fold increased risk of type I diabetes compared to Korean children. In the northeastern United States between 1960 and 1990 there was been a tripling of type I diabetes in children younger than 15 years of age (Crawford and Cotran'94: 913-914).

Viruses are suspected as initiators of this disease where there are seasonal trends in the diagnosis of new cases, often corresponding to the prevalence of common viral infection in the community. The viral infections implicated include mumps, measles, rubella, coxsackie B virus, and infectious mononucleosis. Direct virus- induced injury is rarely severe enough to cause diabetes mellitus. The most likely scenario is that viruses cause mild beta-cell injury, which is followed by an autoimmune reaction against altered beta cells in persons with HLA linked susceptibility. About 20% of patients infected with congenital rubella go on to develop the disease in childhood or puberty. Virus-associated IDDM appears to be a rare outcome of some relatively common viral infections and is probably the result of an opportunistic antibiotic resistant bacterial infection thereof. A number of chemical toxins, including streptozotocin, alloxan, and pentamidine, also induce islet cells destruction in animals. In humans, pentamidine, a drug used for the treatment of parasitic infections, has been occasionally associated with the development of abrupt onset diabetes, and cases of diabetes have also been reported after accidental or suicidal ingestion of Vacor, a pharmacologic agent used as a rate exterminator. Children who ingest cow's milk early in life have an incidence of IDDM higher than that of breast-fed children

(Crawford and Cotran'94: 914). Sometimes a diabetic patient will awaken in the morning with hyperglycemia, even before eating. One cause of this preprandial hyperglycemia is the Somogyi effect, which results from nocturnal hypoglycemia that stimulates secretion of the stress or counterregulatory hormones (glucagon, cortisol, GH and epinephrine) that act to elevate blood glucose. People with this problem generally need a lower nighttime insulin dose. The dawn phenomenon is thought to be a result of sleep-induced GH secretion that antagonizes insulin's effect, thereby producing hyperglycemia. This problem can sometimes be prevented by administering the evening insulin dose at bedtime rather than at dinnertime (Porterfield '01: 104). While there is no cure for type 2 (or type 1) diabetes, pre-diabetes can often be completely reversed with proper medical intervention and changes in lifestyle.

Chronic hyperglycemia is a major contributing factor towards almost all possible complications with diabetes, specifically hypoglycemia, kidney failure, blindness, diabetic neuropathy, gangrene and heart problems. **Hypoglycemia**, trickily refers to high blood glucose concentration, that occurs because when the I/G ratio is low, glucose uptake and utilization are decreased, as is liver glucose production. A majority carbohydrate diet of strictly whole grains and no table sugar is necessary to stabilize blood glucose levels. Two kinds of home blood **glucose monitoring** exist. The first type uses a reagent strip. The second type uses a reagent strip and glucose meter. Use of the glucose meter has become more common due to higher reliability than strips alone. Glucose and ketoacidosis can also be measured in the urine but no longer has a significant role in home testing. Ketoacidosis is a serious but preventable complication from inadequate treatment of diabetes. This dangerous condition is identified by testing for urinary ketones. People with diabetes should visit their health care professional every three months to monitor their hemoglobin A1c levels and to discuss their treatment plan.

Reagent strips are saturated with glucose oxidase, an enzyme that interacts with glucose. When a drop of blood is placed on the strip, the glucose oxidase chemically reacts with the blood glucose. The resultant reaction changes the color of the strip. The higher the glucose level, the greater the reaction, so the more dramatic the color change. The blood glucose level can be determined by comparing the color of the strip with a color chart. For accurate results, test strips should be stored at room temperature and away from moisture. To protect the strips from moisture, bottles should be closed after use. The disadvantage of reagent strips alone is that they do not give an exact glucose measurement. They are accurate enough, however, to alert patients to seriously high or low levels of glucose. Examples of reagent strips available over–the–counter (OTC) are Chemstrip bG and Glucostix.

To determine a more accurate blood glucose level, the reagent strip must be combined with a **blood glucose meter**, which involves taking a small lancet to poke a finger. Usually, this testing is performed just off to the side of the finger's tip, although some meters do allow testing at other sites, such as the forearm. Then, a small quantity of blood is placed on a testing strip that has been inserted into a meter that reports the glucose value. The meter reads the blood glucose level from the reagent strip. Results obtained using a glucose meter are more accurate than those obtained without the meter (that is, with reagent strips alone). However, the results using a home meter vary as much as 20% from the more accurate measurements in a hospital or clinical laboratory. Portable meters are accurate enough, however, for home monitoring and self-adjustment of insulin doses. It is important to know that reagent strips are calibrated for specific meters. Most meters need to be calibrated once a new box of test strips is used. Inappropriate calibration will lead to errors in glucose readings. Using incompatible strips and meters will give unreliable glucose readings. Errors can also be caused when: meters are improperly calibrated;

the meter is dirty; the battery in the meter is dead; reagent strips are stored improperly; the reagent strips have expired; not enough blood is applied to the reagent strip; blood is not left on the reagent strip long enough, or is left too long, before reading; the test is performed under the wrong conditions of temperature and humidity; or patients are dehydrated. The following general guidelines for normal blood glucose ranges in nondiabetics are from the American Diabetes Association. However, there are variations to these guidelines. For example, young children, those who are newly diagnosed, or are beginning insulin pump therapy may have slightly different target ranges. There are also tests for gestational diabetes in pregnant women.

Morning Fasting Blood Glucose

Fasting Glucose Ranges	Indication
From 70 to 99 mg/dL, or 3.9 to 5.5. mmol/L	Normal glucose tolerance, not diabetic
From 100 to 125 mg/dL, or 5.6 to 6.9 mmol/L	Impaired fasting glucose (IGF) or Pre-diabetes
126 mg/dL or higher, or 7.0 or higher	Diabetes

Source: American Diabetes Association 2018

Blood glucose levels higher than normal, but lower than diabetic ranges, classify a person as having impaired glucose tolerance. To see how a person reacts to a glucose load an oral glucose tolerance test (OGTT) may be given to check blood glucose levels 2 hours after being given 75 grams of glucose to drink. If two or more tests show blood glucose higher than the normal ranges above, gestational diabetes will be diagnosed. A 75-gram glucose load may be used but may not be as reliable as the 100-gram glucose test. Blood is not drawn at the 3-hour mark if the 75 gram test is done. Both IFG and impaired glucose tolerance (IGT) are associated with an increase risk in developing type 2 diabetes and lifestyle changes, including weight loss and an exercise program, as well as possible oral medications such as Glucophage are sometimes indicated.

Oral Glucose Tolerance Test Ranges
(except during pregnancy)

2 Hours after drinking 75 grams of glucose	Indication
Less than 140, or 7.8 mmol/L	Normal glucose tolerance, not diabetic
From 140 to 200 mg/dL, or 7.8 to 11.1 mmol/L	Impaired glucose tolerance (IGT), or Pre-diabetes
Over 200 mg/dL, or 11.1 or higher on more than one occasion	Diabetes

Source: American Diabetes Association 2018

Urinary glucose only estimates blood glucose values roughly, and it provides no information at all unless there is glucose in the urine. Glucose appears in the urine when the blood glucose level is over 180 mg/dL, well above the target for most patients. Below that level, urinary glucose is usually negative. Urinary glucose levels should not be confused with checking urinary

microalbumin and protein levels. These tests are performed in the doctor's office at least annually, provide necessary information about kidney function. There are two types of urine glucose tests. Both types rely on a chemical reaction that produces a color change. These tests use either tablets or strips. Generally, the test strip or tablet is placed in urine. The resulting color change is matched against a color chart provided by the manufacturer, which shows the different colors produced by different levels of glucose. The first type, called the copper reduction test, uses cupric sulfate (for example, Clinitest). In the presence of glucose, cupric sulfate (which is blue) changes to cuprous oxide (green to orange). The reaction should be observed closely and the manufacturer's instructions closely followed. The copper reduction tests can react with substances other than glucose in the urine, leading to false positive results. This means the test erroneously shows glucose when it is not present. Examples of these other substances include aspirin, penicillin, isoniazid (Nydrazid, Laniazid), vitamin C, and cephalosporin-type antibiotics. Tablets and solutions utilizing copper reduction may damage the skin and are poisonous if ingested. They should be handled carefully and kept out of the reach of children. The second type of urine glucose test, called the glucose oxidase test, uses the chemical toluidine and the enzyme glucose oxidase (for example, Clinistix). Glucose oxidase converts the glucose in urine to gluconic acid and hydrogen peroxide. The interaction of the hydrogen peroxide with the toluidine causes a change in color. False negative results (meaning the test shows no glucose when glucose really is present) may occur in patients taking vitamin C, aspirin, iron supplements, levodopa (Sinemet), and tetracycline-type antibiotics. Glucose oxidase tests are more convenient to use and less expensive than copper reduction tests. The strips should be kept away from moisture.

Ketone testing is an important part of monitoring in type 1 diabetes. It is a tool that is often also used in pregnancies that are complicated by diabetes. If the reading is below 0.6 mmol/L you are in the normal range. If the number is between 0.6 to 1.5 mmol/L is in this range ketones are present in the blood, which may develop into a problem if not treated. Readings above 1.5 mmol/L indicate a greater risk for developing ketoacidosis (DKA). A healthcare provider should be consulted. Readings above 3.0 mmd/L may warrant a trip to the nearest emergency room for immediate treatment. Ketones are formed when one fasts (for example, sleeping overnight) or when there is a profound lack of insulin. When the body produces an insufficient amount of insulin, the cells are unable to remove glucose from the blood, and the level of glucose in the blood rises. The cells respond to what appears to be a lack of glucose by stimulating the body to produce larger amounts of glucose. Rising blood glucose level causes more urination and dehydration. In addition, ketones are produced by the liver due to low insulin levels. The presence of ketones signals a condition in diabetics called ketoacidosis. Ketoacidosis signifies that the cells are not getting enough insulin. Severe diabetic ketoacidosis is a medical emergency, since it can result in loss of consciousness and even death. There is a correlation between high blood glucose levels, dehydration, and ketones. The higher the glucose level, the more likely that ketones will be made. Therefore, patients with diabetes with blood glucose levels over 240 mg/dL should test promptly for urinary ketones. Patients with type 1 diabetes should test for ketones during any acute illness and during severe stress. Also, urinary ketones should be checked if any symptoms of ketoacidosis occur (such as nausea, vomiting, abdominal pain).

Ketones can normally be found in the urine. For example, after an overnight fast, ketones can be seen in up to 30% of people without diabetes. However, these levels of ketone production are usually below the threshold of measurement by the ketone test strips. The strips can also give false positive results when patients are on drugs such as captopril (Capoten). False-negative readings may be seen if the test strips are old, exposed to air, or if the urine is very acidic (such as after drinking a lot of orange juice, which is also high in vitamin C). These tests are based on

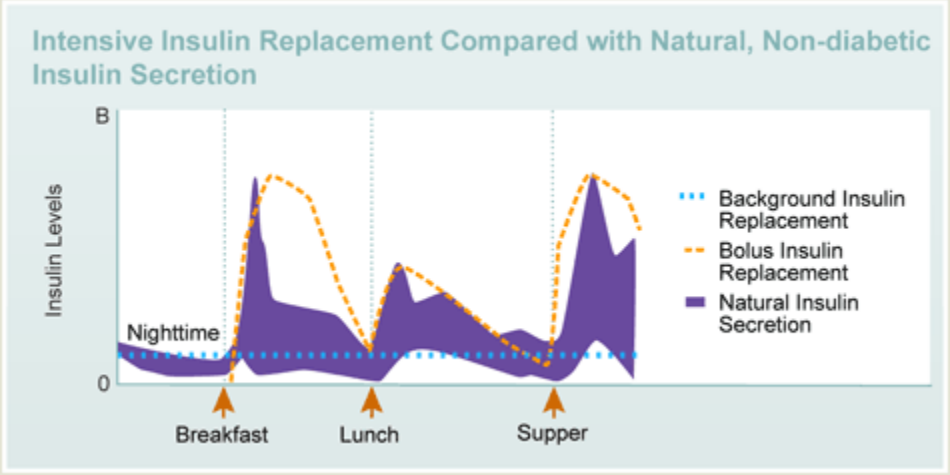
the color change that occurs when ketones react with sodium nitroprusside or similar compounds. The tests are performed in a manner similar to that of urinary glucose testing. Different tests detect the three types of ketones (acetoacetic acid, acetone, and ß-hydroxybutyric acid). For example, Acetest only detects acetoacetic acid and acetone, but not ß-hydroxybutyric acid. Ketostix detects only acetoacetic acid, which can produce false-negative results if only acetone and ß-hydroxybutyric acid are present in the urine. Ketone tests are supplied as strips or tablets. The American Diabetes Association advises that ketone testing materials be available in the office setting and that physicians should prefer using blood ketone measurements over urine ketone measurements if possible. Home testing for blood ketones is also available, though not often used due to higher cost of the test strips (Ferry '14). Most people can tell if they are 'ketotic' by the foul smelling breath that occurs when the body runs out of nutrition and metabolizes its own tissue. Diabetic ketoacidosis (DKA) can eventually cause unconsciousness, from a combination of severe hyperglycemia, dehydration, shock, and exhaustion. Coma only occurs at an advanced stage, usually after 36 hours or more of worsening vomiting and hyperventilation but can also occur much sooner for many reasons. Treatment of DKA consists of intravenous fluids to stabilize the circulation, and intravenous saline with potassium and other electrolytes to replace deficits. Insulin will also be given and the patient will need careful monitoring for complications.

The **hemoglobin A1c test** (HbA1c) is crucial to monitor blood glucose control in patients with diabetes. In brief, hemoglobin A1c refers to the final product of several chemical reactions that occur in the bloodstream as red blood cells are exposed to glucose. A red blood cell typically lives for about three months, so the HbA1c reading provides a report card averaging the prior three months blood sugar levels. The A1C test result is reported as a percentage. The higher the percentage, the higher a person's blood glucose levels have been. A normal A1C level is below 5.7 percent. Many different methods are available to determine the HbA1c level. Regardless, HbA1c level has been shown to predict the risk for developing complications of diabetes, much in the same way that cholesterol levels are predictive of heart disease. The HbA1c test should be performed routinely at three-month intervals in established patients with diabetes. The HbA1c can be tested when a new case of adult diabetes is suspected, although its use to diagnose borderline pediatric diabetes is still debatable. To measure HbA1c, blood obtained in the usual way (from a vein) and can be sent to a laboratory. Alternatively, many clinics specialized in diabetes care now have desktop HbA1c machines, which will read a simpler fingerstick blood sample within minutes. A few conditions can affect HbA1c measurements, most related to problems with red blood cells. For example, results may be falsely low if too few red cells are present (anemia). Falsely low readings can occur when red blood cells lose their proper shape (as with conditions like thalassemias, sickle cell disease, or spherocytosis). The HbA1c is a valuable tool to individualize patient care plans so that glycemic goals can be achieved (Ferry '14).

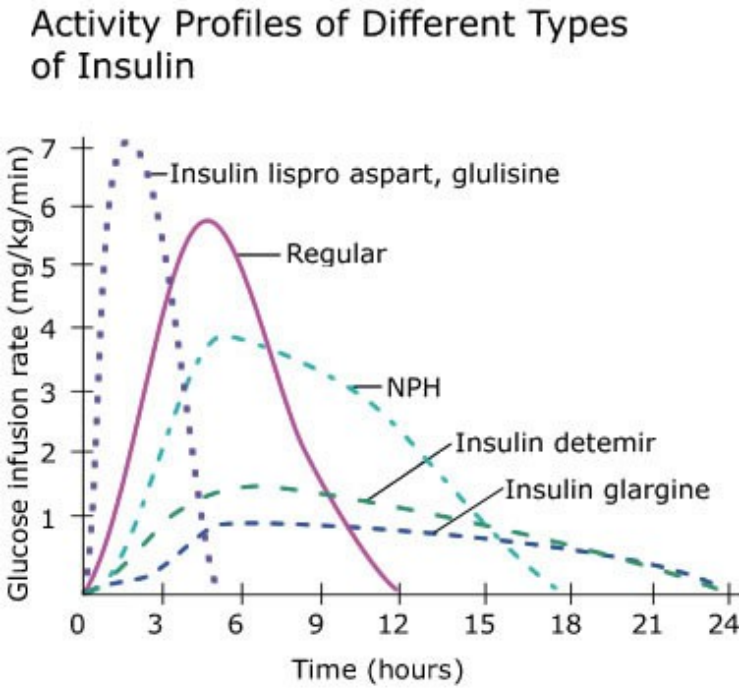
Insulin is a naturally-occurring hormone secreted by the pancreas. Insulin is required by the cells of the body in order for them to remove and use glucose from the blood. From glucose the cells produce the energy that they need to carry out their functions. Researchers first gave an active extract of the pancreas containing insulin to a young diabetic patient in 1922, and the FDA first approved insulin in 1939. Currently, insulin used for treatment is derived from beef and pork pancreas as well as recombinant (human) technology. The first recombinant human insulin was approved by the FDA in 1982. Brands of Insulin (Humulin, Humulin 70/30, Humulin 70/30 Pen, Humulin 50/50, Humulin L, Humulin N, Humulin R, Humulin U Ultralente, Novolin, Novolin 70/30, Novolin 70/30 Innolet, Novolin 70/30 PenFill, Novolin N, Novolin R). Patients with diabetes mellitus have a reduced ability to take up and use glucose from the blood, and, as a result, the glucose level in the blood rises. In type 1 diabetes, the pancreas cannot produce

enough insulin. Therefore, insulin therapy is needed. In type 2 diabetes, patients produce insulin, but cells throughout the body do not respond normally to the insulin. Nevertheless, insulin also may be used in type 2 diabetes to overcome the resistance of the cells to insulin. By increasing the uptake of glucose by cells and reducing the concentration of glucose in the blood, insulin prevents or reduces the long-term complications of diabetes, including damage to the blood vessels, eyes, kidneys, and nerves. Insulin is administered by injection under the skin (subcutaneously). The subcutaneous tissue of the abdomen is preferred because absorption of the insulin is more consistent from this location than subcutaneous tissues in other locations.

Insulin is required in all patients with type 1 diabetes mellitus, and mandatory in the treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic states. The American Diabetes Association (ADA) and many clinicians recommend the use of physiologically based, *intensive* insulin regimens (i.e., 3 or more insulin injections daily with dosage adjusted according to the results of multiple daily blood glucose determinations [e.g., at least 4 times daily]. In general, adjust dosage of insulin based on blood and urine glucose determinations and carefully individualize to attain optimum therapeutic effect. Administer into the thighs, upper arms, buttocks, or abdomen using a 25- to 28-gauge needle, one-half to five-eighths inch in length. Insulin (regular) (i.e., purified pork insulin) generally is given sub-Q in a dosage of 2–4 units, 15–30 minutes before meals and at bedtime no change in dosage usually is required when transferring to human insulin, Initiate replacement therapy at an insulin dosage of 0.5–1 units/kg daily given sub-Q in divided doses ((2/3) of the daily dosage in the morning [(1/3) as short-acting insulin, (2/3) as intermediate-acting insulin] and (1/3) in the evening [½ as short-acting insulin, ½ as intermediate-acting insulin]). In pediatric patients with newly diagnosed diabetes mellitus, may administer 0.1–0.25 units/kg of regular insulin every 6–8 hours during the first 24 hours to determine insulin requirements. The major goal in treating diabetes is to minimize any elevation of blood sugar (glucose) without causing abnormally low levels of blood sugar. Type 1 diabetes is treated with insulin, exercise, and a diabetic diet. Type 2 diabetes is treated first with weight reduction, a diabetic diet, and exercise. When these measures fail to control the elevated blood sugars, oral medications are used. If oral medications are still insufficient, treatment with insulin is considered. Adherence to a diabetic diet is an important aspect of controlling elevated blood sugar in patients with diabetes. The American Diabetes Association (ADA) has provided guidelines for a diabetic diet. The ADA diet is a balanced, nutritious diet that is low in fat, cholesterol, and simple sugars. The total daily calories are evenly divided into three meals. In the past two years, the ADA has lifted the absolute ban on simple sugars. Small amounts of simple sugars are allowed when consumed with a complex meal. Exercise increases or decreases the blood glucose levels depending on the concentration of glucose and insulin in the blood at the time of the exercise. If blood glucose is low or normal, exercise may cause hypoglycemia (low blood glucose) due to the utilization of glucose by the active muscles. On the other hand, exercise may cause hyperglycemia (high blood glucose), if there isn't enough insulin to allow the active muscles to utilize blood glucose (Ferry ’14).



Intensive insulin therapy tries to duplicate the body's natural pattern of insulin secretion. With intensive insulin therapy you need a low steady amount of insulin overnight, while fasting and between meals as illustrated by the dashed line. The ultimate goal of insulin therapy is to mimic normal insulin levels. Unfortunately, current insulin replacement therapy can only approximate normal insulin levels. Insulin therapy for type 1 diabetes requires multiple injections or using an insulin pump (continuous subcutaneous insulin infusion – CSII). Natural insulin (i.e. insulin released from your pancreas) keeps blood sugar in a very narrow range. Overnight and between meals, the normal, non-diabetic blood sugar ranges between 60-100mg/dl and 140 mg/dl or less after meals and snacks. At mealtime, a little insulin is released at the first smell or chew of the food. This gets the body ready to receive the sugar load from the meal. Then, as food is digested, the sugar levels rise which causes a surge of insulin. The insulin levels rapidly climb and peak in about 45 minutes to 1 hour before falling back to the background or basal levels. The situation is different when one has diabetes and is getting insulin replacement therapy. How much carbohydrate are going to be eaten and how much insulin will be needed must be calculated. And one must try to mimic natural overnight, fasting (or between meals) and mealtime insulin release with injected insulin. Basal replacement controls glucose overnight and between meals by keeping fat in fat tissue and curbing glucose production from the liver. Provides a low, continuous level of insulin. Basal replacement can be a long-acting insulin, which you inject once or twice daily such as the insulin analogs, insulin glargine, insulin detemir and NPH. Or basal replacement can be a rapid-acting insulin continuously infused under the skin, using an insulin pump. Represents about 50% or half of the body's daily insulin requirements. There are two kinds of bolus replacement: Mealtime Bolus – to cover the carbohydrate in the meal or snack. High Blood Sugar Correction Bolus – provides extra insulin to return the blood sugar back to the target level when your blood sugar is too high. Bolus Insulin is usually provided by a rapid-acting insulin analogs, such as insulin aspart, insulin Lyspro, and insulin glulisine or Regular insulin. Represents about 10% to 20% of the daily insulin requirement at each meal, or about 50% of the body's daily insulin needs.



Insulins are categorized by differences in: Onset (how quickly they act), Peak (how long it takes to achieve maximum impact), Duration (how long they last before they wear off), Concentration (Insulins sold in the U.S. have a concentration of 100 units per ml or U100. In other countries, additional concentrations are available. Route of delivery (whether they are injected under the skin or given intravenously), Insulin is usually injected into the fatty tissue just under the skin. This is also called subcutaneous tissue. Fast-acting insulin is absorbed quickly from your fat tissue (subcutaneous) into the bloodstream and is used to control the blood sugar during meals and snacks and to correct high blood sugars. Rapid Acting Insulin Analogs (Insulin Aspart, insulin Lyspro, Insulin Glulisine) which have an onset of action of 5 to 15 minutes, peak effect in 1 to 2 hours and duration of action that lasts 4-6 hours. With all doses, large and small, the onset of action and the time to peak effect is similar, The duration of insulin action is, however, affected by the dose – so a few units may last 4 hours or less, while 25 or 30 units may last 5 to 6 hours. As a general rule, assume that these insulins have duration of action of 4 hours. Regular Human Insulin has an onset of action of 1/2 hour to 1 hour, peak effect in 2 to 4 hours, and duration of action of 6 to 8 hours. The larger the dose of Regular, the faster the onset of action, but the longer the time to peak effect and the longer the duration of the effect. Relative to the rapid-acting insulin analogs, Regular human insulin has undesirable features, such as a delayed onset of action, and variable peak and duration of action when it is injected under the skin. Because of this, fewer and fewer medical providers are prescribing Regular insulin. The delayed onset of action is the reason you have to inject the insulin and wait before eating. And the variable duration of action predisposes to low blood sugars long after the meal is over. Intermediate-acting insulin is absorbed more slowly, and lasts longer. It is used to control the blood sugar overnight, while fasting and between meals, it includes NPH Human Insulin which has an onset of insulin effect of 1 to 2 hours, a peak effect of 4 to 6 hours, and duration of action of more than 12 hours. Very small doses will have an earlier peak effect and shorter duration of action, while higher doses will have a longer time to peak effect and prolonged duration. NPH (Neutral Protamine Hagedorn) is a longer-acting human insulin that is used to cover blood sugar between meals, and to satisfy overnight insulin requirements. A fish protein, protamine, has been added to the Regular human insulin to delay its absorption. This long acting insulin is a cloudy suspension that needs to be remixed thoroughly before each injection. Because NPH is a suspension of different sized crystals, it has a very unpredictable absorption rate and action. This results in more frequent low and high blood sugars. The use of NPH has declined with the availability of other long-acting insulin options, specifically, the long-acting insulin analogs, insulin glargine and insulin detemir. Long-acting insulin is absorbed slowly, has a minimal peak effect, and a stable plateau effect that lasts most of the day and is used to control the blood sugar overnight, while fasting and between meals. Long acting insulin analogs (Insulin Glargine, Insulin Detemir)

have an onset of insulin effect in 1 1/2-2 hours. The insulin effect plateaus over the next few hours and is followed by a relatively flat duration of action that lasts 12-24 hours for insulin detemir and 24 hours for insulin glargine. Novolog or another rapid-acting injectable insulins are self injected about 15 minutes before mealtime. Short-acting insulins **s**uch as regular insulin, should be taken 30 to 60 minutes before a meal. Intermediate-acting insulins should be taken up to 1 hour prior to a meal. Pre-mixed insulins, depending on the product used, premixed solutions should be taken 10 minutes or 30 to 45 minutes before mealtime. Injections of long-acting insulins are not "timed" to mealtime because of their long duration of action. Levemir is taken once or twice a day irrespective of mealtime. Lantus is only administered once a day (and should be administered at the same time each day). Finally, the rapid-acting products can also be taken immediately after a meal (rather than 15 minutes before mealtime). Brands of Insulin (Humulin, Humulin 70/30, Humulin 70/30 Pen, Humulin 50/50, Humulin L, Humulin N, Humulin R, Humulin U Ultralente, Novolin, Novolin 70/30, Novolin 70/30 Innolet, Novolin 70/30 PenFill, Novolin N, Novolin R). Humulin is a registered trademark of Eli Lilly & Co. and Novolin of Novo Nordisk a Danish firm with offices in North America.

Type of Insulin & Brand Names	Onset	Peak	Duration	Role in Blood Sugar Management
Rapid-Acting				
Humalog or lispro	15-30 min.	30-90 min	3-5 hours	Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is often used with longer-acting insulin.
Novolog or aspart	10-20 min.	40-50 min.	3-5 hours	
Apidra or glulisine	20-30 min.	30-90 min.	1-2½ hours	
Short-Acting				
Regular (R) humulin or novolin	30 min. -1 hour	2-5 hours	5-8 hours	Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes
Velosulin (for use in the insulin pump)	30 min.-1 hour	2-3 hours	2-3 hours	
Intermediate-Acting				
NPH (N)	1-2 hours	4-12 hours	18-24 hours	Intermediate-acting insulin covers insulin needs for about half the day or overnight. This type of insulin is often combined with rapid- or short-acting insulin.
Long-Acting				
Long-acting insulin covers insulin needs for about one full day. This type of insulin is often combined, when needed, with rapid- or short-acting insulin.				
	Lantus (insulin glargine)	1-1½ hour	No peak time; insulin is delivered at a steady level	20-24 hours
	Levemir (insulin	1-2 hours	6-8 hours	Up to 24 hours

	detemir)			
Pre-Mixed*				
Humulin 70/30	30 min.	2-4 hours	14-24 hours	These products are generally taken two or three times a day before mealtime.
Novolin 70/30	30 min.	2-12 hours	Up to 24 hours	
Novolog 70/30	10-20 min.	1-4 hours	Up to 24 hours	
Humulin 50/50	30 min.	2-5 hours	18-24 hours	
Humalog mix 75/25	15 min.	30 min.-2½ hours	16-20 hours	
*Premixed insulins are a combination of specific proportions of intermediate-acting and short-acting insulin in one bottle or insulin pen (the numbers following the brand name indicate the percentage of each type of insulin).				

Source: Medscape

About 10% of the population over 70 have type II **non-insulin dependent diabetes mellitus** (NIDDM). The underlying causes are largely unidentified genetic factors and the effects of a Western lifestyle- obesity and overeating. There is an inverse relationship between NIDDM and a high level of physical activity. Genetic factors are important and among identical twins the concordance rate is over 90%. Unlike type I however the disease is not linked to any HLA haplotype (except for a weak linkage in Pima Indians). Two metabolic defects that characterize NIDDM are (1) derangement in insulin secretion that is insufficient relative to the glucose load and (2) an inability of peripheral tissues to respond to insulin (insulin resistance) (Crawford and Cotran '94: 922, 914). Early in the course of type II diabetes, insulin secretion appears to be normal and plasma insulin levels are not reduced. However subtle defects in beta cells can be demonstrated. In normal persons, insulin secretion occurs in a pulsatile or oscillatory pattern, whereas in patients with type II diabetes, the normal oscillations of insulin secretion are lost. At about the same time when fasting blood sugars reach 115 gm/mL the rapid first phase of insulin secretion is triggered by glucose is obstructed. This impaired insulin secretion is caused by chronic hyperglycemia, referred to as glucose toxicity. Most patients with type II diabetes have a relative or absolute deficiency of insulin. However, this insulin deficiency is milder than type I diabetes and is not an early feature of this variant of diabetes. There is abundant evidence that insulin resistance is a major factor in the pathogenesis of type II diabetes. In both obesity and pregnancy, insulin sensitivity of tissues decreases. Hence either obesity of pregnancy may unmask subclinical type II diabetes by increasing the insulin resistance. Obesity is an extremely important diabetogenic influence, and, not surprisingly, approximately 80% of type II diabetes patients are obese. In addition to insulin resistance in peripheral tissues, there is increased glucose production in the liver, further aggravating the hyperglycemia (Crawford and Cotran '94: 915).

Type II diabetes (NIDDM) may also present with polyuria and polydipsia, but unlike type I diabetes, the patients are often older (over 40 years) and frequently obese. In some cases

medical attention is sought because of unexplained weakness or weight loss. Frequently, however, the diagnosis is made by routine blood or urine testing in asymptomatic individuals. Although patients with type II diabetes also have metabolic derangements, these are usually relatively mild and controllable, and so this form of the disease is not often complicated with ketoacidosis unless intercurrent infection or stress imposes new burdens. In both forms of long-standing diabetes, atherosclerotic events such as myocardial infarction, cerebrovascular accidents, gangrene of the leg, and the microangiopathic complications (nephropathy, retinopathy, neuropathy) are the most threatening and most frequent concomitants. Diabetics are also plagued by an enhanced susceptibility to infections, such as tuberculosis, pneumoconiosis, pyelonephritis, and those affecting the skin. Collectively, such infections cause the deaths of about 5% of diabetic patients. A trivial infection in a toe may be the first event in a long succession of complications (gangrene, bacteremia, and pneumonia) that ultimately lead to death. It is hoped that islet cell transplantation, will lead to a cure for diabetes mellitus. Studies show that good, early control of hyperglycemia prevents or ameliorates some of the complications of diabetes (Crawford and Cotran ’94: 922). Insulin is prepared commercially from extracts of beef and swine pituitaries. All oral anti-diabetic drugs are prepared synthetically. The sulfonylureas, which are derivatives of sulfanilamide, stimulate the pancreas to produce insulin and affect hepatic enzymes so that glycogen deposition is increased. More than 200 species of plants are listed in folklore for the treatment of diabetes (Lewis and Elvin-Lewis ’77: 218).

Since antiquity, diabetes has been treated with **plant medicines**. Recent scientific investigation has confirmed the efficacy of many of these preparations, some of which are remarkably effective. Only those herbs that appear most effective, are relatively non-toxic and have substantial documentation of efficacy were covered by Holistic online, most of the rare ones were corroborated by Reader’s Digest. Onion (Allium cepa) and garlic (Allium sativum) have significant blood sugar lowering action. The principal active ingredients are believed to be allyl propyl disulphide (APDS) and diallyl disulphide oxide (allicin), although other constitutents such as flavonoids may play a role as well. Experimental and clinical evidence suggests that APDS lowers glucose levels by competing with insulin for insulin-inactivating sites in the liver. This results in an increase of free insulin. APDS administered in doses of 125 mg/ kg to fasting humans was found to cause a marked fall in blood glucose levels and an increase in serum insulin. Allicin doses of 100 mg/kg produced a similar effect. Onion extract was found to reduce blood sugar levels during oral and intravenous glucose tolerance. The effect improved as the dosage was increased; however, beneficial effects were observed even for low levels that used in the diet (eg., 25 to 200 grams). The effects were similar in both raw and boiled onion extracts. Onions affect the hepatic metabolism of glucose and/or increases the release of insulin, and/or prevent insulin's destruction. The additional benefit of the use of garlic and onions are their beneficial cardiovascular effects. They are found to lower lipid levels, inhibit platelet aggregation and are antihypertensive. So, liberal use of onion and garlic are recommended for diabetic patients.

Experimental and clinical studies have demonstrated the antidiabetic properties of fenugreek (Trigonela foenum-graecum) seeds. The active ingredient responsible for the antidiabetic properties of fenugreek is in the defatted portion of the seed that contains the alkaloid trogonelline, nicotinic acid and coumarin. A decoction of the leaves of the blueberry (Vaccinium myrtillus) has a long history of folk use in the treatment of diabetes. The compound myrtillin (an anthocyanoside) is apparently the most active ingredient. Upon injection it is somewhat weaker than insulin, but is less toxic, even at 50 times the 1 g per day therapeutic dose. A single dose can produce beneficial effects lasting several weeks. Blueberry anthocyanosides also increase capillary integrity, inhibit free-radical damage and improve the tone of the vascular system. In

Europe, it is used as an anti-haemorrhagic agent in the treatment of eye diseases including diabetic retinopathy. Asian ginseng is commonly used in traditional Chinese medicine to treat diabetes. It has been shown to enhance the release of insulin from the pancreas and to increase the number of insulin receptors. It also has a direct blood sugar-lowering effect. A recent study found that 200 mg of ginseng extract per day improved blood sugar control as well as energy levels in Type 2 diabetes (NIDDM). Bilberry may lower the risk of some diabetic complications, such as diabetic cataracts and retinopathy. Stevia has been used traditionally to treat diabetes. Early reports suggested that stevia might have beneficial effects on glucose tolerance (and therefore potentially help with diabetes), although not all reports have confirmed this. Even if stevia did not have direct antidiabetic effects, its use as a sweetener could reduce intake of sugars in such patients. Ginkgo biloba extract may prove useful for prevention and treatment of early-stage diabetic neuropathy. Cinnamon triples insulin's efficiency Barberry - One of the mildest and best liver tonics known. Dosage: tincture, 10-30 drops; standard decoction or 3-9 g.

Pterocarpus marsupium (Indian Kino, Malabar Kino, Pitasara, Venga) tree is the source of the Kino of the European pharmacopeas. The gum-resin looks like dried blood (Dragon's blood), much used in Indian medicine. This herb has a long history of use in India as a treatment for diabetes. The flavonoid, (-)-epicatechin, extracted from the bark of this plant has been shown to prevent alloxan-induced beta cell damage in rats. Both epicatechin and a crude alcohol extract of Pterocarpus marsupium have actually been shown to regenerate functional pancreatic beta cells. No other drug or natural agent has been shown to generate this activity. Bitter Melon (Momordica charantia) also known as balsam pear, is a tropical vegetable widely cultivated in Asia, Africa and South America, and has been used extensively in folk medicine as a remedy for diabetes. The blood sugar lowering action of the fresh juice or extract of the unripe fruit has been clearly established in both experimental and clinical studies. Bitter melon is composed of several compounds with confirmed anti-diabetic properties. Charantin, extracted by alcohol, is a hypoglycaemic agent composed of mixed steroids that is more potent than the drug tolbutamide which is often used in the treatment of diabetes. Momordica also contains an insulin-like polypeptide, polypeptide-P, which lowers blood sugar levels when injected subcutaneously into type 1 diabetic patients. The oral administration of 50-60 ml of the juice has shown good results in clinical trials. Excessively high doses of bitter melon juice can cause abdominal pain and diarrhea. Small children or anyone with hypoglycemia should not take bitter melon, since this herb could theoretically trigger or worsen low blood sugar, or hypoglycemia. Furthermore, diabetics taking hypoglycemic drugs (such as chlorpropamide, glyburide, or phenformin) or insulin should use bitter melon with caution, as it may potentiate the effectiveness of the drugs, leading to severe hypoglycemia. Gymnema Sylvestre (Gurmar, Meshasringi, Cherukurinia) assists the pancreas in the production of insulin in Type 2 diabetes. Gymnema also improves the ability of insulin to lower blood sugar in both Type 1 and Type 2 diabetes. It decreases cravings for sweet. This herb can be an excellent substitute for oral blood sugar-lowering drugs in Type 2 diabetes. Some people take 500 mg per day of gymnema extract.

The national epidemic of type 2 diabetes, obesity, and heart disease is the price for a diet that is too rich for a sedentery lifestyle. Exercise works for everyone, and is how to avoid the most lethal complication of type 2 diabetes, early death from heart disease. Diet and exercise can control type 2 diabetes. Although people usually think diabetes is caused by a lack of insulin, the hormone that lowers blood sugar, more often than not the disease is characterized by too much rather than too little insulin. In fact, nine out of ten cases in the United States are type 2 (adult-onset) diabetes, which typically starts out with high insulin levels. But people are usually

more familiar with the less-common type 1 (insulin-requiring) diabetes, because it is an immediate threat to life. Half of people with type 2 diabetes. Too much body fat sets the stage for type 2 diabetes by decreasing the body's ability to use insulin. Extra fat is the result of taking in more calories than we burn, which means that too much food and too little exercise are big contributors to type 2 diabetes. But not everyone with a spare tire gets type 2 diabetes, genetic also plays a role. It appears the genetic tendency is not all that rate. Type 2 diabetes is widespread in industrialized nations, such as the United States, the United Kingdom, and Finland, whereas nations with third world economies, as in parts of Asia and Africa, do not have such epidemics. Type 2 diabetes occurs as a country advances technologically, when people come out of the fields and sit behind desks. It's almost a sign of coming of age, in Saudi Arabia, for example, when oil money started flowing in the late sixties and seventies, there was an increase in the occurrence of type 2 diabetes. Too much food and too little activity are pushing more and more people with the underlying tendency for type 2 diabetes over the edge. A richer food supply leads to new health problems (Hiser '99: ix, 1, 2).

Before the Industrial Revolution, food was often scarce, and what was available did not always provide the balance of nutrients needed to prevent deficiency diseases. In nineteenth-century England, for example. Hundreds of thousands of children died of malnutrition. Among the poor. Bread, potatoes, and porridge provided the bulk of the calories. Those who survived on the poverty line diet often suffered from scurvy, a deficiency of vitamin C form the lack of fresh fruits and vegetables, rickets, from lack of sunlight and vitamin D, and tuberculosis, a bacterial infection that thrives in a malnourished host. The diet of American settlers was one of subsistence based on easily transportable foods that would keep. The typical meal in Laura Ingalls Wilder's memoir: Little House on the Prairie consisted of coffee, cornmeal cakes and salt pork. After the Civil War and the Industrial Revolution, the need to provide more food for the expanding population spawned a wave of technological advances. By the 1890s there were improved canning, flour milling, plant breeding, and refrigeration techniques as well as new disease-resistant varieties of wheat and the first gasoline-driven tractors. In the 1920s Clarence Birdseye introduced a method for freezing produce, by the 1960s there was high-powered machinery, new fertilizers and pesticides, poultry raised in completely controlled environments, new breeds of heat-resistant cattle, McDonald's burgers and fries, and the heart disease epidemic. In 1983, one in four Americans was overweight, in 1995, it became one in three. From 1958 to 1993, the incidence of type 2 diabetes tripled. All in all, it has taken about a hundred years for over-nutrition to become as big a killer as under-nutrition (Hiser '99: 2-4).

Type 2 diabetes is so common because the body of today works the same way as did for prehistoric ancestors of humans. The environment, including what is eaten and lifestyle, is different. But the bodily systems for managing energy and nutrients evolved through natural selection during a time when survival of the fit meant being able to stay alive on as little food as possible. From about 3.5 million years ago to 8,000 B.C. humans were completely at the mercy of nature. As members of wandering groups, humans had to stay on the move to find food, because they had not yet developed the knowledge to plant seeds and wait for the harvest. Humans hunted, fished and gathered food to stay alive Even after humans learned to plant crops and domesticate animals, great famines wiped out entire populations. But it was during the period of hunting and gathering that our finely tuned physiology evolved, allowing our ancestors survive periods of starvation. And key to their survival was the ability to store energy in the form of body fat. Fat is dense, compact and transportable, exactly the type of stored fuel needed to stay on the move in search of the next meal. Pre-humans who were most efficient in storing body fat had the distinct advantage over others who were less efficient, because they could live for longer periods of time without eating. Human brains are hard-wired to go after calories, and

our bodies are geared to store them up in case of famine. Unfortunately what was a good thing throughout most of human history is now a problem for many people. Type 2 diabetes is more of a problem for some people, most of whom have also had to battle their weight (Hiser '99: 4).

Americans of African, Mexican, Hawaiian, and Native American descent are more likely to experience type 2 diabetes and obesity than the population as a whole, and this appears to be connected to inherited tendencies. Worldwide, there are other pockets of people with common gene pools in which type 2 diabetes runs rampant, whereas more heterogeneous population groups get the disease less frequently Since the 1960s researchers have been studying the Pima Indians of Arizona, a group of Native Americans with the highest rate of type 2 diabetes in the world. Once a lean and vigorous people, the Pima Indians are believed to have descended from the Hohokam, a group of Paleo-Indians who origninally came from Asia during the first of the great nmigrations across the Bering land bridge. The Hohokam first settled in what is now northern Mexico, and around 300 B.C. a group migrated to the Gila River valley in what is now Arizona. For more than two thousand years, the ancestors of the present day Pimas lived int eh desert environment by irrigation farming, hunting, and gathering food. They built elaborate irrigation systems, diverting water to cultivated fields, and lived successfully until the end of the nineteenth century when their water supplies were disrupted by white settlers. In this century, health changes have followed cultural and economic changes. Compared to children at the turn of the century, present day Pima children are much heavier for their height. Today, one out of two Pimas under the age of thirty-five has type 2 diabetes, and about 90 percent of the adults are obese. Adult male Pimas, who live on reservations with high rates of unemployment, have an average weight of about 200 pounds and suffer terribly from the ravages of type 2 diabetes. The disease is virtually unknown among their Mexican counterparts, who live in the rugged mountains, gathering and growing their own food, and who weigh an average of about 130 pounds (Hiser '99: 5, 4).

Normal glucose homeostasis is tightly regulated by three inter-related processes (1) glucose production in the liver; (2) uptake and utilization of glucose by peripheral tissues (mostly muscle), and (3) insulin secretion. Insulin secretion is modulated such that glucose production and utilization rise or fall to maintain normal blood glucose levels. The human insulin gene is expressed in the beta cells of the pancreatic islets, where mature insulin mRNA are transcribed. Release of insulin from beta cells is a biphasic process involving two pools of insulin. A rise in the blood glucose levels results in glucose uptake into beta cells, leading to an immediate release of insulin. Insulin is a major anabolic hormone. It is necessary for (1) transmembrane transport of glucose and amino acids; (2) glycogen formation nit he liver and skeletal muscles; (3) glucose conversion to triglycerides; (4) nucleic acid synthesis and (5) protein synthesis. Its prime metabolic function is to increase the rate of glucose transport into certain cells in the body – striated muscle cells, including myocardial cells, fibroblasts and fat cells, representing collectively about two-thirds of the entire body weight. In addition insulin and insulin like growth factors initiate DNA synthesis in certain cells and stimulate their growth and differentiation (Crawford and Cotran ‘94: 910-911).

When diabetes has been present 10 to 15 years morphologic changes are likely to be found in the basement membranes of small vessels (microangiopathy), arteries (atherosclerosis), kidney (diabetic nephropathy), retina (retinopathy), nerves (neuropathy) and other tissues and clinical evidence of dysfunction in these organs is present. Atherosclerosis begins to appear in most diabetics, whatever their age, within a few years of onset of type I or II diabetes. Fewer than 5% of nondiabetics as opposed to approximately 75% of diabetic younger than 40 years of age have moderate to severe atherosclerosis. Thus relatively early in the diabetic’s life atherosclerosis

may result in arterial narrowings or occlusions and attendant ischemic injury to organs, alternatively it may induce aneurysmal dilation, seen most often in the aorta, with the grave potential of rupture. This large vessel disease accounts for the heavy toll exacted by myocardial infarction, cerebral stroke, and gangrene of the lower extremities in these patients. **Gangrene** of the lower extremities is 100 times more common in diabetics than nondiabetics. Diabetic retinopathy is the fourth leading cause of all legal blindness (visual acuity of 20/200 or worse) in the United States. It has been estimated that if a patient is diagnosed as a diabetic by age 30, there is a 10% chance he will have some degree of diabetic retinopathy by age 37, a 50% chance by age 45 and a 90% chance by age 55. However, diabetic retinopathy does not always impose a visual handicap (Crawford and Cotran ’94: 920, 921).

The **morbidity** associated with long-standing diabetes of either type results from complications such as micro-angiopathy, retinopathy, nephropathy, and neuropathy. Most of the available experimental and clinical evidence suggests that the complications of diabetes mellitus are a consequence of the metabolic derangements, mainly hyperglycemia. Insulin is a major anabolic hormone in the body, and therefore derangement of insulin function affects not only glucose metabolism but also fat and protein metabolism. Two important acute metabolic complications of diabetes mellitus are diabetic ketoacidosis and nonketotic hyperosmolar coma. Diabetic ketoacidosis occurs exclusively in type I diabetes and is stimulated by severe insulin deficiency coupled with absolute or relative increases of glucagon, if the urinary excretion of ketones is compromised by dehydration, the plasma hydrogen ion concentration increases and systemic metabolic ketoacidosis results in nausea, vomiting and respiratory difficulties. In type II diabetes, polyuria, polydipsia and polyphagia may accompany the fasting hyperglycemia, but ketoacidosis is rare. Adults, particularly elderly diabetics, develop nonketotic hyperosmolar coma, a syndrome engendered by the severe dehydration resulting from sustained hyperglycemic disuresis (Crawford and Cotran ’94: 918).

The first treatment for type 2 diabetes blood glucose (sugar) control is often meal planning, weight loss, and exercising. Sometimes these measures are not enough to bring blood glucose levels down near the normal range. The next step is taking a medicine that lowers blood glucose levels. All diabetes pills sold today in the United States are members of six classes of drugs that work in different ways to lower blood glucose (blood sugar) levels: Sulfonylureas, Meglitinides, Biguanides, Thiazolidinediones, Alpha-glucosidase inhibitors and DPP-4 inhibitors. (1) Sulfonylureas stimulate the beta cells of the pancreas to release more insulin. Sulfonylurea drugs have been in use since the 1950s. Chlorpropamide (Diabinese) is the only first-generation sulfonylurea still in use today. The second generation sulfonylureas are used in smaller doses than the first-generation drugs. There are three second-generation drugs: glipizide (Glucotrol and Glucotrol XL), glyburide (Micronase, Glynase, and Diabeta), and glimepiride (Amaryl). These drugs are generally taken one to two times a day, before meals. All sulfonylurea drugs have similar effects on blood glucose levels, but they differ in side effects, how often they are taken, and interactions with other drugs. Meglitinides are drugs that also stimulate the beta cells to release insulin. Repaglinide (Prandin) and nateglinide (Starlix) are meglitinides. They are taken before each of three meals. Because sulfonylureas and meglitinides stimulate the release of insulin, it is possible they cause hypoglycemia (low blood glucose levels).

Alcohol and some diabetes pills may not mix. Occasionally, chlorpropamide and other sulfonylureas, can interact with alcohol to cause vomiting, flushing or sickness. Metformin (Glucophage) is a biguanide. Biguanides lower blood glucose levels primarily by decreasing the amount of glucose produced by the liver. Metformin also helps to lower blood glucose levels by making muscle tissue more sensitive to insulin so glucose can be absorbed. It is usually taken

two times a day. A side effect of metformin may be diarrhea, but this is improved when the drug is taken with food. Rosiglitazone (Avandia) and pioglitazone (ACTOS) are in a group of drugs called thiazolidinediones. These drugs help insulin work better in the muscle and fat and also reduce glucose production in the liver. The first drug in this group, troglitazone (Rezulin), was removed from the market because it caused serious liver problems in a small number of people. So far rosiglitazone and pioglitazone have not shown the same problems, but users are still monitored closely for liver problems as a precaution. Both drugs appear to increase the risk for heart failure in some individuals, and there is debate about whether rosiglitazone may contribute to an increased risk for heart attacks. Both drugs are effective at reducing A1C and generally have few side effects. Acarbose (Precose) and meglitol (Glyset) are alpha-glucosidase inhibitors. These drugs help the body to lower blood glucose levels by blocking the breakdown of starches, such as bread, potatoes, and pasta in the intestine. They also slow the breakdown of some sugars, such as table sugar. Their action slows the rise in blood glucose levels after a meal. They should be taken with the first bite of a meal. These drugs may have side effects, including gas and diarrhea.

A new class of medications called DPP-4 inhibitors help improve A1C without causing hypoglycemia. They work by preventing the breakdown of a naturally occurring compound in the body, GLP-1. GLP-1 reduces blood glucose levels in the body, but is broken down very quickly so it does not work well when injected as a drug itself. By interfering in the process that breaks down GLP-1, DPP-4 inhibitors allow it to remain active in the body longer, lowering blood glucose levels only when they are elevated. DPP-4 inhibitors do not tend to cause weight gain and tend to have a neutral or positive effect on cholesterol levels. Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin (Nesina) are the DPP-4 inhibitors currently on the market in the US. Because the drugs listed above act in different ways to lower blood glucose levels, they may be used together. For example, a biguanide and a sulfonylurea may be used together. Many combinations can be used. Though taking more than one drug can be more costly and can increase the risk of side effects, combining oral medications can improve blood glucose control when taking only a single pill does not have the desired effects. Switching from one single pill to another is not as effective as adding another type of diabetes medicine.

Generic versions of some sulfonylureas are available. These cost less than brand-name products and in general are reliable. There is now a generic Metformin (Glucophage). To save more money, ask for the largest tablet strength suitable for the dose needed. One 500-mg tablet, for example, often costs much less than two 250-mg tablets, and can be split. Diabetes pills aren't perfect, but they can help to lower glucose levels for many people with type 2 diabetes. All diabetes pills can interact with other medicines. Any sulfonylurea or meglitinide can cause blood glucose levels to drop too low (hypoglycemia). Metformin or the glitazones rarely cause hypoglycemia unless taken with insulin stimulators (sulfonylureas or repaglinide) or insulin injections. Acarbose or miglitol, taken as prescribed, does not cause hypoglycemia. However, hypoglycemia can occur when acarbose or meglitol is taken in combination with other diabetes medications. For pancreatic cancer diagnosed as insuloma Diazoxide inhibits release of insulin and has a peripheral hyperglycemic effect, a benzothiadizine diuretic should be given with diazoxide. Propranolol and glucocorticoids have also been used. Without any demonstrated improvements with combination therapy 5-FU alone is the most appropriate chemotherapy choice for pancreatic cancer.

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
STIMULATORS OF INSULIN RELEASE (Insulin Secretagogues) – increase insulin secretion from the pancreas				
SULFONYLUREAS (SFUs)				
Tolbutamide Orinase® various generics	1957	500 mg tablets	**Initial:** 1000-2000 mg daily **Range:** 250-3000 mg (seldom need >2000 mg/day) **Dose:** Taken two or three times daily	**SE:** hypoglycemia, weight gain Preferred SFU for elderly Must be taken 2-3 times daily
Glimepiride Amaryl® various generics	11/95	1 mg, 2 mg, 4 mg tablets	**Initial:** 1-2 mg daily **Range:** 1-8 mg **Dose:** Taken once daily	**SE:** hypoglycemia, weight gain Need to take only once daily
Glipizide Glucotrol® Glucotrol XL® various generics	5/84 4/94	5 mg, 10 mg tablet ER: 2.5 mg, 5 mg, 10 mg tablets	**Initial:** 5 mg daily **Range:** 2.5-40 mg[2] (20 mg for XL) **Dose:** Taken once or twice (if >15 mg) daily	**SE:** hypoglycemia, weight gain Preferred SFU for elderly ER = extended release/take once a day
Glyburide Micronase®, DiaBeta®	5/84	1.25 mg, 2.5 mg, 5 mg tablets	**Initial:** 2.5-5 mg daily **Range:** 1.25-20	**SE:** hypoglycemia, weight gain

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
various generics			mg^2 **Dose:** Taken once or twice daily	
Glyburide, micronized Glynase PresTab® various generics	3/92	1.5 mg, 3 mg, 4.5 mg, 6 mg micronized tablets	**Initial:** 1.5-3 mg daily **Range:** 0.75-12 mg **Dose:** Taken once or twice (if >6 mg) daily	**SE:** hypoglycemia, weight gain
GLINIDES				
Repaglinide Prandin®	12/97	0.5 mg (white), 1 mg (yellow), 2 mg (red) tablets	**Initial:** 1-2 mg daily (0.5 mg if A1C <8%) **Range:** 0.5-16 mg Max dose per meal is 4 mg **Dose:** Taken two, three, or four times daily	**SE:** hypoglycemia Safe for elderly Duration of action is only 4 hours Take within 15-30 minutes of meal
Nateglinide Starlix®	12/00	60 mg (pink), 120 mg (yellow) tablets	**Initial:** 120 mg three times daily (if A1C close to goal, use 60 mg) <p**Range: 180-360 mg**	**SE:** hypoglycemia Safe for elderly Duration of action is only 2 hours Take within 30

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
			Dose: Taken three times daily **</p**	minutes of meal
EUGLYCEMICS: Medicines that bring the blood glucose into the normal range. These medicines should not cause hypoglycemia.[3]				
BIGUANIDES: decreases glucose release from liver				
Metformin Glucophage® Extended release (ER): Glucophage XR® Fortamet® Glumetza Riomet® (liquid, 500 mg/5ml)	12/94 10/00	Glucophage: 500 mg, 850 mg, 1000 mg tablets Glucophage XR: 500 mg, 750 mg tablets Fortamet: 500 mg, 1000 mg tablets Glumetza: 500 mg, 1000 mg tablets Generic metformin ER: 500 mg, 750 mg tablets	**Initial:** 500 mg twice daily or 850 mg once daily **Range:** 500-2550 mg **Dose:** Taken two or three times daily ER: **Initial:** 500 mg once daily **Range:** 500-2000 mg **Dosed** once daily	**SE:** Gastrointestinal symptoms (diarrhea, nausea, upset stomach), metallic taste (3%) lactic acidosis (0.03 cases/1000 people) Take with meals (ER with evening meal) Cannot use if have liver or kidney problems, take a drug to treat heart failure, or drink alcohol excessively
ALPHA-GLUCOSIDASE INHIBITORS: STARCH BLOCKERS – delay digestion and absorption of carbohydrates				
Acarbose Precose® various generics	9/95	25 mg, 50 mg, 100 mg tablets	**Initial:** 25 mg three times daily **Range:** 75-300 mg (max 150 mg if <60 kg)	**SE:** flatulence Take with first bite of meal Start with low dose and slowly to

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
			Dose: Taken three times daily	minimize GI intolerance.
THIAZOLIDINEDIONES (Glitazones or TZDs): decrease insulin resistance in the body (muscle and fat tissues)				
Rosiglitazone Avandia®	5/99	2 mg (pink), 4 mg (orange), 8 mg (red-brown) tablets	**Initial:** 4 mg daily **Range:** 4-8 mg **Dose:** Taken once or twice daily	**SE:** anemia, swelling (edema) from fluid retention, weight gain, macular edema (in eye), bone loss and fractures in women May at risk of heart problems such as heart-related chest pain (angina) or heart attack (myocardial infarction) May cause or worsen heart failure Cannot use if have liver problems or severe heart failure Requires liver monitoring[6]
Pioglitazone Actos®	7/99	15 mg, 30 mg, 45 mg (white to off-white) tablets	**Initial:** 15-30 mg daily **Range:** 15-45 mg **Dose:** Taken once daily	**SE:** anemia, swelling (edema) from fluid retention, weight gain, macular edema (in eye), bone loss and

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
				fractures in women May cause or worsen heart failure Cannot use if have liver problems or severe heart failure Requires liver monitoring
GLP-1 ANALOGS: increase insulin secretion, reduce glucose release from liver after meals, delay food emptying from stomach and promote satiety				
Exenatide Byetta®	4/05	5 mcg per dose and 10 mcg per dose Injected under the skin (subcutaneous/SQ) Available as a pen device	**Initial:** 5 mcg SQ twice daily **Range:** up to 10 mcg SQ twice daily **Dose:** Taken twice daily	**SE:** nausea, headache, hypoglycemia (when used with insulin secretagogues) Rare reports of sudden pancreatitis (inflammation of pancreas) May cause mild weight loss
Liraglutide Victoza®	01/10	3 mL pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg Injected under the skin (subcutaneous/SQ) Available as a pen device	**Initial:** 0.6 mg SQ once daily **Range:** up to 1.8 mg SQ once daily **Dose:** Taken once daily	**SE:** nausea, headache, diarrhea, hypoglycemia (when used with insulin secretagogues) Rare reports of sudden pancreatitis (inflammation of pancreas). Cannot

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
				be used if have history of medullary thyroid cancer
DPP-4 INHIBITORS: increase insulin secretion, reduce glucose release from liver after meals				
Sitagliptin Januvia®	11/06	25 mg (pink), 50 mg (light beige), 100 mg (beige) tablets	**Initial:** 100 mg daily **Range:** 25-100 mg daily **Dose:** Taken once daily	**SE:** runny nose, upper respiratory infection, rare severe allergic reactions (swelling of tongue, throat, face or body; severe rash) No weight gain; Lower doses used if kidney problems
Saxagliptin Onglyza®	7/09	2.5 mg (pale to light yellow), 5 mg (pink) tablets	**Initial:** 2.5 or 5 mg daily **Range:** 2.5-5 mg daily **Dose:** Taken once daily	**SE:** upper respiratory infection, urinary tract infection, headache No weight gain; Lower doses used if kidney problems
Linagliptin Tradjenta®	5/11	5mg (light red) tablet	**Initial:** 5 mg daily **Dose:** Taken once daily	**SE:** runny nose, sore throat, rare reports of pancreatitis, rare severe allergic reactions, no weight gain;
COMBINATION ORAL PILLS				
Glyburide/Metformin	7/00	1.25 mg/250 mg (pale yellow), 2.5 mg/500 mg (pale	**Initial:** 1.25 mg/250 mg once or twice daily	Same as above with glyburide and metformin

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
Glucovance® various generics		orange), 5 mg/500 mg (yellow) capsule shaped	**Range:** up to – 20/2000 mg **Dose:** Taken once or twice daily	
Glipizide/Metformin Metaglip® various generics	10/02	2.5 mg/250 mg (pink), 2.5mg/500 mg (white), 5mg/500 mg (pink) oval tablets	**Initial:** 2.5 mg/250 mg daily or 2.5mg/500 mg twice daily **Range:** up to 20/2000 mg **Dose:** Taken once or twice daily	Same as above with glipizide and metformin
Rosiglitazone/Metformin Avandamet® various generics	10/02	2 mg/500 mg (pale pink), 2 mg/1000 mg (yellow), 4 mg/500 mg (orange), 4 mg/1000 mg (pink) oval tablets	**Initial:** 2 mg/5000 mg once or twice daily **Range:** up to 8 mg/2000 mg **Dose:** Taken twice daily	Same as above with metformin and rosiglitazone
Pioglitazone/Metformin ActoPlus Met® various generics	8/05	15 mg/500 mg, 15 mg/850 mg (white to off-white) oblong tablets	**Initial:** 15 mg/500 mg or 15 mg/850 mg once or twice daily **Range:** up to 45 mg/2550 mg Dosed once or twice daily	Same as above with metformin and pioglitazone
Pioglitazone/Glimepiride	7/06	30 mg/2 mg, 30 mg/4 mg (white to	**Initial:** 30 mg/2 mg or 30 mg/4 mg	Same as above with pioglitazone

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
Duetact®		off-white) tablets	once daily **Range:** max of one tablet daily **Dose:** Taken once daily	and glimepiride
Rosiglitazone/Glimepiride Avandryl® various generics	11/05	4 mg/1 mg (yellow), 4 mg/2 mg (orange), 4 mg/4 mg (pink) rounded triangle tablets	**Initial:** 4 mg/1 mg or 4 mg/2 mg once daily **Range:** up to 8 mg/4 mg **Dose:** Taken once daily	Same as above with rosiglitazone and glimepiride
Sitagliptin/Metformin Janumet®	03/07	50 mg/500 mg (light pink), 50 mg/1000mg (red) oblong tablets	**Initial:** 50 mg/500 mg or 50 mg/1000 mg twice daily **Range:** up to 100 mg/2000 mg **Dose:** Taken twice daily	Same as above/below with sitagliptin and metformin
Repaglinide/Metformin PrandiMet®	06/08	1 mg/500 mg (yellow), 2 mg/500 mg (pink) tablets	**Initial:** 1 mg/500 mg twice daily **Range:** 10 mg/2500 mg, Max per dose 4 mg/1000 mg **Dose:** Taken twice or three times daily	Same as above with repaglinide and metformin
Pioglitazone/Metf	05/09	15 mg/1000 mg,	**Initial:** 15	Same as above

Medicine	FDA Approval	Oral Diabetes Drug Formulations (color indicated if available by Brand only)	Dosing	Comments (SE = possible side effects)
ormin XR ActoPlus Met XR®		30 mg/1000 mg (white to off-white) round tablets	mg/1000 mg or 30 mg/1000 mg once daily **Range:** up to 45 mg/2000 mg **Dose:** Taken once daily	with metformin and pioglizatone
Saxagliptin/Metformin XR Kombiglyze XR®	11/10	5 mg/500 mg (light brown to brown), 5 mg/1000 mg (pink), 2.5 mg/1000 mg (pale yellow to light yellow) capsule-shaped tablets	**Initial:** 5 mg/500 mg or 5 mg/1000 mg once daily **Range:** up to 5 mg / 2000 mg **Dose:** Taken once daily	Same as above with metformin and saxagliptin

1. SFUs, repaglinide and nateglinide can cause hypoglycemia. The risk of hypoglycemia is increased when meals are skipped. Avoid skipping meals.
2. "Clinical" maximum daily dose for glyburide is 10 mg and glipizide is 20 mg; higher doses are not likely to further lower the blood glucose.
3. These medicines do not cause hypoglycemia when used alone. However, when used with SFUs, repaglinide, nateglinide, or insulin, hypoglycemia may occur.
4. Lactic acidosis symptoms: feeling very weak, tired or uncomfortable; unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, or suddenly developing a slow or irregular heartbeat.
5. Radiologic tests using iodinated contrast media: stop metformin at the time of or prior to the procedure, and withhold for 48 hours after procedure and restart after kidney function has been re-evaluated and found to be normal.
6. Liver toxicity symptoms: unexplained nausea, vomiting, stomach pain, unusual tiredness, loss of appetite, dark urine, or yellowing of the skin or whites of eyes.

Source: Diabetes Education Online

Insulin resistance is the hallmark of type 2 diabetes. Lowering body fat lowers insulin resistance. Insulin is a hormone secreted by the beta cells in the pancreas in response to eating. As food travels form the mouth to the stomach, enzymes along the way break down the

carbohydrates into glucose, which is absorbed into the bloodstream from the small intestine. The rising levels of blood glucose signal the beta cells to secrete insulin. The main job of insulin is to move blood sugar (glucose) into cells where it can be used as energy. Every second of every day, cells need energy to stay alive, and glucose, the basic product of carbohydrate digestion is a primary source of energy. Cells are encased in a protective covering, a semipermeable membrane that regulate the entry and exit of substances into and out of the cell. Normally, insulin docks with insulin receptors on the cell membrane, which is the signal to allow glucose to pass through. But in a state of insulin resistance, the receptors do not respond properly to insulin, which causes glucose to back up in the blood. When blood glucose stays a little higher than normal between meals and in the fasting state, a person is said to have impaired glucose tolerance. Impaired glucose tolerance is common in older individuals, particularly those who are sedentary, and in younger people who are overweight. When blood sugar stays a lot higher than normal between meals in the fasting state, a diagnosis of type 2 diabetes is made. In type 2 diabetes, blood sugar stays high between meals even though insulin levels remain high, which is a sure sign that cells are responding poorly to insulin's signal. A person in this state is said to be insulin resistant. The goal for managing type 2 diabetes is to increase insulin sensitivity, so that insulin's signal is readily received, allowing glucose to be readily cleared from the blood. Proven methods of increasing insulin sensitivity are (1) stem the flood of calories by eating vegan (2) move around for exercise (3) eat a reasonable amount of carbohydrates. When blood glucose remains high, over time, insulin independent cells, such as the blood, kidneys and central nervous system, become damaged by the excess glucose. Weight loss lowers insulin resistance (Hiser '99: 8, 9).

16. Other endocrine disorders

Diseases of the endocrine system are common, including conditions such as diabetes mellitus, thyroid disease, and obesity. Endocrine disease is characterized by dis-regulated hormone release (a productive pituitary adenoma), inappropriate response to signaling (hypothyroidism), lack of a gland (diabetes mellitus type 1, diminished erythropoiesis in chronic renal failure), or structural enlargement in a critical site such as the thyroid (toxic multinodular goitee). **Hypofunction** of endocrine glands can occur as a result of loss of reserve, hyposecretion, agenesis, atrophy, or active destruction. **Hyperfunction** can occur as a result of hypersecretion, loss of suppression, hyperplastic or neoplastic change, or hyperstimulation. **Endocrinopathies** are classified as primary, secondary, or tertiary. **Primary endocrine disease** inhibits the action of downstream glands. **Secondary endocrine disease** is indicative of a problem with the pituitary gland. **Tertiary endocrine disease** is associated with dysfunction of the hypothalamus and its releasing hormones. As the thyroid, and hormones have been implicated in signaling distant tissues to proliferate, for example, the estrogen receptor has been shown to be involved in certain breast cancers. Endocrine, paracrine, and autocrine signaling have all been implicated in proliferation, one of the required steps of oncogenesis (Kasper '05: 2074).

Endocrine disorders can result from hormone deficiency, hormone excess, or hormone resistance. With some notable exceptions (e.g., calcitonin), hormone deficiency always causes disease. **Hormone deficiency** is usually the result of a destructive process occurring in the gland in which the hormone is produced. Thus, infection by viruses or bacteria infarction due to impaired blood supply, physical compression by tumor growth, or attack by cellular or humoral immune mechanisms all may lead to impaired hormone production in most endocrine glands. Alternatively, hormone deficiency states can result from genetic defects in hormone formation such as gene deletion or mutation, failure to cleave a peptide hormone precursor to the active hormone, or a specific enzymatic defect in the formation of thyroid or steroid hormones.

Hormone excess usually results in disease. The hormone may be overproduced by the gland that normally secretes it or by a tissue that is not normally an endocrine organ. Malignancies are often involved in each of these types of hormone excess. Some tumors of endocrine glands (e.g., pituitary, adrenal) are functional and secrete the appropriate hormone for the gland but in an unregulated manner. Other mechanisms of hormone excess include the effects of antireceptor antibodies stimulating a receptor instead of blocking its activation, as in the common form of hyperthyroidism, and the ingestion of exogenous hormones, as in the glucocorticoid excess resulting from its therapeutic use. **Hormone resistance** as a mechanism of disease has now been described for almost all hormones. In these disorders the hormone is present in normal or increased, amounts, but the expected actions of the hormones do not occur. In some cases because of a mutation, a structurally abnormal peptide hormone is present, causing the resistance (e.g., insulin, PTH). In other instances there are antibodies to the hormone or hormone receptor (e.g., insulin and its receptor). Finally, hormone resistance may also occur as the result of primary receptor defects (e.g., androgen and vitamin D receptors) or defects in the postreceptor mechanisms of hormone action (e.g., insulin, PTH) (Ojeda & Griffin '00: 17). In general, hormone deficiency can be treated by hormone administration, but this can be dangerous because it leads to hormone excess. Hormone excess has come to be treated with specific anti-hormonal therapy in cancer treatment. Hormone resistance such as found in adult onset diabetes can be treated with certain medicines, if diet and exercise are not enough.

There are many causes of **hypopituitarism**, which can involve either hypothalamic or pituitary problems. The deficiencies can be variable for the different anterior pituitary hormones. The symptoms of hypopituitarism are slow in onset and are reflected in deficiencies in the target organs of the anterior pituitary. Hypogonadism, hypothyroidism, hypoadrenalism, and growth impairment (in children) may be present. People with **panhypopituitarism** tend to have sallow complexions because of the ACTH deficiency, and they become particularly sensitive to the actions of insulin because of the decreased secretion of the insulin antagonists, GH and cortisol. They are prone to develop hypoglycemia, particularly when stressed. **Hypogonadism** is manifested by amenorrhea in women, impotence in men, and loss of libido in both men and women. Some of the clinical manifestations of hypothyroidism are cold, dry skin, constipation, hoarseness and bradycardia. The myxedema (nonpitting edema) associated with severe hypothyroidism is rare. Adrenal insufficiency caused by the ACTH deficiency can result in weakness, mild postural hypotension, hypoglycemia, and loss in pubic and axillary hair.

The only symptom associated with the **PRL deficiency** is the incapacity for postpartum lactation. Hyperprolactinemia PRL secreting tumors account for approximately 70% of all anterior pituitary tumors. Finely wrinkled skin is characteristic of a deficiency of both gonadotropin and GH. The GH deficiency can also lead to fasting hypoglycemia in adults and children. In children, growth is impaired and the relative increase in adipose tissue and decrease in muscle mass may produce a "chubby" appearance. The symptoms of the endocrine deficiencies resulting from pituitary malfunction are not as severe as they are in primary thyroid, adrenal and gonadal deficiencies. **Pituitary apoplexy** results from acute hemorrhagic infarction of the pituitary gland, due to tumor, trauma, bleeding disorder or postpartum necrosis (Sheehan's syndrome). **Sheehan's syndrome** occurs when excessive blood is lost during and following delivery, resulting in ischemia of the enlarged pituitary of pregnancy. Damage to the pituitary can result in impaired secretion of some or all of the anterior pituitary hormones. The severity of the loss is variable, and most individuals show relatively normal secretin of the posterior pituitary hormones. **Empty sella syndrome** occurs when the subarachnoid space extends into the sella turcica, thereby partially filling it with cerebrospinal fluid. This compresses the pituitary and enlarges the sella. The flattened pituitary may continue to function, sometimes

even normally. It may be congenital or acquired and is relatively common and represents a major cause of sellar enlargement (Porterfield '01: 43).

A deficiency in antidiuretic hormone (ADH) production by the posterior pituitary gland results in **diabetes insipidus**. People with diabetes insipidus are unable to concentrate urine normally and therefore excrete a large volume of urine. These individuals can have urinary flow rates as high as 25 L/day. Thirst increases as a result of the dehydration caused by the high urinary flow. People with neurogenic diabetes insipidus have high urine volume and a low urinary osmolality. If ADH is administered to people with this condition, they respond with a decrease in urinary volume and an increase in urinary osmolality. Those with nephrogenic diabetes insipidus have normal ADH production but lack a normal renal ADH response. If ADH is administered, the urinary flow rate does not decrease. Those with psychogenic diabetes insipidus are compulsive water drinkers. If water is withheld, the ADH secretion increases and urinary flow decreases while osmolality increases. Individuals with this disorder respond to treatment with ADH. Many disorders can produce inappropriately high ADH concentrations relative to plasma osmolality. Some neoplasms produce ADH and release it into plasma, particularly pulmonary neoplasms, but also including some nonmalignant tumors. The **syndrome of inappropriate secretion of antidiuretic hormone** (SIADH) is associated with pulmonary tuberculosis and Grave's disease. In Graves' disease (the most prevalent form of **hyperthyroidism**) the thyroid is stimulated by abnormal antibodies that are agonists to thyroid-stimulating hormone (TSH). In SIADH, falling serum osmolality does not inhibit ADH secretion because control of ADH secretion is no longer linked to the normal regulatory mechanisms. A person with SIADH has a normal water consumption, water is retained because of inappropriately high ADH levels. The urine osmolality is inappropriately high (the free water clearance decreases). If water is restricted in an individual with this condition, serum sodium and osmolality will return to normal (Porterfield '01: 54-56).

Common symptoms of **hypothyroidism** in adults are decreased BMR, hypothermia and cold intolerance. The skin tends to be dry and cool because of decreased sweating, decreased sebaceous gland secretion, and cutaneous vasoconstriction. There is insufficient adenosine triphosphate (ATP) for normal sweat formation., These people tend to feel cold in a warm room. There are neurologic symptoms as well. Adults with hypothyroidism tend to become dull and lethargic, their speech rate slows, and their reflex time is prolonged. They are prone to depression and will frequently sleep excessively. The term **myxedema madness** describes the psychiatric problems that can result. The patients tend to demonstrate a generalized non-pitting edema called myxedema. The skin thickens and coarsens, hair becomes thin, coarse, and brittle and lacks luster, facial features thicken, the tongue enlarges and there is noticeable periorbital edema. Gastrointestinal disturbances are common, menstrual irregularities, bradycardia, decreased myocardial contractility, and hence reduced cardiac output, ECG is reduced and there may be pericardial effusion as a result of the interstitial edema, may occur. Hypothyroidism can be caused by the destruction of gland due to surgery, irradiation, autoimmune disease (Hashimoto's thyroiditis), cancer or thyroiditis; inhibition of thyroid hormone synthesis due to dietary iodine deficiency, enzyme defects for hormonogenesis, or antithyroid drugs; hypothalamic or pituitary disorders or resistance to thyroid hormone. Treatment must address the cause (Porterfield '01: 75-78). Hypothyroidism can be easily treated using thyroid hormone medicine levothyroxine (i.e., Synthroid, Levoxyl, or Levothroid).

Hypothyroidism in children is different from hypothyroidism in adults because thyroid hormones are important for normal development and maturation. Dietary iodine deficiency beginning in utero impairs the thyroid's ability to synthesize thyroid hormones and results in

endemic **cretinism**. Although technically the term cretinism should be reserved for children with endemic iodine deficiency, the term is often loosely applied to all forms of hypothyroidism beginning at or before birth. For children whose hypothyroidism does not result from iodine deficiency, the term **sporadic congenital hypothyroidism** is more appropriate. There are multiple causes for sporadic congenital hypothyroidism, including thyroid agenesis or dysgenesis and thyroidal defects in hormone biosynthesis, such as organ defects. There are also rare cases of hereditary thyroid hormone resistance. Another cause of neonatal hypothyroidism is the transfer of thyroid-blocking antibodies across the placenta from a mother with autoimmune thyroid disease. The symptoms of hypothyroidis in newborns can include respiratory distress syndrome, poor feeding, hoarse cry, umbilical hernia, and retarded bone age. Routine neonatal thyroid screening is essential to detect the disorder and to begin replacement therapy early enough to prevent mental retardation. **Hypothyroidism** in children is different from hypothyroidism in adults because thyroid hormones are important for normal development and maturation. Untreated hypothyroidism in children results in mental retardation and growth stunting. hypothermia in adults.

Hypothyroidism can be easily treated using thyroid hormone medicine Synthroid® and thyroid extract (or L-thyroxine). Symptoms of hyperthyroidism include nervousness, heat intolerance, palpitations, muscle weakness, increased defecation frequency, increased appetite, moist, warm skin, bruit over thyroid, goiter, tremor, fatigue, pretibial myxedema (Graves' disease), and eye problems (Graves' disease). Radioactive iodine taken by mouth, is absorbed by the thyroid gland, where it causes the gland to shrink and symptoms to subside, usually within three to six months. Anti-thyroid medications such as propylthiouracil and methimazole (Tapazole) gradually reduce symptoms of hyperthyroidism by preventing the thyroid gland from producing excess amounts of hormones. Symptoms usually begin to improve in six to 12 weeks, but treatment with anti-thyroid medications typically continues at least a year and often longer. Thyroidectomy is rarely used. Patients with primary hyperparathyroidism have high serum calcium levels and, in most cases, low serum phosphate levels. Hormone replacement therapy may help bones retain calcium. Bisphosphonates also prevent the loss of calcium from bones and may lessen osteoporosis caused by hyperparathyroidism. Calcimimetics, sold as cinacalcet (Sensipar) mimic calcium circulating in the blood, tricking the parathyroid glands into releasing less parathyroid hormone, approved by the FDA to treat hyperparathyroidism caused by chronic kidney disease or parathyroid cancer. Some doctors may prescribe it to treat primary hyperparathyroidism, particularly if surgery hasn't successfully cured the disorder or a person isn't a good candidate for surgery. The antibiotic mithramycin (plicamycin) is sometimes used in the treatment of hypercalcemia of malignancy because it inhibits bone resorption.

Hypoparathyroidism is associated with low serum calcium levels and high serum phosphate levels. The disorder is frequently treated with a high-calcium diet, vitamin D (calcitriol), and occasionally thiazide diuretics to decrease renal calcium clearance. Thiazide diuretics increase calcium reabsorption in the thick ascending limb of the loop of Henle. Acute hypocalcemia can be treated with intravascular calcium gluconate infusion. **Adrenal insufficiency** results in a lack of essential hormones, and therefore treatment focuses on replacing or substituting those hormones. Cortisol is replaced orally with tablets taken once or twice a day. Aldosterone is replaced with oral doses of a mineralocorticoid, called fludrocortisone acetate, to maintain the right levels of salt and fluids in the body. Adrenocortical hormone excess is termed **Cushing's syndrome**, pharmacologic use of exogenous corticosteroids is now the most common cause of Cushing's syndrome. Increased cortisol section causes a tendency to gain weight, with a characteristic centripetal fat distribution and a "buffalo hump". The face will appear round (fat deposition), and the cheeks may be reddened. Medications to control excessive production of

cortisol include ketoconazole (Nizoral), mitotane (Lysodren) and metyrapone (Metopirone). The Food and Drug Administration has also approved the use of mifepristone (Korlym) for people with Cushing syndrome who have type 2 diabetes or glucose intolerance. Mifepristone does not decrease cortisol production, but it blocks the effect of cortisol on your tissues. Spironolactone is the most effective drug for controlling the effects of hyperaldosteronism, though it may interfere with the progression of puberty. Newer drugs that possess greater specificity for the mineralocorticoid receptor than spironolactone does are becoming available.

Thyrotoxicosis results when tissues are exposed to excessive quantities of thyroid hormones. Symptoms of **hyperthyroidism** include nervousness, heat intolerance, palpitations, muscle weakness, increased defecation frequency, increased appetite, moist, warm skin, bruit over thyroid, goiter, tremor, fatigue, pretibial myxedema (Graves' disease), and eye problems (Grave's disease). The most prevalent form of hyperthyroidism is **Graves' disease**. This is an autoimmune disorder in which it become sensitized to antigens known as thyroid-stimulating immunoglobulins (TSIs). There is strong familial predisposition for the disorder, and women have 7 to 10 times the incidence of men. Some symptoms of hyperthyroidism result, including lid retraction (resulting in a "wide-eyed" stare), tachycardia and tremor. Eye changes exophthalmos) are common in Graves' disease. The most common observations are lid lag (upper lid is slow to follow the movement of the gaze downward), upper lid retraction, stare, extra-ocular muscular weakness, diplopia, peri-orbital edema, and proptosis. **Proptosis** may become so severe that the eyelids cannot close and corneal ulceration results. Dermopathy (pretibial myxedema) may be associated with Graves' disease. Between 2% and 10% of the patients have myxedema in the pretibial area (pretibial myxedema) and/or feet. In these regions, the skin thickens and forms "piglike" plaques.

Other forms of thyrotoxicosis include toxic multinodular goiter, toxic adenoma, and sometimes Hashimoto's thyroiditis. Subacute **thyroiditis** is an acute inflammation of the thyroid that probably the result of viral infection. The symptoms generally include fever and tenderness of the gland. Symptoms of hyperthyroidism may be present. Although excessive thyroid hormones may be released early in the inflammation, transient hypothyroidis may follow. Although approximately 10% of patients have permanent hypothyroidism, more typically the thyroid disorder resolves spontaneously. **Hashimoto's thyroiditis** is a common cause of acquired hypothyroidism. The gland becomes inflamed and lymphocytes infiltrate the gland. Structural damage of the gland occurs, hypothyroidism develops, serum T_4 and T_3 levels fall, and TSH levels rise. The patient usually has a goiter and most typically is either euthyroid or hypothyroid. Hashimoto's thyroiditis can sometimes be part of a syndrome involving multiple autoimmune endocrine disorders that can include the adrenals, pancreas, parathyroids and ovaries (Schmidt's syndrome). Excessive levels of thyroid hormones can produce osteoporosis (Porterfield '01: 78-81, 120). Radioactive **iodine** taken by mouth, is absorbed by the thyroid gland, where it causes the gland to shrink and symptoms to subside, usually within three to six months. **A**nti-thyroid medications such as propylthiouracil and methimazole (Tapazole), gradually reduce symptoms of hyperthyroidism by preventing the thyroid gland from producing excess amounts of hormones. Symptoms usually begin to improve in six to 12 weeks, but treatment with anti-thyroid medications typically continues at least a year and often longer. Thyroidectomy is rarely used.

Patients with primary **hyperparathyroidism** have high serum calcium levels and, in most cases, low serum phosphate levels. Hypercalcemia is a result of bone demineralization, increased CI calcium absorption (mediated by calcitriol), and increased renal calcium reabsorption. The major symptoms of the disorder are directly related to increased bone resorption, hypercalcemia,

and hypercalciuria. High serum calcium levels decrease neuromuscular excitability. People with hyperparathyroidism often show psychologic disorders, particularly depression, that may be associated with increased serum calcium levels. Other neurologic symtoms include fatigue, mental confusion, and, at very high levels (greater than 15 mg/dl), coma. Hypercalcemia can cause cardiac arrest. Kidney stones (nephrolithiasis) are common because hypercalcemia eventually leads to hypercalciuria and increased phosphate clearance leads to phosphaturia. The high urinary calcium an dphosphate concentrations increase the tendency for precipitation of calcium –phosphate salts in the soft tissues of the kidney. **Hypercalcemia** can result in peptic ulcer formation because calcium increases gastrin secretion. When serum calcium levels exceed about 13 mg/dl with a normal phosphate level, the calcium-phosphate solubility product is exceeded. At this level, insoluble calcium-phosphate salts form, which results in calcification of soft tissues such as blood vessels, skin, lungs and joints. People with hyperparathyroidism have evidence of increased bone turnover, such as elevated levels of serum alkaline phosphatase and osteocalcin, which indicate high osteoblastic activity, and increased urinary hydroxyproline levels, which indicates hgh bone resorptive activity. Many malignant tumors produce hypercalcemia as a result of tumor production of bone-mobilizing substances that can act like PTH. Some tumors produce substances that are structurally and functionally similar to PTH. These compounds, termed PTH-related protein (PTHrP), cross-react with the PTH receptors. They stimulate local production of bone-mobilizing substances such as prostaglandins and osteoclastic-activating actors such as IL-1, as well as increase calcitriol production. In general, serum PTH levels are suppressed in these individuals because of the high serum calcium levels. The antibiotic mithraycin (plicamycin) is sometimes used in the treatment of hypercalcemia of malignancy because it inhibits bone resorption. PTHrP can also be produced in normal tissue and may play a role in calcium balance in the fetus and infant (Porterfield '01: 121-123).Hormone replacement therapy may help bones retain calcium. Bisphosphonates also prevent the loss of calcium from bones and may lessen osteoporosis caused by hyperparathyroidism. Calcimimetics, sold as cinacalcet (Sensipar) mimic calcium circulating in the blood, tricking the parathyroid glands into releasing less parathyroid hormone, approved by the FDA to treat hyperparathyroidism caused by chronic kidney disease or parathyroid cancer. Some doctors may prescribe it to treat primary hyperparathyroidism, particularly if surgery hasn't successfully cured the disorder or a person isn't a good candidate for surgery. The antibiotic mithraycin (plicamycin) is sometimes used in the treatment of hypercalcemia of malignancy because it inhibits bone resorption.

Pseudohypoparathyroidism is a rare familial disorder characterized by tissue resistance to PTH. In many instances, the problem is thought to originate with the PTH receptor. Often there is a decrease in levels of the guanine nucleotide-binding protein, Gs. Individuals with pseudohypoparathyroidism demonstrate increased PTH secretion and low serum clacium levels, sometimes associated with congenital defects of the skeleton including shortened metacarpal and metatarsal bones. **Hypoparathyroidism** is associated with low serum calcium levels and high serum phosphate levels. The hypocalcemia results from both a PTH and a calcitriol deficiency. Consequently, there is Ta decrease in bone calcium mobilization by both osteoclastic resorption and osteocytic osteolysis. Because calcitriol is deficient, GI absorption of calcium is impaired. The PTH deficiency decreases renal calcium reabsorption, thereby decreasing fractional calcium reabsorption. The urinary calcium level is generally low. Urinary cAMP concentration also decreases. Alkalosis occurs because bicarbonate excretion decreases; this further lowers the free calcium level in serum. Although the serum calcium level is low, bone demineralization is usually not a problem because of the hgh serum phosphate level. **Hypocalcemia** increases neuromuscular excitability, increasing the possibility of tetany and even convulsions. Hypocalcemia alters cardiac function. It can produce a first-degree heart block. The low serum

calcium level decreases myocardial contractility. The most prominent symptom of hypoparathyroidism is increased neuromuscular excitability. Low serum calcium concentrations decrease the neuromuscular threshold. The increased neuromuscular excitability can result in tingling in the fingers or toes (paresthesia), muscle cramps, or even tetany. Laryngeal spasms can be fatal. **Overt tetany** is demonstrated by carpal-pedal spasm. This is called Trousseau's sign. Another test is to tap the facial nerve, which evokes facial muscle spasms (Chvostek's sign). Treatment of hypoparathyroidism is difficult because of the lack of readily available effectibe human PTH. The disorder is frequently treated with a high-calcium diet, vitamin D (calcitriol), and occasionally thiazide diuretics to decrease renal calcium clearance. Thiazide diuretics increase calcium reabsorption in the thick ascending limb of the loop of Henle. Acute hypocalcemia can be treated with intravascular calcium gluconate infusion (Porterfield '01: 123, 124).

Hypomagnesemia resulting from either severe malabsorption or chronic alcoholism can cause hypoparathyroidism. Hyopmagesemia impairs the secretion of PTH and decreases the biologic response to the PTH. Vitamin D deficiency produces hypocalcemia and hypomagnesemia and decreases GI absorption of calcium and phosphate. Because the level of the calcium-phosphate product in serum, and hence in body fluids, is low, bone mineralization is impaired and demineralization is increased. This leads to osteomalacia in adults or rickets in children. The secondary elevation in PTH can product osteoporosis. Osteoid is formed, but it does not mineralize adequately. If the calcium-phosphate product level or the pH in bone fluid bating the osteoid is low, demineralization rather than mineralization is favored. Rickets is caused by a calcium (calcitriol) deficiency before skeletal maturation; it involves problems in not ony the bone but also cartilage of the growth plate.

Osteomalacia is the term used when inadequate bone mineralization occurs after skeletal growth is complete and the epiphyses have closed. Paget's disease results in bone deformities. It is characterized by an increase in bone resorption flowed by an increase in bone formation. The new bone is generally abnormal and often irregular. Serum alkaline phosphatase and osteocalcitonin levels are increased, as are those of urinary hydroxyproline. Pain, bone deformation, and bone weakness can occur. Renal osteodystrophy are bone problems of renal failure. Approximately 0.9g, or more than 50% of dietary phosphate, is normally lost in the urine in a day. Consequently, the kidney serves as the major excretory route for phosphate. As renal function, and hence phosphate clearance, decreases, the serum phosphate concentration rises. The increase in serum phosphate concentration wil lower serum calcium levels by exceeding the solubility product and hence increasing calcium-phosphate precipitation. A drop in the serum calcium level is an effective stimulus for PTH, and serum PTH levels rise. In addition, vitamin D activation by 1α hydroxylase occurs in the renal proximal tubules. In kidney failure, vitamin D activation is impaired, which decreases G absorption of calcium and phosphate. This results in a further drop in the serum calcium level and aggravates the preexisting problem with excess PTH secretion. The result is to stimulate bone resorption and demineralization, which aggravates hyperphosphatemia. The placenta plays a major role in regulating calcium flux to the fetus. PTHrP is produced and released from the placental trophoblast in response to a decrease in extracellular calcium concentration, and this may regulate fetal calcium availability (Porterfield '01: 124-127).

When the pituitary-adrenal system is suppressed by exogenous administration of corticosteroids, both the corticotropes and the adrenal cortex (zona fasciculate and zona reticularis) atrophy. If steroid administration is withheld, acute adrenal insufficiency will result, which can be unpleasant and even life threatening. It takes months to restore normal function of the

corticotropes after long-term glucocorticoid treatment. Adrenocortical hormone excess is termed **Cushing's syndrome**. Pharmacologic use of exogenous corticosteroids is now the most common cause of Cushing's syndrome. The next most prevalent cause is ACTH-secreting tumors such as functional pituitary adenoma or functional adrenal tumor. If the disorder is primary or if it is a result of corticosteroid treatment, ACTH secretion will be suppressed and increased skin pigmentation will not occur. However, if the hypersecretion of the adrenal is a result of an ACTH-secreting nonpituitary tumor, ACTH levels sometimes become high enough to increase skin pigmentation. Increased cortisol section causes a tendency to gain weight, with a characteristic centripetal fat distribution and a "buffalo hump". The face will appear round (fat deposition), and the cheeks may be reddened, in part becasuse of the polycythemia. The limbs will be thin as a result of skeletal muscle wasting (from increased proteolysis), and muscle weakness will be evident (from muscle proteolysis and hypokalemia). The abdominal fat accumulation, coupled with atrophy of the abdominal muscles and thinning of the skin, will produce large, protruding abdomen. Purple abdominal striae are seen as a result of the damage to the skin by the prolonged proteolysis, increased intraabdominal fat, and loss of abdominal muscle tone. Capillary fragility is seen as a result of damage to the connective tissue supporting the capillaries. Patients are likely to show signs of osteoporosis and poor wound healing. They have metabolic disturbances that include glucose intolerance, hyperglycemia and insulin resistance. Prolonged hypercortisolism can lead to manifestations of diabetes mellitus. Mineralocorticoid activities of the glucocorticoids and the possible elevation of aldosterone secretion produce salt retention and subsequent water retention, resulting in hypertension and osteoporosis. Medications to control excessive production of cortisol include ketoconazole (Nizoral), mitotane (Lysodren) and metyrapone (Metopirone). The Food and Drug Administration has also approved the use of mifepristone (Korlym) for people with Cushing syndrome who have type 2 diabetes or glucose intolerance. Mifepristone does not decrease cortisol production, but it blocks the effect of cortisol on tissues (Porterfield '01: 148, 149).

Adrenocortical insufficiency (Addison's disease) is primary adrenal insufficiency; typically both mineralocorticoids and glucocorticoids are deficient. The most prevalent cause of Addyson's disease is autoimmune destruction ofhte adrenal cortex, and tuberculosis is the second most common cause of the disorder. Because of the cortisol deficiency, ACTH secretion increases. ACTH can cause skin darkening, particularly in skin creases, scars and gums. The loss of mineralocorticoids results in contraction of extracellular volume, producing circulatory hypovolemia and therefore a drop in blood pressure. Because the loss of cortisol decreases the vasopressive response to catecholamines, peripheral resistance drops, thereby adding to the tendency toward hypotension. Hypotension predisposes people to circulatory shock. These people are also prone to have hypoglycemia when stressed or fasting. The hyperglycemic actions of other hormones, such as glucagon, epinephrine and growth hormone, generally will prevent hypoglycemia at other times. The loss of cortisol impairs the ability to increase free water clearance in response to a water load and hence rid the body of the excess water. Patients with this condition will exhibit hyperkalemic acidosis. Because cortisol is important for muscle function, muscle weakness occurs in cortisol deficiency. The loss of cortisol results in anemia, decreased GI motility and secretion, and decreased iron and vitamin B_{12} absorption. The appetite will decrease because of the cortisol deficiency, and this decreased appetite coupled with the GI dysfunction will predispose these persons to weight loss. The patients often show disturbances in mood and behavior and are more susceptible to depression (Porterfield '01: 146, 147). Adrenal insufficiency results in a lack of essential hormones, and therefore treatment focuses on replacing or substituting those hormones. Cortisol is replaced orally with tablets taken once or twice a day. Aldosterone is replaced with oral doses of a mineralocorticoid, called

fludrocortisone acetate, that are taken once a day. Fludrocortisone helps to maintain the right levels of salt and fluids in the body.

Excessive **androgen secretion** in women can produce hirsutism, male pattern baldness and clitoral enlargement (adrenogenital syndrome). Primary hyperaldosteronism is called **Conn's syndrome**. It frequently occurs as a result of aldosterone-secreting tumors. Excessive mineralocorticoid secretion results in potassium depletion, sodium retention, muscle weakness, hypertension, hypokalemic alkalosis and polyuria. Edema is not uncommon. Any enzyme blockage that decreases cortisol synthesis will increase ACTH secretion and produce **adrenal hyperplasia**. The most common form of congenital adrenal hyperplasia occurs as a result of a deficiency of the enzyme **21-hydroxylase** (CYP21). These individuals cannot produce normal quantities of cortisol, deoxycortisol, DIC, corticosterone, or aldosterone. Because of impaired cortisol production and resultant elevated ACTH levels, steroidogenesis is stimulated, increasing the synthesis of those products formed before the blockage. Because this includes the adrenal androgens, a female fetus will be masculinized. Because they are unable to produce the mineralcorticoids, aldosterone, DOC and corticosterone, patients with this disorder have difficulty retaining salt and maintaining extracellular volume. Consequently, they are likely to be hypotensive. If the blockage is at the next step, **11β-hydroxylate** (CYP11B), DOC will be formed and the levels of DOC will accumulate. Because DOC is a mineralocorticoid and the levels become high, these individuals tend to retain salt and water and become hypertensive. The elevated androgen levels can cause masculinization of a female fetus. If there is a deficiency of **17α-hydroxylase**, neither cortisol nor sex hormones are produced. The inability to produce normal androgen levels during fetal development can result in a female phenotype for both males and females. A complete deficiency of **3β-hydroxysteroid dehydrogenase** (3β-HSD) is fatal. An incomplete deficiency results in the inability to produce adequate quantities of mineralocorticoids, glucocorticoids, and strong androgens or estrogens. The adrenal produces large quantities of the weak androgen DHEA. This can result in some masculinization of a female fetus and incomplete masculinization of a male fetus (Porterfield '01: 149, 150). Spironolactone is the most effective drug for controlling the effects of hyperaldosteronism, though it may interfere with the progression of puberty. Newer drugs that possess greater specificity for the mineralocorticoid receptor than spironolactone does are becoming available. Alternative medications for patients in whom aldosterone antagonists are contraindicated include amiloride and triamterene, as well as calcium channel antagonists and alpha-adrenergic antagonists (especially $alpha_1$-specific agents such as prazosin and doxazosin); in patients with angiotensin II–responsive disease, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are indicated.

Although sperm production typically begins to decline after age 50 years, many men can maintain reproductive function and spermatogenesis throughout life. Men with an extra X chromosome have the genetic disorder called **Klinefelter's syndrome**. Although there are multiple permutations of the disorder, the most common form results in a 47,XXY karyotype. Individuals with this syndrome are phenotypically male because of the presence of the Y chromosome, but they typically have small testes and decreased germ cells. The testosterone levels are low to normal, and estradiol and gonadotropin levels are high. The high estradiol/testosterone ratio can lead to feminization, including the potential for gynecomastia. Patietns with this disorder do not have norma spermatogenesis, and FSH levels are high because of abnormal Sertoli cell function. A **deficiency of 5α-reductase** results in decreased DHT formation. These individuals will typically have normal internal genitalia by incompletely masculinized external genitalia, they are often mistaken for females at birth, thereby potentially producing incomplete male hermaphroditism. The testosterone production is normal, and at

puberty, when testosterone production occurs, some masculinization of the external genitalia may occur. Normal development of male-type internal genitalia occurs because of the action of testosterone on wolffian duct development. Androgen insensitivity syndrome (AIS; testicular feminization) results from a hereditary defect of the X chromosome gene controlling androgen receptor expression. Because the defect can range from partial to complete inability of the androgen receptor to respond to androgens, the magnitude of symptoms in individuals with the genetic defect is variable.

Male pseudohermaphroditism can result because, although the karyotype is 46,XY, the wolffian duct does not develop because androgen actin is deficient and the müllerian duct regresses because testes and therefore MIS are present. Consequently, there are no functional internal genitalia. The external genitalia typically develop as female, therapy giving the individuals a female phenotype. People with severe AIS have labia, a clitoris, and a short vagina because these structures do not develop from the müllerian ducts. Pubic and axillary hair is absent or sparse because the development of sexual hair is androgen dependent. Menstruation does not occur, and serum androgen levels are high or normal. When androgen production rises at puberty, estradiol production increases, both from the testes and from peripheral aromatization of androgens. Plasma androgen and LH levels are high becaue the receptor deficiency impairs feedback inhibition of LH secretion. The testes typically remain in the abdomen because androgens stimulate testicular descent. **Kallmann's syndrome** is primary isolated gonadotropin deficiency. This genetic disorder is often associated with anosmia, or the loss of smell. People affected with this disorder have undescended testes (cryptorchism). Although there is normal embryonic development of the wolffian duct-derived structures, penis development is deficient and microphallus results. These effects probably result from the fact that early fetal development of the internal genitalia is controlled by testicular androgens that are regulated by placental hCG rather than fetal LH. The inability of the fetus to secrete normal quantities of LH has an impact on testicular function later in development, when androgens regulate growth of the external genitalia. The severity of the impairment of LH secretion is variable, as is the severity of the reproductive problems associated with the disorder (Porterfield '01: 172-174).

Turner's syndrome (gonadal dysgenesis) is the most common cause of congenital hypogonadism. In about 50% of cases, it results from the complete absence of the second X chromosome so that the karyotype of the individual is 45, XO. The germ cells do not develop, and the gonads consist of a connective tissue-filled streak. The major characteristics these individuals express include short stature, a characteristic webbed neck, low-set ears, a shield-shaped chest, short foruth metacarpals, and sexual infantilism, resulting from gonadal dysgenesis. Internal and external genitalia are typically female. Chronically anovulatory women with high circulating androgen, estrogen and LH levels often have the disorder called **polycystic ovarian syndrome**. The continuous gonadotropin secretion leads to ovarian enlargement, and the ovaries typically show a thickened capsule and numerous follicles, many of which are undergoing atresia. FSH levels are low, which inhibits granulosa cell function, and the high intrafollicular androgen level inhibits follicular maturation. A significant portion of the high circulating estrogen levels is estrone formed from peripheral aromatization of anrostenedione. These high androgen levels can produce hirsutism and acne. Hirsutism is the abnormal formation of coarse sexual hair in regions atypical for a woman, such as the face, back, and chest. The exact cause of polycystic ovarian syndrome is not well understood, but the primary defect appears to be inappropriate signals between the hypothalamic-pituitary axis and the ovary.

Although not truly a pathologic disorder in most women, **premenstrual syndrome** (PMS) produces minor discomfort in many women and major discomfort I some women. A multitude of symptoms is associated with PMS, characterized as being manifested cyclically during the

luteal phase of the cycle. The symptoms subside at or during menstruation. These symptoms can include irritability, depression, bloating, weight gain, breast tenderness and headaches. **Dysmenorrhea** is painful menstruation. Primary dysmenorrhea is a common problem in ovulatory women, it is thought to result from ischemia caused by periodic uterine contractions. The uterine contractions result from uterine prostaglandin production. Pain can be projected to the back and legs and can be accompanied by nausea and diarrhea. Prostaglandin synthetase inhibitors provide relief for some women. Birth control pills administered to prevent ovulation can reduce the discomfort. Secondary dysmenorrhea results from uterine problems such as endometriosis or congenital anomalies.

Diabetogenicity of pregnancy occurs during the last half of pregnancy, when hPL levels are highest, maternal energy metabolism shifts from an anabolic state in which nutrients are stored, to a catabolic state, sometimes described as accelerated starvation, in which maternal energy metabolism shifts toward fat utilization with glucose sparing. A maternal glucose use for energy decreases, lipolysis increases and fatty acids become major energy sources. The peripheral response to insulin decreases and pancreatic insulin secretion increases. Beta cell hyperplasia occurs in pregnancy. Pregnancy aggravates existing diabetes mellitus, or diabetes mellitus can develop for the first time in pregnancy. If the diabetes resolves spontaneously with delivery, the condition is referred to as gestational diabetes. Other hormones contributing to the diabetogenicity of pregnancy are estrogens and progestins, because both of these hormones decrease insulin sensitivity (Porterfield '01: 196-198, 218).

17. Urinary tract obstruction

The **kidneys** are bean-shaped, reddish organs that lie retroperitoneally on either side of vertebral column in the posterior part of the abdomen. In the kidney a series of tubules act to filter the blood and remove from it metabolic waters and excess material by the process of urine formation and excretion. By monitoring acid-base balance, osmotic relationships, and the content of organic and inorganic solutes, the kidney regulates the composition and physical properties of the blood. **Urine**, colored yellow by urobilinogen, a breakdown product of hemoglobin, is more hypertonic than plasma and somewhat more acid, it consists of urea, uric acid, creatinine, ammonia and hydrogen and potassium ions. The kidney also acts to control the volume of body fluids through the mediation of an antidiuretic hormone released from the pituitary. The volume of urine varies inversely with the amount of hormone secreted, which in turn depends on the amount of solute concentration of the blood reaching the hypothalamus. **Diuretics** are chemicals that induce a net loss of fluid from the body by the urinary tract. They are used to eliminate excess liquid and toxic products from the tissues and the vascular system. Of the many groups of diuretics (osmotic diuretics, mercurial compounds, carbonic anhydrase inhibitors, thiazides) only the xanthines (purine bases) are derived from natural sources. Coffee and tea have long been known to influence the flow of urine, by the xanthine caffeine is only weakly diuretic. Theophylline is about three times as active and used today, as aminophylline. Tea made from the *Chimaphila umbellate* (spotted wintergreen of the North Temperate zone, *Ericaceae*) retards the excretion of urine (Elvin-Lewis ’77: 311, 312).

The normal capacity of the **bladder** is about 400 mL. Frequency may be caused by residual urine, which decreases the functional capacity of the organ. When the mucosa, submucosa, and even the muscularis become inflamed (e.g., infection, foreign body, stones, tumor), the capacity of the bladder decreases sharply. This decrease is due to two factors: the pain resulting from even mild stretching of the bladder and the loss of bladder compliance resulting from inflammatory edema. When the bladder is normal, urination can be delayed if circumstances

require it, but this is not so in acute **cystitis**. Once diminished bladder capacity is reached, any further distention may be agonizing, and the patient may urinate involuntarily. Infection, fibrosis, low or high urine pH of the bladder cause frequent urination. **Nocturia** may be a symptom of renal disease related to a decrease in the functioning renal parenchyma with a loss of concentrating power. Nocturia can occur in the absence of disease in persons who drink excessive amounts of fluids in the evening. Coffee and alcoholic beverages, because of their specific diuretic effect, often product nocturia if consumed late in the day. **Dysuria** is painful urination usually related to acute inflammation of the bladder, urethra or prostate. The pain is present only with voiding and disappears soon after urination is complete. More severe pain sometimes occurs in the bladder just at the end of voiding, suggesting that inflammation of the bladder is the likely cause. Dysuria often is the first symptom suggesting urinary infection and is often associated with urinary frequency and urgency. **Enuresis** means bedwetting at night. It is physiologic during the first 2 or 3 years of life but becomes troublesome, after that age. If enuresis persists beyond age 5 or 6 urologic investigation is essential as it may be the result of a functional delayed neuromuscular maturation or the urethrovesical component or a symptom of organic disease (e.g. infection, distal urethral stenosis in girls, posterior urethral valves in boys, neurogenic bladder) (McAninch '88: 34).

Bladder outlet obstruction results in hesitancy, loss of force and decrease of caliber of the stream, terminal dribbling, urgency, acute and chronic urinary retention, interruption of the urinary stream, sense of residual urine and cystitis. There are many reasons for incontinence, when the patient loses urine without any warning, this may be a constant or periodic symptom. **Oliguria** and anuria may be caused by acute renal failure (due to shock or dehydration), fluid-ion imbalance, or bilateral ureteral obstruction. **Pneumaturia** is the passage of gas urine almost always because there is a fistula between the urinary tract and the bowel. Cloudy urine is usually alkaline, causing the precipitation of phosphate, but can also be caused by infection. Chyluria is the passage of lymphatic fluid or chyle as a milky white urine. **Hematuria**, bloody urine, is a danger signal that cannot be ignored. Is it painful? Is it due to jogging, beets, rhodamine B red coloring agent or laxatives containing phenolphthalein. Hematuria associated with renal colic suggests ureteral stone, bleeding renal tumor, tubercular or schistosomal infection of the bladder. **Urethral discharge** in men is one of the most common complaints in urology. The causative organism is usually *N. gonorrhoeae* or *C. trachomatis*. The discharge is often accompanied by local burning on urination or an itching sensation in the urethra.

An **ulceration of the glans penis** or its shaft may represent syphilitic chancre, herpes simplex or squamous cell carcinoma. Venereal warts of the penis are common. Edema of the legs may result from compression of the iliac veins by lymphatic metastases from prostatic cancer. Edema of the genitalia suggest filariasis or chronic ascites. Inflammation of the prostate or seminal vesicles can cause hematospermia, bloody ejaculation. **Gynecomastia**, males growing breasts, is common in elderly men, particularly those taking estrogens for control of prostatic cancer, choriocarcinoma and interstitial cell and Sertolic cell tumors of the testis. Certain endocrinologic diseases, e.g. Klinefelter's syndrome, may also cause gynecomastia. **Micropenis** is probably due to fetal testosterone deficiency. **Megalopenis** is caused by overactivity of the adrenal cortex and is often seen in association with interstitial cell tumor of the testis. Male infertility can due to a number of causes including mumps, torsion of the spermatic cord, epididymitis and exposure to testicular toxins (e.g. x-ray radiation)(McAninch '88: 34-37).

Obstruction and stasis of urinary flow are among the most important of urologic disorders. Either leads eventually to **hydronephrosis**, a peculiar type of atrophy of the kidney that may terminate in renal insufficiency or, if unilateral, complete destruction of the organ. Furthermore,

obstruction leads to infection, which causes additional damage to the organs involved. **Obstruction** may be classified to etiology (congenital or acquired), duration (acute or chronic), degree (partial or complete), and level (upper or lower urinary tract). The common site of congenital narrowing are the external meatus in boys (meatal stenosis) or just inside the external urinary meatus in little girls, the distal urethra (stenosis), posterior urethral valves, ectopic ureters, ureteroceles, and the ureterovesical and ureteropelvic junctions. Another congenital cause of urinary stasis is damage to sacral roots 2-4 as seen in spina bifida and myelomeningocele. **Vesicoureteral reflux** causes both vesical and renal stasis. Acquired obstruction are numerous and may be primary in the urinary tract or secondary to retroperitoneal lesions that invade or compress the urinary passages. Among the common causes of urinary obstruction are (1) urethral stricture secondary to infection or injury; (2) benign prostatic hyperplasia or cancer of the prostate; (3) vesical tumor involving the bladder neck or one or both orifices; (4) local extension of cancer of the prostate or cervix into the base of the bladder, occluding the ureters; (5) compression o the ureters at the pelvic brim by metastatic nodes from cancer of the prostate or cervix; (6) ureteral stone; (7) retroperitoneal fibrosis or malignant tumor; and (8) pregnancy. Neurogenic dysfunction affects principally the bladder The upper tracts are damaged secondarily by ureterovesical obstruction or reflux and, often, complicating infection. Severe constipation, especially in children, can cause bilateral hydroureteronephrosis from compression of the lower ureters. Elongation and kinking of the ureter secondary to vesicoureteral reflux commonly lead to ureteropelvic obstruction and hydronephrosis. Unless a voiding cystourethrogram is obtained in all children with this lesion the primary cause may be missed and improper treatment given (Tanagho '88: 168).

A **urethral catheter** will relieve the obstruction somewhat by eliminating the trigonal stretch. Normal intravesical pressure is about 30 cm of water at the beginning of micturition. Pressures 2-4 times as great may be reached by the trabeculated (hypertrophied) bladder in its attempt to force urine past the obstruction. This pressure tends to push mucosa between the superficial muscle bundles, causing the formation of small pockets, or **cellules**. If cellules force their way entirely through the musculature of the bladder wall, they become saccules, then actual **diverticula**, which may be embedded in the perivesical fat or covered by peritoneum. Diverticula have no muscle wall and are therefore unable to expel their contents into the bladder efficiently even after the primary obstruction has been removed. When **secondary infection** occurs, it is difficult to eradicate; surgical removal of the diverticula may be required. If a diverticulum pushes through the bladder wall on the anterior surface of the ureter, the ureterovesical junction will become incompetent. The pressure within the renal pelvis is normally close to zero. When this pressure increases because of obstruction or reflux, the pelvis and calices dilate. The degree of **hydronephrosis** that develops depends on the duration, degree, and site of the obstruction. The higher the obstruction, the greater the effect on the kidney. As urine is excreted into the renal pelvis, fluid and particularly soluble substances are reabsorbed.

Urethral catheters are used with therapeutic intention for relief of urinary retention, for drainage of urine and monitoring of urinary output perioperatively and postoperatively, and for urethral stenting after urethroplasty or urethral trauma. Catheters differ in size and shape, type of material, numbers of lumens, and type of retaining mechanisms. Standard sizes of external diameters of catheters and most endoscopic instruments are given according to Charrié [Charr]). Thus, 3F equals 1 mm in diameter and 30F equals 10 mm in diameter. For one-time intermittent catheterization of the urethra, plain straight catheters (robinson) of 16-18F size are appropriate; the same sizes are used in self-retaining indwelling Foley catheters. In men, larger sizes of indwelling catheters tend to cause retention of urethral secretions and, subsequently, urethritis and possible urethral stricture; epididymitis may occur if large catheters are used over prolonged

periods. Nevertheless, after transurethral endoscopic surgery of the prostate or the bladder, catheters with a larger diameter (20-24F) may be necessary to prevent retention of blood clots. For most case, straight urethral catheters are adequate. If negotiation of the male urethra is difficult, curved-tip catheters should be used. The Councill catheter has a hole at its tip that can be passed coaxially over a guide wire, a thin ureteral catheter, or a filiform, which can be attached to a catheter stylet. Silicone catheters are the most biocompatible and should be chosen if long-term use is anticipated, as the risk of urethritis and urethral stricture is reduced even if catheters are only changed every 4-6 weeks. Latex is the standard material used for urethral catheters. It is soft but is more likely to be encrusted than silicone if used in long-term indwelling catheters. Polyethylene and polyvinyl chloride catheters are more rigid and have a better lumen-to-external-diameter ratio, but they are not as biocompatible as silicone catheters for long-term use, these material are therefore best used for one-time catheters and for small catheters (e.g. ureteral catheters).

In men the catheter is grasped near its tip with sterile gloves or forceps and is inserted into the external meatus while the penis is stretched with the other hand. The penis must be grasped laterally to avoid squeezing the urethra against the corpora. The catheter must be advanced gently, and if there is resistance, the site of resistance should be determined by palpation f the catheter tip. The male urethra normally offers resistance at the membranous urethra due either to involuntary constriction of the external sphincter because of discomfort or anxiety or due to resistance at the infrapubic angulation between the bulbous and the membranous urethra. Once the resistance of the external sphincter has been overcome, the catheter can usually be easily advanced into the bladder, even in the presence of an obstructing prostatic adenoma. Care must be taken not to injure the urethra by overly forceful manipulation or by passing the tip of the stylet through a side hole of the catheter. **In women**, short, straight catheters are best, especially for self-catheterization. Insertion of a vaginal speculum helps to engage a urethral catheter if the meatus is difficult to visualize. If transurethral catheter insertion is difficult the tip of the catheter can be guided by a finger inserted in the vagina (Thüroff '88: 154- 156).

Under normal circumstances, the **ureterovesical junction** allows urine to enter the bladder but prevents urine from regurgitating into the ureter, particularly at the time of voiding. In this way the kidney is protected from high pressure in the bladder and from contamination by infected vesical urine. When this valve is incompetent, the chance for development of urinary infection is significantly enhanced, and pyelonephritis is then inevitable. With few exceptions, **pyelonephritis** is a fever and myalgia secondary to vesicoureteral reflux. Vesicoureteral reflux damages the kidney through one or both of 2 mechanisms: (1) pyelonephritis and (2) hydroureteronephrosis (Tanagho '88: 181, 186). Pyelonephritis is the end stage of a severely infected and obstructed kidney. The kidney is functionless and filled with thick puss and gas liberated by infecting organisms. Correction of the obstruction is usually sufficient treatment. If significant reflux is demonstrated and does not subside spontaneously after relief of obstruction, surgical repair may be needed. Repair becomes imperative if there is considerable hydronephrosis in addition to reflux. Preliminary drainage of the bladder by an indwelling catheter is indicated. If tortuous, kinked, dilated, or atonic ureters have developed vesicle drainage will not protect the kidneys from further damage; the urine proximal to the obstruction must be diverted by nephrostomy or ureterostomy. The kidneys then may regain some function. If obstruction or reflux persists, surgical repair is indicated. Permanent urinary diversion (e.g. ureteroileal conduit) may be necessary. If one kidney has been irreversibly damaged nephrectomy may be necessary. Once the obstruction is removed, every effort should be made to eradicate infection. If the infection has been severe and prolonged, antibiotics may fail to

sterilize the urinary tract (Taghano '88: 181, 186-170, 173-175). Metronidazole (Flagyl ER) is recommended.

The return of function in these kidneys after repair of their obstructions is remarkable. In 2 well-documented human cases function was recovered after obstruction of 56 and 69 days. However, irreversible loss of function can begin as early as 7 days, as evidenced by dilatation and necrosis of the proximal tubules, which progressively increase with time. Temporary drainage, especially by nephrostomy, followed by tests to assess renal function is the best measure. A plain film of the abdomen may show enlargement of renal shadows, calcific bodies suggesting ureteral or renal stone, or tumor metastases to the bones of the spine or pelvis. Stagnation of urine leads to infection, which then may spread throughout the entire urinary system. Often the invading organisms are urea-splitting (*Proteus*, *staphylococci*), which causes the urine to become alkaline. Calcium salts precipitate and form bladder or kidney stones more easily in alkaline urine. If both kidneys are affected, the result may be renal insufficiency.

18. Urinary tract infection

Urinary tract infections (UTIs) are a common problem, accounting for over eight million doctor visits each year in the United States. Infections of the urethra and bladder (cystitis) often occurring together, can be caused by numerous microorganisms that normally inhabit the gut or adjacent skin and mucous membranes. Those most commonly isolated are *Streptococcus agalactae*, *Escherichia coli*, *Klebsiella species* and *Proteus* species, although urine may also yield the yeast *Candida albicans* in diabetics. Urethral infections with *Neisseria gonorrhoeae*, *Mycoplasma hominis*, *Trichomonas vaginalis*, and *Chlamydia* species also develop through venereal contact. In the absence of obstruction, patients may recover spontaneously from urethritis or cystitis. However surgery is used to correct anatomical problems related to retention of bladder urine and bladder lavage with antibiotics is used to eradicate additional bacteria. Most urinary tract infections not acquired in a hospital, where antibiotic resistant mutants abound, are successfully treated with metronidazole, even penicillin or Bactrim and by administration of vitamin C, which lowers the urine pH. But since urine helps flush bacteria from the urinary tract, anything that obstructs the flow can lead to a UTI. That includes an enlarged prostate gland, which is a common condition in older men. If the problem is confined to the lower part of the urinary tract, the symptoms may be relatively mild, unusually frequent urination sometimes with pain or burning. But if the infection reaches the kidneys, it can cause severe pain, nausea, fever, and significant malaise. Infected kidneys can be damaged permanently unless the condition is addressed. Treatment usually begins with a urine test to identify the bacterium responsible for an infection, and then appropriate antibiotics are prescribed. Painkillers may be needed as well. When the UTI is not severe, symptoms often disappear a day or two after treatment starts. However, the bacteria may linger longer. Follow-up urine tests are recommended to make sure the infection is gone before medication is discontinued (Huffnagle ’07: 164). Metronidazole might lead to a swifter cure than other antibiotics commonly used in urology with a narrower spectrum of antibiotic activity.

The nonspecific infections of the genitourinary tract are caused mainly by aerobic gram-negative rods (e.g., *Escherichia coli*, *Proteus mirabilis, Enterobacter spp., Gardnerella vaginalis [Haemophilus vaginalis], Klebisella spp., Proteus mirabilis, Proteus spp* [indole-positive], *Pseudomonas aeruginosa, Serratia spp.*) and gram-positive cocci (e.g. staphylococcus, *Staphylococcus aureus*, *S. epidermidis*, *S. saprophyticus*; enterococci; *Streptococcu*s Group D, *S. fecalis S. bovi*, Streptococcus, group B) and to a lesser extent by obligate anaerobic bacteria (e.g. *Bacteroides fragilis*, *peptrostreptococci*). In addition, nonspecific infections of the urethra

frequently are caused by organisms that require special techniques of identification (e.g. *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Gardnerella vaginalis, Candida spp.*). Most uncomplicated urinary tract infections acquired outside the hospital environment are caused by coliform bacteria, chiefly *E. coli*. These pathogens tend to be susceptible to a variety of oral antimicrobial agents and respond quickly to short-term therapy. Hospital-acquired (nosocomial) infections often involve more resistant pathogens (e.g., *Pseudomonas aeruginosa*, *Serratia marcescens*) and may require parenteral antimicrobial agents. Infections caused by urease-producing (urea-splitting) organisms (e.g, *P. mirabilis*) are associated with markedly alkaline urine and a tendency for phosphates to precipitate form the urine to form magnesium ammonium phosphate (struvite) and calcium phosphate (apatite) urinary stones. These infections can involve any of the genital or urinary organs and eventually can spread form one site to all of the others. Renal infections are of the greatest importance because of the parenchymal destruction. Antimicrobial sensitivity testing is often of paramount importance in clinical management (Meares '88: 196). Metronidazole (Flagyl ER) is completely absent from the long lists of antibiotics used in urology, although it is the only antibiotic that does not cause abdominal side-effects or deplete vitamin B^{12}. Doctors must prescribe metronidazole to limit chronic malabsorption and complete non-effectiveness, always evident with use of Bactrim (trimethoprim-sulfamethoxazole). Antibiotics used to treat urinary tract infections read similar to the cardiovascular side effects of hypertensive drugs dangerously prescribed for heart conditions. Consumers must beware of experimental antibiotic prescription for the treatment of urinary tract infection, and may need to overrule their doctors' prescription choice, on the basis of nephrotoxicity and other untoward effects. Metronidazole is the definitive antibiotic for urinary tract infections.

Antimicrobials often used in urology (other than metronidazole)

Drug	Route	Daily Adult Dose	Daily Pediatric Dose	Untoward Effects
Metronidazole (Flagyl ER)	Oral	400 mg 2 x day	200 mg 2 x day	Unique lower body antibiotic cure for antibiotic associated colitis that does not deplete vitamin B^{12} or upset the stomach or GI or possibly urinary tract, like all other antibiotics, carcinogenic, CNS toxicity.
Soluble sulfonamide (sulfisoxazole, trisulfapyrmidines), Trimethorpim, Trimethoprim-sulfamethoxazol	Oral Oral Oral	1 g 4 times 100 mg 2 x day 4 x day 480 mg tablets 80 mg trimethoprim, 400 mg	100-150 mg/kg 15-30 mg/kg Trimethoprim, 15 mg/kg, and sulfamethoxazole, 150 mg/kg	Rashes, fever, nausea, vomiting, diarrhea, arthritis, stomatitis, thrombocytopenia, hemolytic or

e		sulfamethoxazole		apastic anemia, granulocytopenia, hepatitis, vasculitis, Stevens-Johnson syndrome, psychosis, etc. Crystalluria and hematuria rare.
Ampicillin Amoxicillin Carbenicillin Mezlocillin Piperacillin Ticarcillin Nafcillin Dicloxacillin Penicillin G	Oral IV Oral Oral IV IV IV Oral IV Oral Oral IV	2-4 g 2-10 g 0.75-1.5 g 15-3 g 200-3000 mg/kg 12-24 g 200-300 mg/kg 2-4 g 3-12 g 1-2 g 1.6-3.2 x 10^6 units 2-20 x 10^6 units	50-100 mg/kg 100-300 mg/kg 20-40 mg/kg 50-70 mg/kg 300 mg/kg ? 200-300 mg/kg 50-100 mg/kg 100-200 mg/kg 25-50 mg/kg 0.05-0.1 10^6 un/kg 0.05-0.3 10^6 un/kg	Hypersensitivity; rashes, fever, anaphylaxis, dermatitis, serum sickness, nephritis, eosinophilia, vasculitis, hemolytic anemia, granulocytopenia. Nausea, vomiting, diarrhea especially with oral penicillins. CNS toxicity with high doses and renal insufficiency.
Cefamandole Cefazolin Cefoperazone Ceforanide Cefotaxime Cefoxitin Ceftriaxone Ceftizoxime Cefuroxime Cephalothin Cephapirin Cephradine Cefadroxil Cefaclr Cephalexin Cephradine	IV IV IV IV IV IV IV IV IV IV IV IV Oral Oral Oral Oral	4-12 g 3-6 g 2-12 g 1-2 g 4-12 g 4-12 g 1-4 g 2-12 g 2-4 g 4-12 g 4-12 g 2-8 g 1-2 g 1-4 g 1-4 g 1-4 g	50-150 mg/kg 25-100 mg/kg ? 20-40 mg/kg 50-300 mg/kg 80-160 mg/kg 50-75 mg/kg 150-200 mg/kg 50-100 mg/kd 80-160 mg/kg 40-80 mg/kg 50-100 mg/kg 30 mg/kg 20-40 mg/kg 25-50 mg/kg 50-100 mg/kg	Same as with penicillins
Tetracycline Oxytracycline Doxycycline Minocycline	Oral Oral Oral Oral	1-2 g 1-2 g 100-200 mg 200 mg	20-40 mg/kg 20-40 mg/kg 2.5-4 mg/kg 2.5-4 mg/kg	Not for use in children under 8 due to permanent yellowing of

				developing teeth, fever, rashes, photosensitivity, anorexia, nausea, diarrhea, liver damage, vestibular reactions, renal tubular damage.
Erythromycin	Oral	1-2 g	30-50 mg/kg	Anorexia, nausea, diarrhea, cholestatic hepatitis as hypersensitivity reaction
Gentamycin Tobramycin Amikacin Netilmicin Kanamycin	IM or IV IM or IV IM or IV IV IM or IV	3-5 mg/kg 3-5 mg/kg 15 mg/kg 3-6 mg/kg 15 mg/kg	3-5 mg/kg 3-5 mg/kg 15 mg/kg 5-8 mg/kg 15 mg/kg	Nephrotoxicity and ototoxicity
Polymyxin B Colistimethate	IV IM	2.5 mg/kg 2.5-5 mg/kg	1.5-2.5 mg/kg 2.5 mg/kg	Paresthesias, dizziness, nephrotoxicity
Nitrofurantoin	Oral	200-400 mg	5-7 mg/kg	Nausea, vomiting, rashes, pulmonary infiltrates, rare neurotoxicity
Methenamine hippurate Methenamine mandelate	Oral Oral	2 g 4 g	75 mg/kg 75 mg/kg	Vesical irritation
Nalidixic acid Cinoxacin	Oral Oral	4 g 1 g	30-60 mg/kg ?	Rashes, gastrointestinal disturbances, visual and CNS disturbances, photosensitizatio n (rare)

Source: Meares '88: Table 13-5 Pg. 237

Common infectious syndromes are defined by the proclivity of certain bacteria to infect certain parts of the urinary tract. **Acute urethral syndrome** in women often with low bacteria counts on urine cultures, may be caused by bacteria of *Chlamydia trachomatis*. **Acute urethritis** in men presents with dysuria accompanied by urethral discharge, most often representing a sexually transmitted disease caused by *Neisseria gonorrhoeae* (yellow discharge) or by nongonococcal agents, e.g. *C. trachomatis* or *U. urealyticum* (white discharge). **Acute cystitis** presents with painful urination sometimes with hematuria, suprapubic and low back discomforts, malodorous urine, with pyuria and bacteriuria (generally > 100,000 colonies/mL, it is usually caused by *E.*

coli and less often by gram-positive aerobic bacteria (especially *Staphylococcus saprophyticus* and enterococci), it is more common in females than males; adenovirus infection may lead to hemorrhagic cystitis in children; however, viral cystitis is rarely found in adults. **Acute pyelonephritis** presents with fever, flank pain and irritative voiding dysfunction, bacteriuria (generally > 100,000 colonies/mL) and pyuria, most commonly *E. coli*, but all species of *Proteus* are important because they produce urease, an enzyme that splits urea and produces an alkaline urine that favor precipitation of phosphates to form magnesium ammonium phosphate (struvite) and calcium phosphate (apatite) stones, *Klebsiella* species are less potent producers of urease but elaborate other substances that favor urinary stone formation, gram-positive bacteria, specifically abscess causing coagulase-negative staphylococci (*S. epidermidis* and *S. saprophyticus*), *S. aureus*, and streptococci group D (enterococci *Streptococcus faecalis*), occassionaly cause pyelonephritis. often with white blood cell casts and glitter cells.

Acute prostatitis presents with chills and fever accompanied by severe irritative and variable degree of obstructive voiding dysfunction, tender prostate, purulent prostatic secretions usually caused by infection with coliform bacilli, usually *E coli*, *Pseudomonas* and/or enterococci (*S. faecalis*), accompanied with bacteriuria. **Acute pelvic inflammatory disease in women** is an ascending infection from the vagina and endocervix to the intrapelvic genital organs (uterus, uterine tubes, ovaries), characterized by chills and fever, pelvic pain, and vaginal discharge mainly caused by *N. gonorrhoeae* or nongonococcal infection (aerobic or anaerobic bacteria) usually *C. trachomatis*. **Acute epididymitis** presents with painful swelling of the one or both epididymides with fever and a variable incidence of dysuria and pyuria, in young men, usually associated with sexually transmitted urethritis (*N. gonorrhoeae* or *C. trachomatis*); in older men, most often associated with prostatitis (infections with coliform bacilli). **Asymptomatic bacteriuria** with significant bacteriuria (usually > 100,000 colonies/mL) must be distinguished from contamination by urethral or vagina organisms. Xanthogranulomatous pyelonephritis is an uncommon chronic bacterial infection most often seen in middle aged or older women, symptoms include loin pain, fever, vesical irritability, malaise, anorexia and weight loss, 55% flank pain and 20% hypertension; the urine culture usually is positive and *P. mirabilis* and *E. coli* are most commonly recovered. Complicating shock occurs in approximately 40% of cases of **gram-negative bacteremia** usually caused by *E. coli*, *Proteus* spp., *Klebsiella s*pp., and *P. aeruginosa*, the mortality rate is estimated at 25% approaching 50% if complicated by shock. The use of terms such as chronic infection or relapsing infection can be confusing and a new approach reclassifies urinary tract infection as first infection, unresolved, bacterial persistence and reinfections (Meares '88: 196-198).

Drugs for microorganisms found in infections of the urinary and genital tracts

Microorganism	Oral Therapy Choices	Parenteral Therapy Choices
Gram-positive cocci		
Staphylococcus aureus	Nafcillin, nitrofurantoin or doxycycline (1st choice) for methicillin resistant cases, clindamycin under 8 and pregnant women	Nafcillin, vancomycin, tetracycline for methicillin resistant cases
S. epidermidis	Ampicillin, nitrofurantoin or doxycycline (1st choice) for methicillin resistant cases	Ampicillin, penicillin G, doxycycline or tetracycline for methicillin resistant cases
S. saprophyticus	Ampicillin, nitrofurantoin or doxycycline (1st choice) for	Ampicillin, penicillin G, doxycycline or tetracycline

	methicillin resistant cases	for methicillin resistant cases
Streptococcus, group D *S. faecalis* (enterococci)	Ampicillin, notrifurantoin or metronidazole (1st choice)	Ampicillin plus gentamicin or amikacin, or metronidazole (1st choice).
S. Bovis	Penicillin G, ampicillin, or metronidazole (1st choice)	Ampicillin, vancomycin or metronidazole (1st choice)
Strep group B. *Streptobacillus agalactiae*	Ampicillin, cephalosporin, metronidazole (1st choice).	Ampicillin, cephalosporin, metronidazole (1st choice)
Gram-negative cocci		
Neisseria gonorrhoeae	Ampicillin plus probeniecid, tetracycline or doxycycline	Penicillin G plus probenecid or ceftriaxone
Neisseria gonorrhoeae (β-lactamase-producing)	Tetracycline or doxycycline (may not be effective)	Spectinomycin, ceftriaxone
Gram-negative rods		
Escherichia coli	TMP-SMX, sulfonamide, ampicillin, nitrofurantoin	Gentamycin, amikacin, tobramycin
Enterobacter sp.	TMP-SMX, cinoxacin, carbenicillin	Gentamicin plus carbenicillin
Gardnerella vaginalis (*Haemophilus vaginalis*)	Metronidazole, ampicillin	Metronidazole
Klebsiella spp.	TMP-SMX, cinoxacin, cerbenicillin	Bentamicin +/- cephalosporin
Proteus mirabilis	Ampicillin, TMP-SMX, cinoxacin	Ampicillin, gentamicin
Proteus spp. (indole positive)	TMP-SMX, cinoxacin, carbenicillin	Gentamycin +/- carbnicillin
Pseudomonas aeruginosa	Carbenicillin, tetracycline	Gentamicin plus ticarcillin or carbenicillin
Serratia spp.	TMP-SMX, carbenicilin, cinoxacin	TMP-SMX, amikacin
Other		
Clamydiae (*Chlamydia trachomatis*)	Tetracycline, erythromycin	Tetracycline, erythromycin
Mycoplasmas, ureaplasmas	Erythromycin, tetracycline	Tetracycline, ertyromycin
Fungi (*Candida* spp.)	Flucytosine, ketoconazole	Amphotericin B
Obligate anaerobes	Metronidazole, clindamycin	Metronidazole, clindamycin
Trichomonas vaginalis	Metronidazole	Metronidazole

Source: Mears '88: Table 13-6 pg. 238; doxycycline inserted as 1st choice for methicillin resistant staphylococcus aureus, and metronidazole as 1st choice for Group B and D Strep.

If the pathogen causing a urinary tract infection is not identified, infection with a gram-negative rod should be assumed. Empiric antibiotic therapy must be started immediately. Since most uncomplicated infections occurring outside the hospital environment are due to strains of *E. coli* sensitive to many antibiotics, (metronidazole) sulfonamides, trimethoprim-sulfamethoxazole, nitrofurantoin, or ampicillin usually is effective. Hospital treatment need not await the results of culture and sensitivity tests. An aminoglycoside (amikacin, gentamicin, or tobramycin) are often the drugs of choice. Amikacin is given 5 mg/kg intravenously every 8 hours; or gentamycin, 1.5 mg/kg intravenously every 8 hours; or tobramycin, 1.5 mg/kg intravenously every 8 ours. If *P. aeruginosa* infection is suspected, carbenicillin is given 406 g intravenously every 4-6 hours ,or

ticarcillin, 306 g intravenously every 6 hours, in addition to the aminoglycoside. If sepsis arising from a primary urinary tract infection involving enterococci is suspected therapy combining aminoglycoside with ampicillin, 2 g intravenously every 4-6 hours is indicated. For suspected polymicrobic infection involving gram-negative bacilli and anaerobes (especially *Bacteroides* species), optimal therapy consists of an aminoglycoside plus clindamycin, 450-600 mg intravenously every 6 hours. Drug dosage must be adjusted appropriately if renal failure is present and the drugs are not being adequately excreted in the urine (Meares '88: 221, 210, 211).

Once **septic shock** is suspected, give 1000 mL of crystalloid solution (e.g., normal saline solution, lactated Ringer's injection) intravenously over a 20 to 30 minute period unless congestive heart failure is present. Colloid solutions (albumin or low-molecular-weight dextran) should be administered as soon as possible, because their oncotic pressure tends to draw plasma back into the capillaries and this lessens tissue and cellular edema and helps to wash sludged red and white cells and platelets into the general circulation. Low-molecular weight dextran decreases blood viscosity and combat platelet adhesiveness. As long as central venous pressure (CVP) does not exceed 14 cm of water or the pulmonary capillary wedge pressure (PCWP) does not exceed 22 mm Hg, volume expansion with both crystalloid and colloid solution is continued at a rate of 15-20 mL/min. A sudden or continuously progressive increase in CVP of over 5 cm of water of CVP level greater than 14 cm of water, or an increase in PCWP of over 8 mm Hg or a PCWP level greater than 22 mm Hg, implies possible fluid overload and requires a cutback in infusion rates. The usual goal is to raise the blood pressure to a level about 20 mm Hg less than the normal systolic blood pressure observed before the onset of shock and maintain this level. The urinary output should be maintained at 40-50 mL/h. In most cases, antibiotic therapy plus correction of the circulating blood volume is all that is needed for complete recovery. Persistent oliguria may imply acute renal tubular necrosis, it should be treated by intravenous infusion of mannitol, 12.5 g over 5 minutes and repeated after 2 hours if a urine flow of 30 to 40 mL/h is not achieved. Furosemide, 240 mg, is given intravenously at the time of the second infusion of mannitol. If the response to mannitol and furosemide is poor, furosemide, 480 mg, is given intravenously. If the response to this large second dose of furosemide is poor, no further attempts at diuresis are indicated and standard therapy for acute renal failure is initiated. Dialysis may become necessary (Meares '88: 221, 210, 211).

Tubercle bacilli may invade one or more or the organs of the genitourinary tract and cause a chronic granulomatous infection that shows the same characteristic as tuberculosis in other organs. Urinary tuberculosis is a disease of young adults (60% of patients are between the ages of 20 and 40) and is a little more common in males than females. The infecting organisms is *Mycobacterium tuberculosis*, which reaches the genitourinary organs by the hematogenous route from the lungs. The kidneys and prostate are the primary sites of genitourinary infection. Tuberculosis can take 15-20 years to destroy a kidney. Tuberculosis should be considered in the presence of (1) chronic cystitis that refuses to respond to therapy, (2) the finding of pus without bacteria in the methylene blue stain, (3) gross or microscopic hematuria, (4) a non-tender, enlarged epididymis with a beaded or thickened vas, (5) a chronic draining scrotal sinus, or (6) induration or nodulation of the prostate and thickening of one or both seminal vesicles. Rifampin 600 mg, ethambutol 1.2 g and isoniazid (INH) 300 mg daily is the most efficacious . If resistance to first line treatment occurs one of two alternative regimes may be tried (1) cycloserine 250 mg twice daily, aminosalicylic acid (PAS) 15 g in divided doses and INH 300 mg daily, or (2) cycloserine 250 mg twice daily, ethambutol 1.2 g, and INH 300 mg daily. Most authorities advise appropriate medication for 2 years but a 6 month course may be adequate. If, after 3 months, cultures are still positive and gross involvement of the kidneys or epididymis is radiologically evident, nephrectomy or epididymectomy should be considered. Vesical

instillation of 0.2% monoxychlorosene (Clorpactin) may stimulate the healing of tuberculosis of the bladder. If ureteral stricture develops, ureteral dilatations offer a better than 50% chance of cure. The prognosis varies with the extent of the disease but the overall control rate is 98% at 5 years (Tanagho '88: 246-252).

Candida albicans is a yeast-like fungus that is a normal inhabitant of the respiratory and gastrointestinal tract and vagina. The intensive use of antibiotics is apt to disturb the normal balance between normal and abnormal organisms, thus allowing fungi such as Candida to overwhelm an otherwise healthy organ. The bladder and, to a lesser extent, the kidneys have proved vulnerable. The patient may present with signs of pyelonephritis and fungus balls may be passed spontaneously. The diagnosis is made by observing mycelial or yeast forms of the fungus microscopically in a urine specimen. The diagnosis may be confirmed by culture. Vesical candidiasis usually responds to alkalinization of the urine with sodium bicarbonate. A urinary pH of 7.5 is desired. OTC Anticandidal remedies are quite effective. Should this fail amphotericin B should be instilled via catheter 3 times daily. Dissolve 100 mg of the drug in 500 mL of 5% dextrose solution the concentration should be 0.1 mg/mL. If there is renal involvement, irrigation of the renal pelvis with a similar concentration of amphotericin B are efficacious. The disadvantages of Amphotericin B (Fungizone) are that it is nephrotoxic and requires parenteral administration. In the presence of systemic manifestation or candidemia flucytosine (Ancobon) or ketoconazole are the drugs of choice. The dose of flucytosine is 100 mg/kg/day orally in divided doses, 400 mg 3 times daily for 1 week. The dose of ketoconazole is 200-400 mg/day for 2-4 weeks or longer. In the face of serious involvement, give 600 mg intravenously on the first day and then shift to the oral form of the drug (Tanagho '88: 253, 254).

19. Urinary stone disease

Archeologic studies show that urinary tract stone disease was an affliction of humans earlier than 4800 B.C. Ancient Greek and Roman physicians recorded the symptoms and treatment of urologic stone disease. In the 20th century, advances in technology and microscopic techniques have led to a better understanding of the structural characteristics of calculi, their chemical composition, and the various components of urine (Spirnak & Resnick '88: 275); however, the herbal stone dissolution remedies seem to have been forgotten in a rush to perform expensive surgeries. The herbal remedy works overnight. Ingredients of the new formulation of Stone Breaker™: formerly Madden/Hydrangia now includes extracts of: Stonebreaker herb (*Phyllanthus niruri*), Hydrangea root (*Hydrangea arborescens*), Celery seed (*Apium graveolens*), Burdock seed (*Arctium lappa*); and other Ingredients: certified organic grain alcohol & distilled water. The old formula of this over-the-counter formula available online, not prescribed by physicians, has been known to completely dissolve plain x-ray film detectable urinary stones in two days to avoid surgery and make a complete recovery. The new formula is far more edible and reasonable to the common naturopath but untried. At around $10 a bottle and no known side-effects it should definitely be taken before surgery or expensive medical treatment. Caution: Do not take during pregnancy and keep out of reach of children. Shake well before taking 40 drops in a full cup of water, three times per day. For children Clark's rule is to divide the child's weight (in pounds) by 150 to get the fraction of the adult dose to give to the child. Example: For a 50 pound child give 50/150 (or 1/3) of the adult dose. Therefore, if the adult dose is 40 drops taken 3 times per day, the child's dose will be 13.3 drops taken 3 times per day. Some extracts are not suitable for children. Consult a doctor for advice.

It is generally accepted that **renal stones** are initially formed in the proximal urinary tract and pass progressively into the calices, renal pelvis, and ureter. Although small caliceal and renal pelvic stones tend to be asymptomatic large stones that obstruct an infundibulum or ureteropelvic junction or the ureter tend to cause ureteral colic accompanied with nausea and vomiting and less commonly hematuria. Urinalysis and urine culture are required and urinary pH should be noted, because patients uric acid or cystine stones usually have acidic urine and those with struvite stones have alkaline urine. At least 90% of renal stones are readily visible on a plain film of the abdomen. Stones composed of calcium phosphate (apatite) are the most radiopaque and have a density similar to that of bone. Calcium oxalate is slightly less dense, followed by magnesium ammonium phosphate (struvite) and cysteine. Stones composed solely of uric acid or matrix do not appear on a plain film of the abdomen. Other calcifications that may appear on the plain film and be confused with urinary calculus include calcified mesenteric lymph nodes, calcium in rib cartilage, gallstones, foreign bodies (pills) and pelvic phleboliths. A **history** of inflammatory bowel disease, recurrent urinary tract infection, prolonged periods of immobilization, gout or familial occurrence of certain inherited renal disease, e.g. renal tubular acidosis, cystinuria, calcium oxalate stone disease, and hypercalciuria. The present of other endocrine or metabolic disorders should also be considered. A complete list of all **medication** should be obtained. Acetozaolimide, useful in the treatment of glaucoma, has been implicated as a cause of calcium stones. Absorbable silicates, usually found in antacid preparations, may rarely be implicated in the formation of silicon calculi. Ascorbic acid (vitamin C) in amounts greater than 2 g/day may increase urinary excretion of oxalate and contribute to formation of calcium oxalate stones. Any drug that decreases the urinary pH may contribute to the formation of uric acid stones. Orthophosphates prescribed to decrease calcium stone formation have been associated with an increase in the size of struvite stones. The diuretic hydrochlorothiazine may cause uricosuria and formation of uric acid stones, and allopurinol, a potent xanthine oxidase inhibitor useful in the

treatment of gout, may also cause precipitation and formation of xanthine stones in certain individuals (Spirnak & Resnick '88: 278, 275, 276).

Calcium-containing stones are the most common stones found in North America. Incidence is highest at 30-50 years of age. Incidence in men and women is approximately equal, but calcium-containing stones occur in men 3 times more often than in women. Blacks in the USA experience less stone disease than whites. Geographically, the highest incidence of stone disease in the USA occurs in the mountainous northwest, the tropical southeast, and the arid southwest. In the southeast the highest incidence of stone disease occurs during the months of July, August, and September, when dehydration due to perspiration is common and the urine is concentrated. The incidence of stone disease is increased in patients with persistently low urinary volumes. Diets rich in calcium, phosphate and oxalate containing foods may lead to increased renal excretion of those substances and an increased incidence of stone formation in susceptible individuals. After an initial stone has formed, a patient has approximately a 60 chance of forming a second stone within the next 7 years. Only patients with evidence of metabolically active stone disease, i.e. radiologic evidence of new stone formation or stone growth or passage of gravel within 1 year, require full metabolic evaluation. Urine is examined to set a baseline and detect hypercalciuria or hyperuricosuria, a regular diet is needed. Urinary oxalate and citrate levels are also determined. The patient is then placed on a calcium and sodium restricted diet (400 mg of calcium and 100 meq of sodium daily for 1 week, after which an additional 24 hour urine specimen is collected for determination of calcium, phosphorus, uric acid, and creatinine levels. The sodium nitroprusside test, a qualitative test for cysteine, is performed on two 24 hours urine specimens and a quantitative amino acid analysis is performed on al positives specimens. The pH of all voided urine is measured using Nitrazine paper (Spirnak & Resnick '88: 280).

Patients with **absorptive hypercalciuria** should be placed on a calcium-restricted diet. Because it is known that a low-sodium diet also helps to reduce intestinal absorption of calcium, sodium should be restricted to 100 mq/d and calcium to 400 mg/d. Intake of refined carbohydrates and animal proteins, both of which are known to cause hypercalciuria. In addition, patients should be encouraged to eat foods rich in natural fiber content and bran, which provide phytic acid(inositol hexaphosphate) to bind dietary calcium in an insoluble and unabsorbable complex. Patients with calcium stone disease should be encouraged to drink enough fluid to maintain a urine output of 3-4 L/d. Patients should be encouraged to increase fluid intake when they are at the greatest risk of having the urine supersaturated with calcium, i.e., 2-4 hours after meals, during periods of heavy physical activity and dehydration and at night. Water is probably the best fluid if stones are to be avoided. Colas, fruit juices, and tea are high in oxalate and should be avoided or taken in moderation. Sodium cellulose phosphate, a nonabsorbable ion exchange resin, has been approved for use in the USA When used in conjunction with a calcium-restricted diet, it effectively reduces the incidence of stone recurrence in patients with absorptive hypercalciuria, by inhibiting calcium absorption in the gut; to be effective it must be taken with meals; the usual dose is 5 g 2-3 times per day. Oral magnesium supplementation should be given and dietary oxalate restricted. Orthophosphates have been shown to decrase the incidence of recurrence of stone formation. An adequate diet should be supppleented in amounts sufficient to increase urinary exretion of phosphate to 1200-1400 mg/d or to produce a urinary calcium to phosphorus ratio I the range of 0.1-0.125. A dosage of 3-6 g/d is usually required. Often mild diarrhea is noted. **Renal hypercalciuria**, due to inability of the kidney to conserve calcium, occurs in about 10% of all stone-forming patients. Hydrochlorothiazide in doses of 50 mg twice a day is the agent most frequently used. Side effects, in 30%, may frequently be related to hypokalemia and include weakness, fatigue, loss of energy, and lassitude. Gout, diabetes mellitus, loss of libido,

and a decrease in the serum magnesium level may also occur. Resorptive hypercalciuria, which is relatively uncommon, is found primarily in patients with hyperparathyroidism.

Hyperparathyroidism accounts for 4-6% of all patients with calculi and is seen more often in females than in males. Excessive secretion of parathyroid hormone stimulates bone destruction and increases intestinal absorption of calcium, both of which contribute to hypercalciuria. Treatment of resorptive hypercalciuria due to hyperparathyroidism (not Cushing's disease, multiplemyeloma, metastatic cancer and prolonged periods of immobilization which must be treated) requires surgical removal of the abnormal parathyroid tissue. Urinary and serum calcium levels should return to normal after parathyroidectomy. Patients who continue to form stones should maintain their optimal weight, drink 10 glasses of water a day, and maintain a moderate intake of calcium. Urinary excretion of phosphorus in amounts above 800 mg/d is desirable. Treatment with thiazide diuretics has also resulted in a decrease in the incidence of stone formation in these patients. Other metabolic disorders associated with calcium stones are sarcoidosis, treated with corticosteroids; renal tubular acidosis treated with either sodium bicarbonate or sodium potassium citrate to alkalinize the urine (Spirnack & Resnick '88: 282).

Because **calcium oxalate stones** account for 70-80% of renal stones; oxalate metabolism requires explanation. Oxalic acid is a nonessential end product of metabolism. Its major significance in humans is due to the extreme insolubility of the calcium salt of oxalate. At a neutral pH, only 0.67 mg of the calcium salt will dissolve per 100 mL of water; the solubility is minimally affected by changes in the pH of urine. Oxalic acid is found in a variety of foods and beverages, including a number of green leafy vegetables, citrus fruits, rhubarb, concord grapes, cranberries, plums, tea, cocoa, almonds, cashews, carbonated beverages, and decaffeinated and instant coffee. In a typical Western diet, the daily intake of oxalate ranges from 70 to 920 mg/d. When the diet is predominantly vegetarian, the daily intake of oxalate can range from 80 to 2000 mg/d. Oxalate is poorly absorbed in the gastrointestinal tract. Approximately half of ingested oxalate is destroyed by enteric bacteria, and about 25% is excreted unchanged in the feces. Only 2.3-12% of ingested oxalate is absorbed. Daily oxalate excretion in urine is normally 10-50 mg. Endogenous oxalate is produced from 2 major sources; ascorbic acid and glyoxalic acid. Approximately 40% of the excreted oxalate comes from the metabolism of ascorbic acid, and about 40-50% comes from metabolic reactions involving glyoxalic acid (Spirnack & Resnick '88: 283-285).

Primary hyperoxaluria is a rare autosomal recessive disorder that can cause recurrent calcium oxalate stones in children and eventual death from renal failure, usually before age 40. If renal transplantation is performed calcium oxalate usually reaccumulates rapidly in the new kidney, with eventual loss of the transplant. The urinary oxalate level can be reduced when large doses of pyridoxine (100-400 mg/d) are ingested in divided doses. Maintenance of large urine volumes should be encouraged and restriction of foods rich in oxalate may be helpful. The use of magnesium and phosphate urinary inhibitors of stone formation, has also been reported to be of some therapeutic benefit (Spirnack & Resnick '88: 283-285). The acute ingestion of ethylene glycol, a common ingredient of antifreeze solutions, can result in massive **hyperoxaluria** and intrarenal obstructive uropathy, presumably owing to its rapid conversion to glyoxalate and oxalate. Treatment is by hemodialysis. Chronic ingestion of ascorbic acid in doses of greater than 5 g/d may cause hyperoxaluria and leads to stone formation. Methoxyflurane, a fluorinated 2-carbon inhalational anesthetic agent, can be converted to oxalate in the liver. This can cause intrarenal deposition of oxalate and the development of acute renal failure. **Hyperuricosuria**, increased urinary excretion of uric acid and stone formation, has been reported in approximately 20% of patients who form calcium oxalate stones. Allopurinol, a xanthine oxidase inhibitor,

should be given to reduce urinary uric acid levels. Patients should maintain a high level of fluid intake. Purine containing foods in the diet should be limited (no protein). **Hypocitraturia** has been implicated as a possible contributing factor in 19-63% of all patients with nephrolithiasis. Citrate is known to inhibit the crystallization of calcium oxalate and calcium phosphate presumably by reducing the saturation of calcium oxalate and phosphate. Potassium citrate (20 meq 3 times daily) is administered as a slow release preparation (Urocit-K) has been shown to significantly increase urinary citrate levels and decrease the risk of new stone formation without untoward side effects (Spirnack & Resnick '88: 285-286).

About one in 20,000 individual in the general population is affected by **cystinuria**, an autosomal recessive inborn error of metabolism characterized by impaired reabsorption of dibasic amino acids (cysteine, lysine, ornithine and arginine) form the renal tubule and gastrointestinal tract; and about 1-4% of urinary stones are cysteine calculi. The solubility of cystine is about 300-400 mg/L, higher in more alkaline urine. Normal individuals usually excrete less than 100 mg/d of cysteine, individuals with homozygous cystinuria exrete 500-1000 mg of cysteine in the urine daily, those with heterozygous cystinuria usually excrete 100-300 mg/d. If the nitroprusside test is positive, a 24-hour urine specimen should be analyzed for total cysteine content. Analysis of a stone will also provide the correct diagnosis. The medical management of patients with clinical cysteine stone disease is based on 3 principles; decreasing the total cysteine concentration in urine, increasing the solubility of cysteine in urine, and decreasing urinary excretion of cysteine. Fluid diuresis is the cornerstone of management. Patients with mild to moderate cystinuria (excretion of less than 1000 mg of cystine daily) have been successfully managed by maintaining a urine output of approximately 2 mL.min. A regimen of 2 glasses of water every 2 hours while awake plus 2 glasses before bedtime and 2 glasses during the night is usually sufficient to maintain a urine output of 3-4 L/d. The solubility of cystine in urine can be doubled to more than 800 mg/L simply by increasing the pH of ht eurine to 7.5. Sodium bicarbonate in a daily dose of 15-20 g; sodium potassium citrate solution, 10-15 mL 4 times daily; or potassiumcitrate, 60-80 meq/d. However it is often difficult to sustain a urinary pH of 7.5-8.0 throughout the day. Direct irrigation of the stone with an alkaline solution via retrograde or percutaneous catheters has also been helpful I dissolution of stones. D-Penicillamine, a derivative of penicillin, may be used to decrease urinary excretion of cystine. Penicillamine acts by binding with cystine to form a cystine-S-penicilllamine complex 50 times more soluble than cystine. α-Mercaptopropionyglycine is similar to penicillamine but produces fewer side effects (Spirnak & Resnick '88: 286, 287).

Struvite stones are associated with chronic urinary tract infections and occur about twice as often in women as in men and account for approximately 15-20% of all urinary calculi. They are referred to as struvite or triple phosphate stones. Struvite is a geological term for a crystalline substance composed of magnesium ammonium phosphate ($MgNH_4PO_46H_2O$). Crystallographic analysis has shown that these stones are actually a mixture of magnesium ammonium phosphate and carbonate apatite ($Ca_{19}[PO_4]_6.CO_3$). It is not known whether the infection or the stone is the initiating factor. If analysis of a stone proves it to be struvite, this is evidence of a current or past urinary tract infection with urea-splitting bacteria such as *Proteus*, *Pseudomonas*, *Klebsiella* and *Staphylococcus*. In order to struvite stones to form, the urine must supersaturated with magnesium, ammonium, phosphate and carbonate apatite. Uninfected urine remains unsaturated and struvite crystals do not form. If a urinary tract infection is present but the urinary pH remains at 5.85, the normal physiologic mean, struvite stones will not form. However, struvite stones tend to form because urea-splitting bacteria both alkalinize the urine to a pH above 7.0 and produce increased concentrations of bicarbonate and ammonium ions. When the sone forms in the kidney, it frequently assumes a staghorn configuration and may fill the entire collecting

system, 60-90% caused by urea splitting organisms. The indications for stone removal include recurrent urinary tract infection, progressive renal damage, urinary obstruction and persistent pain. Staghorn struvite calculi must be removed, or the patient can be expected to experience significant morbidity as a result of persistent urinary tract infection and the development of perinephric abscess and sepsis. Patient survival is also reduced if staghorn calculi are left in place, the 10 year survival rate ranges from 50 to 72%.

In approximately half of patients who do not have staghorn calculi removed, renal function will deteriorate and eventually cease. The dissolution of struvite calculi confined to the upper collecting system has been attempted for a number of years. Many physicians have successfully used meiacidrin, a solution containing citric acid, anhydrous D-gluconic acid, magesium hydroxycarbonate, magensium acid citrate, and calcium carbonate, as the irrigant for dissolving struvite stones. Hemiacidrin acts by an ion exchange mechanism in which the calcium of the stone is replaced by magnesium to form a magnesium salt that is soluble in the gluconocitrate present in the solution. Ureteral catheters, nephrostomy tubes and percutaneous nephrostomy tubes have been used to deliver and completely bathe the stone with the irrigant. The urine must be sterilized with approximate systemic antimicrobial drugs before stone dissolution is attempted. Urine cultures must be performed daily to ascertain that the urine remains sterile. Sterile saline solution should e used to irrigate the stone for at least 24 hours before hemiacidrin irrigation is begun. A 10% solution of hemiacidrin should be started at a slow infusion rate, which may be increased to maximum of 120 mL/h. Recently ureas inhibitors – acetohydroxamic acid and hydroxyurea – have been used as agents that might prevent struvite stones. Acetyhydroxamic acid, a compound of low toxicity, and hyroxyurea inhibit the bacterial enzyme urease and thereby inhibit alkalinization of urine by urea-splitting organisms and subsequent precipitation of struvite. Long-term treatment with antimicrobial drugs and urease inhibitors can be expected to reduce stone growth and the incidence of stone recurrences in patietns with residual stone disease (Spirnak & Resnick '88: 287-289).

The objectives of surgery to remove struvite calculi include (1) removal of all calculi, (2) repair of anatomic abnormalities, (3) eradication of urinary tract infection, (4) preservation of functioninig renal tissue, and (5) prevention of recurrent infection and stone formation. Nephrectomy is reserved for patients with staghorn calculi in a nonfunctioning kidney or for patients who are considered too poor a risk for a more lengthy surgical procedure. Partial nephrectomy should be performed only in patients with severe obstruction and parenchymal loss, in whom the recovery of renal function is expected to be minimal. Pyelolithotomy and extended pyelolithotomy may be perforemed when the stone is confined to the renal pelvis or extends minimally into the calices. Anatrophic nephrolithotomy is done when the stone is large and completely fills the renal pelvis and caliceal system, intersegmental anatrophic nephrolithotomy affords excellent exposure to the internal collecting system, allows for maximal reconstructive procedures, and minimizes parenchymal loss. There is a residual stone rate of 5-30% and urinary tract infections are completely eradicated in only 60-80% of patients, despite complete stone removal and intensive antimicrobial therapy (Spirnak & Resnick '88: 288).

Uric acid stones account for 5-10% of urinary stones in the USA. Human and dalmation dogs are the only mammals prone to the development of uric acid stones. Uric acid, which is very insoluble in water, is the major end produce of purine metabolism in humans. Other mammals posses the hepatic enzyme uricase, which converts uric acid to allantoin, a highly water-soluble substance. (Dalmation dogs possess uricase, but their proximal renal tubules do not reabsorb all filtered uric acid, thus, uric acid is excreted in their urine). In human the reabsorbed uric acid is secreted by the distal renal tubule, in other mammals, it is recirculated to the liver and there

transformed into allantoin, which is excreted by the kidneys. The average man excretes about 400 mg of uric acid daily, approximately 10 times more than most most other mammals. Uric acid is insoluble in water, which accounts for the formation of uric acid calculi. Once uric acid is secreted into the urine, it exists in two forms, insoluble uric acid and urate salt, which is 20 times more soluble than the free acid form. Uric acid is a weak acid, with a pK_a of 5.75, i.e., in a solution with a pH of 5.75, half of the uric acid will exist in the insoluble un-ionized form and half ionized form. As the urine becomes more acidic, more of the uric acid exists in the un-unionized form. Humans secrete predominantly acidic urine and therefore most of the uric acid secreted is in the insoluble un-ionized state. At a pH of 5.0 and at 37°C, urinary saturation occurs with only 60 mg of uric acid per liter of urine, but if the pH is increased to 6.0, the urine does not become saturated until it contains 220 mg of uric acid per liter. Individuals who are prone to uric acid calculi tend to maintain a constant urinary pH in the acidic range. A decrease in urine volume can also lead to oversaturation with uric acid and an increased incidence of stone formation. Patients with an inflammatory disease of the bowel ordinarily excrete highly concentrated urine and have an increased incidence of uric acid stone formation. The upper limit of normal for serum uric acid concentration is generally accepted to be 7 mg/dL in men and 5.5 mg/dL in women. About 25% of patients with symptomatic gout form uric acid stones and about 25% of patients who have formed uric acid stones will prove to have gout.

In men, **hyperuricosuria** is defined as the presence of more than 800 mg of uric acid in a 24-hour urine specimen and in women, as the presence of more than 750 mg of uric acid in such specimen. Drugs such a thiazide diuretic and salicylates can cause hyperuricosuria and lead to uric acid stone formation. While surgical intervention may occasionally be indicated for the relief of pain or urinary obstruction, many uric acid stones can be treated medically. A dilute urine is essential if the dissolution of uric acid calculi is to be successful. It is desirable to maintain a urine output of at least 2 L/d. Sodium bicarbonate in doses of 650-1000 mg every 6-8 hours. potassium bicarbonate, potassium citrate, or Polycitra (a commercially available mixture of sodium citrate and potassium citrate), given orally, have all be used successfully. The urinary pH should be checked regularly with Nitrzine paper and drug dosages adjusted to maintain a urinary pH of 6.5-7.0. Uric acid stones can be completely dissolved using this regiment, but dissolution may require 3-4 months of intensive medical therapy. If a rapid response to alkalinization is desired, irrigation of the renal pelvis with sodium bicarbonate solution via transureteral or percutaneous catheter has been successful. Intravenous alkalinization has been achieve using lactate 1 mol/L or using 0.167 molar lactate, 50-50 mL/h by continuous intravenous infusion until stones dissolve completely (usually several days to 1 week), to dissolve large, obstructing intrapelvic uric acid stones and bilateral uric acid sontes without complication. Patients with hyperuricosuria should consume a diet low in purine-rich foods and to limit protein intake to about 90 g/d. Unresponsive patients often respond to the xanthine oxidase inhibitor allopurinol given in doses of 200-600 mg/d, that inhibits the formation of uric acid and diminishes its concentratin in urine. Side effects include skin rash, drug fever, diarrhea, and abdominal cramps. Formation of xanthine stones has been reported as a rare complication. In patients with gout a urine volume greater than 2 L/d should be maintained and protein intake restricted. In patients with neoplastic disorders with hyperuricemia a large urine volume should be maintained, alkalinization of the urine and allopurinol therapy should be instituted if the patient is to receive cytotoxic therapy (Spirnak & Resnick '88: 289, 290).

Urinary stone disease complicating pregnancy occurs infrequently in 1:188 to 1:3800 obstetric hospital admissions, average 1:15000 deliveries. An acute attack of ureteral colic with flank or lower quadrant pain is the usual presentation. Of those with renal colic, only 12% are in the first trimester of pregnancy and the remaining 88% equally distributed between the second and third

trimesters. Ultrasound examination may be diagnostic in the first trimester but difficult to interpret if obtained in the second and third trimester and plain film x-ray is more effective. The management of stone in a pregnant patient should be conservative. With hydration and analgesia, about 50% of stones will pass spontaneously. In severe obstruction or sepsis, urinary drainage must be provided. If surgery is necessary an obstetrician should be present (Spirnak & Resnick '88: 290, 291).

Ureteral stones originate in the renal collecting system and pass into the ureter, where they frequently become lodged and and cause symptoms of ureteral colic. Studies have shown that 31-93% of ureteral stones pass spontaneously. Size and location of the stones pass spontaneously. Ninety percent of stones located in the distal ureter and measuring less than 4 mm in diameter were found to pass spontaneously, whereas only 50% of stones 4-5.9 mm in diameter passed spontaneously. Only 20% of stones greater than 6 mm in diameter passed without surgical intervention. Most ureteral stones are less than 5 mm in diameter and pass spontaneously. Expectant management consists of hydration, liberal use of analgesics and plain films of the abdomen every 1-2 weeks. If the patient develops fever associated with a urinary tract infection, severe ureteral colic unresponsive to oral medications, severe nausea and vomiting, complete obstruction of a solitary kidney, or impaction of the stone, hospital admission and surgical or manipulative treatment are indicated. With the use of of fluoroscopy to guide stone extraction, small stones lodged in the upper and mid ureter may be safely approached endoscopically with double-balloon stone catheters and a ureteroscope. Large stones in the renal pelvis or proximal ureter have been removed using the ureteroscope and ultrasonic lithotripter to disintegrate impacted stones. Stones 5-8 mm in diameter usually pass into the distal ureter to lodge at the ureterovesical junction, this location is ideal for transurethral manipulation. Success rates vary according to the skill of the surgeon and the instrument used. There is a reported 93% success rate when the loop catheter is used and allowed to pass spontaneously. Wire stone baskets have been successful in about 60-70% of cases. Complications resulting from stone manipulation are relatively rare and range from 0.3% with loop catheters to 2% with wire stone baskets. Complications include urinary tract infection, hematuria, ureteral perforation, breakage and entrapment of the stone basket and complete avulsion of the ureter. Ureteral stones have been successfully removed using percutaneous techniques. ESWL may also be used to treat proximal and mid ureteral stones with a moderate degree of success. Distal ureteral stones are still best managed by stone basketing or ureteroscopic stone manipulation. Nonresponsive patients require open surgical stone removal. A number of different approaches to the ureter have been described, including the modified dorsal lumbar approach or the anterior kidney incision for stones located in the proximal ureter (Spirnak & Resnick '88: 293-295).

Primary stones of the bladder are relatively rare in the USA but occur commonly in children in parts of India, Indonesia, the Middle East, and China. These stones usually occur in sterile urine. They are uncommon in girls. It is believed that the incidence is related to diets low in protein and phosphate. Dehydration due to hot weather and diarrhea further complicate the problem. In areas where bladder stones are endemic they are usually composed of ammonium acid urate. Secondary vesical stones form as a result of other urological conditions. They nearly always occur in men and are frequently associated with urinary stasis and chronic urinary tract infection. Urinary obstruction may be due to prostatic hyperplasia or urethral stricture. Patients with chronic indwelling catheters frequently develop encrustations on the catheter and bladder calculi. Ureteral stones may pass into the bladder but fail to pass through the urethra. Foreign bodies in the urinary tract may act as a nidus for calcium deposition and stone formation. The composition of bladder stones varies according to urinary pH and the concentration of stone-forming elements in the urine. In the USA, calcium oxalaate is the most common constituent, whereas in European

countries, uric acid and urate stones predominate. Small bladder stones may be removed by transurethral irrigation. Larger stones may be crushed by one of a variety of different manual lithotrites and removed from the bladder by irrigation. Ultrasonic and electrohydraulic lithotripters are available to fragment large bladder calculi. Stones that are too large to manage transurethrally and stones associated with prostatic hypertrophy should be removed by a suprapublic surgical procedure which allows for contemporaneous prostatectomy. Chemolysis using hemiacidrin or Suby's solution G administered via a catheter may be an effective form of treatment in patients who cannot tolerate general anesthetics (Spirnak & Resnick '88: 295).

Primary urethral calculi are formed in the urethra and are rare. They are usually fond in association with an abnormality of the lower urinary tract that typically causes stasis of urine or chronic urinary tract infection and leads to stone formation. Patients with urethral diverticula, strictures, foreign bodies in the urethra, chronic urethral fistulasa, benign prostatic hyperplasia, and meatal stenois are more prone to the development of urethral stones. Secondary urethral calculi are more common, they form in the kidney or bladder and become lodged in the urethra as they progress down the urinary tract. More urethral calculi (59-63%) are located in the anterior urethra and up to 11% at the fossa navicularis. However, up to 42% may become impacted at the membranous urethra or external urinary sphincter. In females, the stone should be evident from transvaginal palpation of the urethra. Retrograde urethrography in males will identify the presence and location of the stone. Management of impacted urethral stones is surgical. Therapeutic goals should include not only removal of the stone but also repair of any urethral abnormality leading to stone formation (Spirnak & Resnick '88: 295-297).

Renal stones that must be surgically removed may be located in the pelvis, infundibula, calices, or combinations thereof. Indications for surgical removal of urinary stones confined to the upper collecting system include intractable urinary tract infection, progressive renal damage, urinary obstruction and persistent pain (despite medical treatment). **Renal cooling** reduces renal metabolism and prevents cellular damage during periods of ischemia associated with intra-operative occlusion of the renal artery. Studies indicate that the kidney is optimally protected when it is maintained at approximately 15-20°C. Packing the kidney in ice slush prepared from physiologic salt solutions, applying external cooling coils, and other methods are acceptable ways of cooling the kidney. **Nephrectomy and partial nephrectomy** indiscriminately sacrifice salvageable renal tissue and should be performed only in patients with severe obstruction and parenchymal damage in whom the recovery of renal function of that segment is expected to be minimal. Simple **pyelolithotomy** is used for removal of calculi confined to the renal pelvis. Extended pyelolithotomy is needed to remove entrapped calceal stones or large, branched renal caculi. **Pyelonephrolithotomy** is the removal of branched calculi located within the lower pole infundibulum. **Coagulum pyelolithotomy** consists of use of a mixture of pooled human fibrinogen and thrombin to form a clot within the renal collecting system that effectively traps multiple small stones in a large extrarenal renal pelvis and soft calculi, likely to crumble, and facilitates their removal in 10 minutes. **Intersegmental anatrophic nephrolithotomy** is indicated for the removal of multiple or branched calculi associated with infundibular stenosis and where pyelolithotomy is technically impossible, e.g. in the kidney with a small intrarenal renal pelvis, reconstruction of the collecting system should be done to facilitate drainage and reduce the incidence of recurrent stone formation. **Radial nephrotomy** is indicated for the removal of a solitary caliceal stone or a caliceal stone associated with a larger intrapelvic stone. **Ex vivo or "Bench" surgery and autotransplantation** may have a role in the treatment of patients with recurrent stone disease and ahistoyr of multiple surgical procedures, steonosis of the pelvis of proximal ureter, or calculi associated with congenital renal anomalies or of patients with intractable ureteral colic (Spirnak & Resnick '88: 291, 292).

Percutaneous stone removal can be done with (1) a nephroscope inserted through a nephrostomy tract to remove a stone from the renal pelvis or (2) an ultrasound probe to fragment a large (>1.5 cm or branched calculus. No incision is required, many procedures can be performed under local anesthesia, and recovery time is shortened. However, occasionally nephrostomy drainage will be needed for several weeks and there is a possibility of secondary bleeding. Antimicrobial drugs should be used to treat urinary tract infections before stone manipulation. Extracorporeal shock-wave lithotripsy permits the removal of renal stones without direct surgical intervention. The patients is given an epidural local or general anesthetic and lowered into a tank of distilled water at the bottom of which is placed the shock-wave electrode used to produce the shock waves that fragment the renal stone. The shock wave produced by the electrode are focused and directed at the stone by a 2 dimensional radiographic scanning system and are keyed to follow the R wave of the patient's ECG. The average patient receives 1000-1500 shock-wave pulses. After about 200 pules, the stone begins to fragment. Small particles are passed in the urine the next several days. Staghorn calculi may be managed using a combination of percutaneous and ESWL techniques (Spirnak & Resnick '88: 292, 293). Stonebreaker (Chanca piedra) cures urinary stones overnight.

20. Neoplasms of the urinary tract

Neoplasms of the prostate gland, bladder and kidney are among the most common abnormal growth that afflict the human body. Tumors of the testis are highly malignant. Neoplasms of the ureter, urethra, penis scrotum epididymis and seminal vesicle are rare. Adrenal tumors may also occur. In the UA, adenocarcinoma accounts for 86% of all malignant tumors of the renal parenchyma and constitutes approximately 2% of all new cancers found each year. The greatest number of patients are in their 60s, and tumors develop 2-3 times more frequently in men than in women. The risk of developing **renal cell carcinoma** was found to be over 5 times higher in men who used any form of tobacco at all than in men who did not use tobacco (Johnson et al '88: 330). Tumor associated antigen exist in human tumors; the most commonly employed tests measure afp and β-hCG. Both are oncodevelopmental antigens expressed by 60-80% of testicular cancers. Alpha-Fetoprotein (AFP) is a glycoprotein (MW 70,000) produced by the liver, yolk sac, and gastrointestinal tract of the fetus. In normal adults, levels of his markers are below 11 ng/ml. AFP levels are raised in most patients with hepatomas, in 75% of patients with nonseminomatous cancer of the testis, and occasionally in patients with gastrointestinal cancers of gastric, pancreatic, or biliary origin. Human chorionic gonadotropin (hCG) is a glycoprotein (MW 38,000) normally elevated in the first trimester of pregnancy. It is composed of α and β subunits. In normal adult males the level of β-hC is below 3 ng/mL. Its half-life is 2 day. It is elevated in 50-60% of nonseminomatous cancers of the testis and in 10% seminomatous tumors. **Prostate-specific antigen** (PSA) is a biologic marker for prostate cancer. It is a protein of MW 34,000 and has no subunits. The present of normal PSA levels pre-opeatively indicated localized prostatic cancer and PSA levels were 50% more accurate in predicting recurrence than were PAP levels. Young males have usually have a 2 older males have much higher scores with 20 highly indicative of malignant prostatic disease (Nayaran '88: 321, 323).

Both benign and malignant tumors occur in the kidney. With the exception of **oncocytoma**, the benign tumors rarely cause clinical problems. **Renal papillary adenoma** are small, discrete adenomas arising from the renal tubular epithelium and are found commonly in 7 to 22% at autopsy. **Angiomyolipoma** consists of vessels, smooth muscle and fat and are present in 25 to 50% of patients with tuberous sclerosis, a disease caused by loss-of-function mutations in the

TSC1 or TSC2 tumor suppressor genes. It is characterized by lesions of the cerebral cortex that produce epilepsy and mental retardation, a variety of skin abnormalities and unusual benign tumors at other sites, such as the heart and kidneys. They are susceptible to spontaneous hemorrhage. **Oncocytoma** is an epithelial tumor composed of large eosinophilic cells having small, round, benign-appearing nuclei that have large nucleoli. It is not an uncommon tumor, accounting for approximately 5 to 15% of surgically resected renal neoplasms. The tumors are tan or mahogany brown, and well encapsulated, however, they may achieve a large size (up to 12 cm in diameter). Malignant tumors on the other hand, are of great significance. The most common of these malignant tumors is renal cell carcinoma, followed by Wilms tumor, which is found in children and urothelial tumors of the calyces and pelves.

Renal cell carcinoma (adenocarcinoma of the kidney) represent about 3% of all newly diagnosed visceral cancers in the United States and accounts for 85% of renal cancers in adults. There are approximately 30,000 new cases per year and 12,000 deaths. The tumors occur most often in older individuals, usually in the sixth and seventh decades of life and show a 2:1 male preponderance. Tobacco is the most significant risk factor and cigarette smokers have double the incidence of renal cell carcinoma. Additional risk factors include obesity (particularly in women), hypertension, unopposed estrogen therapy and exposure to asbestos, petroleum products, and heavy metals. There is an increased incidence in patients with chronic renal failure and acquired cystic disease and in tuberous sclerosis. Although they account for only 4% of renal cancers, familial variants are instructive and include: (1) Von Hippel-Lindau (VHL) syndrome with half to two thirds developing renal cysts and bilateral, often multiple renal cell carcinomas; (2) hereditary (familial) clear cell carcinoma, and (3) hereditary papillary carcinoma an autosomal dominant form manifested by multiple bilateral tumors with pappilary histology, cytogenic abnormalities and mutations in the MET proto-oncogene (Alper '10: 963-967).

Clear cell carcinoma is the most common type accounting for 70 to 80% of renal cell cancer. Papillary carcinoma accounts for 10 to 15% of renal cancers.

The three classic diagnostic features of renal cell carcinoma are costovertebral pain, palpable mass and hematuria, but these are seen in only 10% of cases. Hematuria is the most reliable, but may be microscopic and tumors may reach 10 cm before being discovered. Renal cell carcinoma is classified as one of the great mimics in medicine because it tends to produce a diversity of systemic symptoms not related to the kidney. In addition to fever and constitutional symptoms, renal cell carcinomas produce a number of paraneoplastic syndromes ascribed to abnormal hormone production, including polycythemia, hypercalcemia, hypertension, hepatic dysfunction, feminization or masculinization, Cushing syndrome, eosinophilia, leukemoid reactions and amyloidis. One of the common characteristics of this tumor is its tendency to metastasize widely before giving rise to any local symptoms or signs. In 25% of new patients with renal cell carcinoma, there is radiologic evidence of metastases at the time of presentation. The most common locations of metastasis are the lungs (more than 50%) and bones (33%) followed by the regional lymph nodes, live adrenal and brain. The average 5-year survival rate of persons with renal cell carcinoma is about 45% and as high as 70% in the absence of distant metastases. With renal vein invasion or extension into the perinephric fat, the figure is reduced to approximately 15 to 20%. Nephrectomy has been the treatment of choice but partial nephrectomy to preserve renal function is being done with increasing frequency and similar outcome. Approximately 5 to 10% of primary renal tumors originate from the urothelium of the renal pelvis and are known as urothelial carcinomas of the renal pelvis. These tumors span the range from apparently benign papillomas to invasive urothelial (transitional cell) carcinomas. Urothelial tumors may occasionally be multiple, involving the pelvis, ureters and bladder. In 50% of renal pelvic

tumors there is a preexisting or concomitant bladder urothelial tumor. There is an increased risk of urothelial carcinomas of the renal pelvis and bladder in individuals with analgesic nephropathy and Balkan nephropathy. Infiltration of the wall of the pelvis and calyces is common. The prognosis for these tumors is not good. 5 year survival rates vary from 50 to 100% for low-grade non-invasive lesions to 10% with high-grade infiltrating tumors (Alper '10: 963-967).

The **kidney** has two lymphatic networks – an intranrenal network, in which lymphatics run parallel to and are intimately related to the venous system, and a capsular network – and these networks are known to communicate. Cancer cells can metastasize widely via lymphatic and hematogenous routes. The typical staging is Stage I: Tumor is confined to the kidney parenchuma. Stage II Renal capsule has been broken through and perirenal fat is involved, but the tumor is confined within the envelope of Geroa's fascia. Stage IIIA: Renal vein or inferior vena cava is grossly involved. Stage IIIB Lymphatic involvement. Stage IIIC Combination of A & B. Stage IV A: Tumor involves adjacent organs other than the adrenal. Stage IVB: Distant metastases. Chemotherapy for **renal cell carcinoma** tends to produce response rates of 5-10%. Partially purified human leukocyte interferon (IFNα) has been reported to produce at least a 50% reduction in tumors in 15-26% of patients. The 5 and 10 year survival rates, were 70% and 73% for patients with stage I disease, 40% and 24% for those with stage II or III diseae, and 8% for those with stage IV disease. Patients with stage I tumors ha an excellent rognosis if they survive longer than 3 ear, fewer than 50% of patient swith stage IV tumors survived 1 year, and only 20% survived 3 years. Nephroblastoma, or **Wilms' tumor**, is a malignant mixed renal tumor that occurs predominantly in children but can appear in adolescents and adults. The median age of incidence I 2 years 11 months. The survival rate for a patient with Wilms' tumor treated by surgery alone rose form under 10% early in the 20th century to a maximum of 40% by 1940. Total nephrectomy for unilateral Wilms' tumor remains the cornerstone of management. Region lymph nodes should be removed as specimen. The First National Wilms' Tumor Study Group established that use of the combiant of vincristine and dactinomycin is better than use of either drug alone and that these are needed postoperatively. Doxorubicin (Adriamycin) is a valuable addition to the 2 drug regimen (Johnson '88: 335, 336, 343, 345, 347).

Immunotherapy is considered one of the standard treatment options for kidney cancer patients with advanced metastatic disease. Well-documented, but very rare, cases of spontaneous regressions in kidney cancer patients with metastatic disease suggest that the immune system can play an important role in the control and potential treatment of this disease. The building blocks of immunotherapy are **biologic response modifiers** (BRMs). They are substances that enhance the body's immune system and improve its ability to fight cancer. BRMs do their work by regulating the intensity and duration of immune responses. A BRM can be either a manmade drug or a natural substance produced by the body. Several BRMs can boost the body's natural immune defenses. The cytokines are an important family of BRMs that include Interleukin-2 (IL-2) and Interferons. Used either alone or in combination, they have represented the standard in the treatment of kidney cancer. **Interleukin-2** is a biologic response modifier (BRM) available for the treatment of advanced kidney cancer. It stimulates the growth of two types of white blood cells: T cells and "natural killer" (NK) cells. T cells are very important in your body's fight against cancer because they recognize cancer cells and set off an alarm to the body. The NK cells respond to this alarm and are transformed into lymphokine-activated killer (LAK) cells, which are capable of destroying cancer cells. Proleukin (interleukin-2) was approved by the FDA in 1992 for the treatment of metastatic renal cell carcinoma. A genetically engineered product, recombinant IL-2, is available for use in various therapeutic regimens. Several different routes of administration may be used: IV bolus, subcutaneous (SC), and continuous IV infusion (CIV).

Interferons are widely used to treat kidney cancer, alone or in combination with other drugs. Interferon therapy is typically self-administered by injection under the skin several times per week. Interferons work by "interfering" with the life processes within the cancer cell, preventing its growth and making the cell more susceptible to attack by other elements of the immune system. There are three major types of interferons — alfa, beta, and gamma — but interferon alfa has been most widely studied in the treatment of kidney cancer. Several interferon alfa products are available in the United States and have been used in the treatment of kidney cancer. INTRON* A, a product of Schering Corporation (Kenilworth, NJ), has been designated as interferon alfa-2b. Roferon*-A is manufactured by Roche Laboratories (Nutley, NJ) and has been designated as interferon alfa-2a. These drugs are very similar, and kidney cancer may be treated with either. Most insurance companies recognize the value of interferon alfa in treating kidney cancer and reimburse for this therapy. In several dozen clinical trials, an overall response rate of about 13% has been achieved with interferon alfa. However, in patients with high performance status (i.e., lack of symptoms related to their disease), previous nephrectomy, and metastases predominantly in the lung, the major response rate (complete plus partial responses) with interferon alfa treatment is usually from 6 to 10%. It is also recognized that patients who receive interferon alpha, when compared with those who are treated with hormones or chemotherapy, have improved survival rates. Response to interferon alfa is characterized by slow regression of tumors; the average time from start of treatment to objective response is three to four months. The most common side effects of interferon therapy are flu-like in nature.

Though it is not considered a primary form of therapy, radiation can be used in the treatment of kidney cancer that has metastasized to the bone, brain or spine. Although chemotherapy is the standard treatment for most solid tumors, kidney cancer is generally resistant to chemotherapy. The reason for the resistance of kidney cancer cells to chemotherapy is not completely understood. However, it is now known that kidney cancer cells produce an overabundance of multidrug-resistance-associated protein, which acts to repel various chemotherapeutic agents away from the cancer cell. 5-Fluorouracil (5FU) appears to be the most effective conventional chemotherapeutic agent currently available for kidney cancer, but response rates are only in the range of 5% to 8%. In 2005 and 2006, the U.S. Food and Drug Administration (FDA) approved the first new medications to treat kidney cancer in more than a decade: sorafenib tosylate and sunitinib malate. Both of these new drugs disrupt the angiogenesis process. Known as tyrosine kinase inhibitors, they interfere with the proteins inside cancer cells, thus interfering with certain cell functions. These drugs are also known as "multi-kinase inhibitors" because they target both the tumor cell and the tumor blood vessel structures. They work by interfering with reproduction of cancer cells as they attempt to grow and divide uncontrollably. They also have the advantage of being administered orally. The goal of treatment with these newer medications is to slow the rate of growth of the cancer and, if possible, shrink the size of existing tumors. Some patients may experience a significant decrease in the amount of cancer in their body. Some patients may not experience shrinkage in the size of their tumors, but have long periods of "stable" disease. A physician will discuss how the cancer is responding to treatment, and will have additional options to consider for treatment when necessary. It should be noted that some patients will not receive any benefit from a medication. In some cases, a medication that was effective in treating a patient's cancer stops working and other treatment options must be considered. **Sutent** (sunitinib malate) claims to reduce tumor size and is not only seems to be the most highly recommended chemotherapy for kidney cancer, but is available in capsule form for oral consumption, but hepatoxicity and cardiotoxicity has been deadly, it is prescribed once a day for four weeks and two weeks off.

Nexavar (sorafenib tosylate) is a medication that targets the blood supply of a tumor, depriving it of the oxygen and nutrients it needs for growth. By blocking the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), Nexavar can interfere with the tumor cell's ability to increase its blood supply. By blocking the Raf-kinase pathway, Nexavar can also interfere with tumor cell growth and proliferation. Clinical studies show that it can significantly slow the progression of tumors. In the Phase III trial which led to the FDA approval of Nexavar, the median time for tumor progression was doubled for patients taking Nexavar, compared with patients taking a placebo. **Sutent** (sunitinib malate) also deprives tumor cells of the blood and nutrients needed to grow by interfering with VEGF and PDGF signaling pathways. Sutent was approved by the FDA in 2006 for kidney cancer patients because of its ability to reduce the size of tumors. Clinical studies showed a favorable response rate in patients with metastatic kidney cancer whose tumors had progressed following immunotherapy. **Torisel** (temsirolimus) is another recently approved kidney cancer drug. It was designed to inhibit the mTOR (mammalian target of rapamycin) kinase, which is important in cell growth and cell survival. By blocking the mTOR pathway, Torisel can interfere with the tumor's ability to multiply as well as reducing its ability to stimulate angiogenesis. **Afinitor** (everolimus), approved by the FDA in March 2009, is an orally administered mTOR inhibitor. Afinitor works by blocking a specific protein known as the mammalian target of rapamycin (mTOR) and acts as a multifunctional inhibitor of cell growth and proliferation, angiogenesis, and cell metabolism. The drug is intended for those patients with advanced renal cell cancer who have already tried a kinase inhibitor, such as Sutent or Nexavar. **Votrient** (pazopanib), the sixth drug to be approved for kidney cancer since 2005, is an oral medication that interferes with angiogenesis, the growth of new blood vessels needed for solid tumors to grow. It is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma. **Inlyta** (axitinib), approved by the FDA in January 2012, is a prescription medicine used to treat advanced kidney cancer (advanced renal cell carcinoma or RCC) when one prior drug treatment for this disease has not worked. As with antibiotics chemotherapeutic drugs require **probiotic supplementation** to avoid vitamin B_{12} deficiency, chronic diarrhea, pernicious anemia and dental cavities.

Tumors of the bladder are the second most common genitourinary neoplasm. Only prostatic tumors occur more frequently. Cancer of the bladder accounts for approximately 2% of all malignant disease, and is highest in incidence in industrialized nations. Bladder tumors are seen twice as often in en as in women. The average age of patients is 65 years and fewer than 1% of cases are reported in people under 40. The predominant symptom is hematuria, in 75-80% of patients. Stage 0: Tumor is limited to the mucosa, including both papillary (Ta and in situ (TIS) carcinoma. Stage A: Lesions have invaded into the lamina propria but not into the muscle of the bladder wall Stage B_1: Neoplasms have penetrated less than halfway through the muscle wall (T2). Stage B_2: Tumors have invaded the muscle wall to a depth grater than halfway but are still confined to the muscularis (T3a). Stage C: Neoplasms have invaded the perivesical fat (T3b). Stage D_1: Malignant disease extends beyond the limits of the bladder and perivesical fat but is still confined to the pelvis either at or below the level of the sacral promontory, included are tumors invading contiguous organs (T4a), tumors involving the pelvic wall or rectus muscles below the level of the umbilicus (T4b), or lymph node metastases below the bifurcation of the common iliac artery. Stage D_2: Tumor have metastasized to distant organs or to lymph nodes above the sacral promontory (bifurcation of the common iliac artery) or are external to the inguinal ligament. Surgical treatment alone reported only 5 out of 97 patients were free of disease after 5 years of radical cystectomy. Of 22 patients who had demonstrable D_2 disease none survived 5 years. Radical surgery alone was associated with a a 5 year survival rate of only 10%. Treatment for stage D_1 disease traditionally has been irradiation alone, 6000 rads given in 30 fractions over 6 weeks (5 fractions of 200 rads per week). The 5 year survival rate for

patients treated in this manner is 17%. Consequently the preferred treatment is combination chemotherapy consisting of cisplatin, cyclophosphamide, and doxorubicin (CISCA) or methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC); These drug programs have result in long-term survivals with complete eradication of tumor (Johnson '88: 355, 357, 356, 360).

As the prostate undergoes involution and atrophy in older men, hyperplastic and neoplastic alterations occur so often that the prostate has become the organ most frequently involved in tumor formation. It is estimated that 80% of men 50-60 years of age or older have benign prostatic hyperplasia and approximately 10% of men over age 65 will eventually develop clinically apparent **prostatic cancer**. The prostate is described as having 5 lobes. Benign prostatic hyperplasia and prostatic cancer are not sequential manifestations of the same pathologic process but, rather, are entirely different entities. Nevertheless, a 75% incidence of hyperplastic changes and carcinoma has been detected incidentally in 5-15% of patients undergoing surgery for benign prostatic hyperplasia. Benign prostatic hyperplasia (hypertrophy) is a benign enlargement of the prostate associated with voiding dysfunction has been recogznied for centuries. While the glands of the peripheral prostate undergo atrophy with aging, the inner glands grouped around the urethra undergo both stromal and epithelial hyperplasia. Nodules containing tall columnar epithelial cells lining large convoluted alveolar glands are formed. As these nodules increase in size and number they compress the prostatic urethra and produce symptoms of bladder outlet obstruction, while the gland itself also increase in size. Benign prostatic hyperplasia is not necessarily a progressive process and not all patients require immediate surgery. The probability of a 40 year old man requiring surgery for benign prostatic hyperplasia by the age of 80 is 10.9%. For those patients with severe obstruction and evidence of bladder or upper urinary tract dilatation , surgical relief of obstruction is mandatory. Catheterization is often sufficient. Acute urinary retention is best managed by an indwelling Foley catheter left in place for 2-3 days. When the catheter is removed, the patient usually resumes a fairly normal voiding pattern, since vescial tone has been reestablished and prostatic congestion relieved (Johnson et al '88: 361-364).

80% of 200 patients using **phenoxybenzamine**, an α-adrenergeni blocker, experienced symptomatic relief. Uroflowometry in 102 patients showed the flow to be more than doubled in nearly one-half of patients and increased by more than 50% in another one-fourth. Improvement was noticed within the first 2 days of therapy and reached its maximum after 7 days of treatment. The drug did not reduce the size of the prostate. Side-effects, reported by 30%, include hypostatic hypotension resulting in dizziness and tachycardia, retrograde ejaculation, fatigue and nasal congestion, only 10% felt it was so severe they discontinued treatment. **Castration** was observed to relieve urinary obstruction due to benign prostatic hyperplasia in the late 1800s. An 87% decrease in prostate size was reported in 111 patients so treated. In a series of 61 patients in 1896 reported that urinary retention disappeared in 27 and that 50 showed overall marked improvement following castration. Androgen deprivation affects the prostate. Androgen deprivation can be achieved by administration of estrogens but estrogens play a direct role in the development of benign prostatic hyperplasia. **Cyproterone acetate**, an anti-androgen, caused 11 of 13 patients in 1969 to experience subjective improvement including increased urinary flow rate and decreased volume of residual urine. An objective decrease in the epithelial cell size was apparent in 8 of 11 patients whose prostatic biopsies were available. **Flutamide**, a non-steroidal veterinary anti-androgen, is a potent inhibitor of testosterone-induced prostatic growth, however a study in 1975 found that early subjective improvement in 30 patients was not maintained, and no significant change occurred in the size of the prostate or the volume of residual urine. A study of **Megestrol acetate** demonstrated a decrease in prostate size and improved urinary flow

rates in 8 of 13 patients, however, the changes were insignificant. Cyproterone acetate seems to be the most highly recommended experimental treamtents (Johnson et al '88: 364, 365).

The most effective method of relieving obstruction due to benign prostatic hyperplasia is **surgical extirpation**. The objective of surgery is to remove the portion of the enlarged prostate that is causing the obstruction by a technique that is considered effective and safe. Mandatory indications include cases in which ther is total outflow obstruction due directly to enlargement o the prostate and cases in which ther is chronic outflow obstruction impairing renal function or producing distressing symptoms. Bladder tumors may necessitate transurethral resection of the prostate to provide easy access to the bladder for endoscopic inspection, resection of tumors, and obliteration of residual urine. Recurrent gross hematuria or chronic congestive cardiac failure exacerbated by prostatic obstruction may require surgical intervention. When chronic urinary retention produces severe symptoms such as overflow urinary incontinence, urgency, intense frequency, or severe nocturia, surgery is mandatory. **Transurethral resection** of the prostate is employed in over 90-95% of patients. The mortality rate ranges from 0 to 1.3%, with 0.4% considered the average for experienced urologists. Those not recommended for transurethral resection are (1) patients with a life expectancy less than 6 months who might best be treated by catheter drainage instead, and (2) patients with a physical deformity that prevents proper positioning for endoscopic surgery. Patients with a serum creatinine level of 1.5 mg/kg have a 6-fold increase in post-resection morbidity and mortality rates, but they can be treated safely if ther fluid and electrolyte status is continually monitored. During resection, a patients absorbs (on average) about 900 mL of irrigating fluid through the prostatic fossa and open veins. Patients with active urinary tract infections should receive appropriate antimicrobial drugs before they undergo surgery. Many urologists limit their use of transurethral resection to prostates that weight no more than 45 g, while other urologists are comfortable resecting 100 g of tissue or more. Greater morbidity and mortality among patients with glands 60 g or larger has been reported. More than 90% of patients can anticipate a satisfactory result from surgery, with excellent urinary control and a satisfactory urinary stream. Total permanent urinary incontinence is a postoperative complication that occurs in fewer than 1% of patients. Intermittent hematuria may occur in the first 4-6 weeks post-operatively. Urethral stricture has been reported in 6% of patients and epididymitis in 2%. Erectile impotence is rare. Retrograde ejaculation has been reported in 40-50% of patients and is an important issue for preoperative discussion (Johnson et al '88; 365, 366).

Open prostatectomy, enucleation of adenomatous hyperplastic tissue can be performed by (1) an anterior transcapsular incision (retropubic); (2) a posterior transapsular incision (perineal); or (3) an incision above the pubis and through the bladder neck (suprapubic). In none of these procedures is the entire prostate removed. Indications for an open prostatectomy include, protates in excess of 60 g, large bladder diverticular or calculi that can be corrected at the time of open surgery, the presence of a sever impassable urethral stricture, and orthopedic conditions that do not allow proper patient positioning for endoscopic surgery. Prolonged postoperative catheter drainage by a urethral catheter, a suprapubic tube, or both is generally necessary for 7-10 days or until healing is complete. Intraoperative bleeding is greater in open prostectomy than in endoscopic surgery and 15% of patients require blood replacement. Postoperative complications of delayed bleeding, urinary incontinence, erectile impotence, and urethral stricture are uncommon. Retrograde ejaculation occurs frequently. About 50% of cases remain clinicially stable for years, and a few may even improve spontaneously. In most patients, progression of symptoms eventually requires removal of the obstructing adenoma (Johnson et al '88; 365, 366).

Although malignant transformation can involve any of the cellular components of the prostate gland, over 95% of prostatic cancers are **adenocarcinomas** of the tubuloalveolar or acinar origin. It is probably the most prevalent malignant transformation occurring in men. It is rarely diagnosed before age 50 reaching a peak in the eighth decade. In the USA about 75,000 cases are diagnosed annually, and about 24,000 deaths occur each year as a direct result of the disease. Blacks are more susceptible and have nearly twice the mortality rate of whites. A Westernized diet high in animal fat is associated with the higher mortality rate, while a diet rich in green and yellow vegetables appears to have a protective effect (and tomatoes are known to be medicinal). Men who work with batteries and are chronically exposed to cadmium, a known antagonist of zinc, have a higher incidence of prostatic carcinoma. Particular air pollution explains the higher incidence in urgan than in rural areas. Occupations in the rubber, fertilizer and textile industries have likewise been linked to higher rates of prostatic cancer. A temporal relationship between the incidence of gonorrhea and a subsequent increase in the incidence of prostatic cancer, has been noticed. Malignant transformation occurs in the stem cells of the acinar prostatic epithelium. Some tumors are difficult to distinguish from the normalprostate while others manifest bizarre alterations in cellular structure and form a solid pattern with no glandular differentiation. Stage A: Tumors microscopic and intracapsular. Stage B: Tumors macroscopic and intracapsular. Stage C: Tumors macroscopic and extracapsular. Stage D: Metastatic disease. Prostate specific antigen (PSA) is a tumor marker that can be used to confirm the presence of prostatic carcinoma with 95% accuracy. When a malignant process is suspected the diagnosis must be confirmed by biopsy. Fine-needle aspiration of the prostate is safe and comfortable, easily performed in the nonanesthetized patient (Johnson et al '88: 367, 368).

Therapy for prostatic carcinoma includes transurethral resection of the prostate, radical prostatectomy, interstitial irradiation, external-beam megavoltage irradiation, or a combination; endocrine therapy and chemotherapy. Approximately one-third of patients have metastatic disease at the time of diagnosis. 98% of patients diagnosed with stage A cancer survive, 93% without disease progression. Another study however found no survival at 15 years when the tumor was poorly differentiated. Patients with moderately or poorly differentiated stage A tumors are best treated with external-beam megavoltate irradiation. **Radical prostatectomy** has a mortality rate less than 1%., it is best for stage B disease, and comes with a 51% 15 year survival rate. The most frequent post-operative complication is erectile impotence, occurring in 85-90% of patients. Urinar incontinence occurs postoperatively in almost al patients when the indwelling urethral catheter is removed, but leakage subsides, usualy with 6 months, in 85-90% of patients. A 15 year survival rate of 65% was found for patients with stage C disease treated with radical prostatectomy plus adjunctive therapy. The high risk of metastasis in patients with clinical evidence of extracapsular disease makes cure by radical prostatectomy alone unlikely. Radiation therapy has been employed in cases of prostatic cancr since the early 1900s. **Implantation of ^{125}I** is done for the control of locally advanced prostatic carcinoma. A pelvic lymphadenectomy is performed and the prostate is implanted with ^{125}I seeds. A tumoricidal dose is considerd to be approximately 15,000 rads deliverd over 1 year. The tumor must be discrete and if extracapsular extension has occurred, the tumor must be small with well-defined borders, patients are unsuitable for implantation if tumor has invaded the rectum or trigone or has extended to the pelvic sidewals. In follow-up studies of 91 patients with either stage B or C disease, treated in this way, 71% were alive at 5 years, but only 33% were free of disease. In **combined interstitial and external-beam irradiation** radioactive gold is implanted in the prostate to achieve a dose of approximately 3000-3500 rads and is then followed by external-beam irradiation, employing a linear accelerator to achieve a minimum tumor dose of 6500-7000 rads. A 61% tumor-free survival rate at 7 years for 23 patients with stage B disease was seen. A 16% rate of earl compliacations, including thrombophlebitis and lymphocele formation, and an

8% rate of late complications, including edema and irritative and obstructive symptoms on voiding, was found with interstitial therapy. One major advantage of interstitial therapy is that over 90% of patients repot no damage to erectile potency following therapy. When tumors are confined to the prostate and periprostatic tissue, tumoricidal doses of 6500-7000 rads are generally delivered at a rate of 175-200 rads daily. Teletherapy using ^{60}Co linear accelerators or betaron can produce photon beams with energies of 6-15 million electron volts. Early follow-up studies of teltherapy reported actuarial survival rates at 5 years of 75% for 193 patients with stage B disease and 52% for 177 patients with stage C disease. The 10 year survival rates were 47% and 28% respectively. Local tumor control is estimated at 80-90% (Johnson '88: 375-377).

Endocrine manipulation is the principle form of therapy for advanced prostatic carcinoma. About 95% of circulating serum androgen is in the form of testosterone, which originates in the Leydig cells of the testis. Once taken up by the prostatic cell, testosterone is converted by the enzyme 5α-reductase to dihydrotestosterone (DHT), which binds with the receptor complex in the cytosol and is translocated to the nucleus, there, its metabolites are responsible fro promoting increased protein synthesis and cellular proliferation. Testosterone production by the testis is regulated by the pituitary gonadotropin lueinizing hormone (LH), which in turn is regulated by luteinizing hormone-releasing hormone (LHRH) produced by the hypothalamus. Serum testosterone is bound with high affinity (95%) to a serum β-globulin called sex hormone-binding globulin (SHBG), also known as testosterone-estrogen-binding globulin (TEBG). Small amounts of the weak androgens androstenedione (3 mg/d) and dehydroepiandrosterone (24 mg/d) are produced by the adrenal gland under the control of adrenocorticotropic hormone (ACTH). Bilateral scrotal orchiectomy is the most rapid and effective way to ablate the source of androgen production, it reduces testosterone concentration from normal adult male levels of 500-700 ng/dL to approximately 50 ng/dL. Estrogen administered in the form of diethylstilbestrol, reduces the level of circulating serum testosterone by suppressing the release of pituitary gonadotropins. A dosage of 3 mg or more daily appears to be necessary to consistently achieve castrate serum levels of testosterone, however daily doses of 1 mg have been able to effect clinical regression of metastatic disease. Other estrogenic substances that can effectively reduce the serum testosterone level include conjugated estrogens such as Premarin, 2.5 mg orally 3 times daily, and ethinyl estradiol, 0.5 mg 3 times daily. Chlorotrianisene (Tace), is only weakly suppressive. Aminoglutethimide inhibits androgen synthesis by inhibiting the conversion of cholesterol to pregnenolone, while cyproterone acetate, medrogestone and spironolactone can inhibit androgen synthesis farther along the pathway. The antifungal agent ketoconazole has been found to be a potent inhibitor of androgen synthesis by both the testis and adrenal gland. Estrogen induces gynecomastia in most patients, but it can be prevented or minimized by giving radiation therapy before estrogen is administered. Following therapy with buserelin, 17 of 21 patients (81%) demonstrated significant regression of tumors. After beginning any type of endocrine therapy, the disease status of 80-90% of patients can be expected to improve, but only in approximately 40% can the response be considered an objective regression. Of patients who had metastatic disease, only 10% lived longer than 10 years and 50% were dead within 36 months, regardless of therapy. Randomized chemotherapy trials in the early 1970s demonstrated that single agents such as cyclophosphamide, 5-fluorouracil, streptozocin, estramustine phosphate (Estracyt) and imidazole-carboxamide (DTIC) were able to produce subjective improvement and, in some instance, tumor regression in 0-40% of patients. The response has been limited to about 6 months and has not lengthened the survival time beyond 1 year. In 1983 62 hormone-refractory patients were treated with a combination of doxorubicin, mitomycin C and 5-fluorouracil and achieved an objective response rate of 48% with a median survival of 47.5 weeks for responding patients compared to 23.8 week for nonresponders. Despite occasional dramatic responses, the role of chemotherapy is limited to

palliation. Follow-up care requires examination every 3-4 months for the first 3 years to monitor the outcome of therapy. Digital rectal examination should be performed to detect local recurrence. In addition serum levels of acid and alkaline phosphatase and prostate specific antigen (PSA) should be measured and a chest x-ray and plain abdominal x-ray (kidney, ureter, and bladder film) performed to monitor for metastasis. Periodic bone scans and CT scans of the abdomen and pelvis at 6 month intervals are necessary to monitor progression of metastasis of bones or regional lymph nodes.

Sarcoma of the prostate is a rare tumor constituting approximately 0.1% of all primary neoplasms of the prostate gland. In one-third of cases, tumor appear early in childhood and are usually of the rhabdomyosarcoma type; later in life, leimyosarcomas predominate. Other sarcomas that can involve the prostate include malignant fibrous histiocytoma, fibrosarcoma, angiosarcoma and lymphoma. The dimension of the mass may be defined by ultrasonography or CT scanning. Lymph node metastasis occurs in 40% of patients with embryonal rhabdomyosarcoma. Results of treating localized disease with single-modality therapy such as radical surgery or irradiation have been disappointing and rate of local recurrence high. Similarly, chemotherapy has been disappointingly unable to achieve long-term survivals when disease is advanced or metastatic. Combination treatment programs have thus far proved to most effective in children with rhabdomyosarcomas. Chemotherapy combining vincristine, dactinomycin, and cyclophosphamide has been able to achieve tumor regression in over 50% of patients with extensive disease. This treatment is used either as adjuvant following complete eradication or disease by surgery or preoperatively to diminish the size of the primary tumor, thus facilitating surgical excision or radiation therapy. Sarcomas of the prostate treated surgically require radical cystoprostatectomy and urinary diversion. **Transitional cell carcinoma of the prostatic ducts** may occur in association with malignant transformation of the bladder urothelium or as a distinct and separate entity. Although successful conservative therapy by surgical excision has been reported the degree of invasiveness usually demands radical cystoprostatectomy combined with urethrectomy. Radiation therapy has not proved effective. (Johnson '88: 379, 380).

Malignant urethral tumors developing in patients who have neither a concomitant nor an antecedent history of bladder cancer are rare. It is the only urothelial malignant disease that occurs more commonly in women than in men. Malignant disease arising in the female urethra accounts for fewer than 1% of cases of cancer in the female genital tract and 0.02% of all neoplasms occurring in women. Malignant tumors may occur at any age but are seen most commonly during the seventh decade. Most primary urethral carcinomas are squamous cell carcinomas (68%), adenocarcinoma (18%), transitional cell carcinoma, (8%), melanoma (4%), and undifferentiated tumor (2%). Primary urethral carcinoma spreads initially by contiguous growth and local invasion. The tumor metastasizes chiefly through the lumphatics to the inguinal and external iliac nodes. Visceral metastases are infrequent (14%), but when they occur, the most common sites are the lungs, liver, bones and brain. The staging system: Stage 0: In situ (tumor limited to mucosa). Stage A: Tumor does not extend beyond the submucosa. Stage B: Tumor infiltrates periurethral muscle. Stage C_1: Tumor infiltrates the muscular wall of the vagina. Stage C_2: Tumor infiltrates the muscular wall of the vagina and invades the vaginal mucosa. Stage C_3: Tumor infiltrate other adjacent structures such as the bladder, labia, or clitoris. Stage D_1: Metastsis to inguinal lymph nodes. Stage D_2: Metastsis to the pelvic lymph nodes blow the aortic bifurcation. Stage D_3: Metastasis to distant organs. The prognosis is fair, with 5-year disease-free survival rates ranging from 31 to 50%. The prognosis for patients with tumor located in the distal or meatal region is reportedly better than for those whose lesions involve the proximal or entire urethra. **Primary carcinoma of the male urethra** is rare; fewer

than 500 cases have been reported, mostly in the sixth decade of life. Carcinoma of the male urethra is frequently mistaken for sexually transmitted disease or disease due to urethral stricture. Many patients have a history of sexually transmitted disease (40%(and urethral stricture. Partial penectomy is recommended for distal penile in cases in which the patient would still have sufficient penile length to stand and direct his urinary stream after at least a 2-cm surgical margin had been excised. Otherwise, a total penectomy, preserving sufficient length of the corpus spongiosum for perineal nurethrostomy, is required. Radiotherapy has proven disappointing. About half of patients with posterior urethral tumors have disease too extensive for surgical removal. Palliative measure may include suprapubic urinary diversion, local irradiation, and neurosurgical procedures for control of pain. Patients usually die within 3 months of diagnosis, whether or not they receive therapy Five-year survival rates exceed 60% for patients with anterior urethral tumors (Johnson et al '88: 381-384).

Diet may be responsible for one-third to one-half of all human cancers. Consumption of both saturated and unsaturated fats should be reduced in the average North American diet from 40% to 30% or less of total calories. This will probably decrease the incidence of breast and colon cancers. Citrus fruits, carotene-rich vegetables and whole-grain cereal products should be included in the daily diet. The consumption of foods preserved by salt curing or smoking should be minimized. The carcinogenicity of intentional additives and inadvertent contaminants should be determined to that safe levels in foods can be established. Mutagens and carcinogens, identified in food, should be eliminated. Alcoholic beverage consumption, particularly when combined with cigarette smoking, has been associated with increased risk of upper gastrointestinal and respiratory tract cancers, and should be reduced or eliminated (Spivack '88: 401). Cigarette smoking has specifically been indicated as being causative of kidney cancer. The risk of developing renal cell carcinoma was found to be over 5 times higher in men who used any form of tobacco at all than in men who did not use tobacco (Johnson et al '88: 330).

Surgical excision is the most effective means of removing the primary lesion of most neoplasms. It also provides palliation of symptoms. Although more than 80% of apparently solitary metastases are eventually found to be multiple, an occasional cure results from their excision. Radiotherapy has also produced long-term survival in patients. A basic goal of cancer chemotherapy is the development of agents that have "selective toxicity" against replicating tumor cells but at the same time spare replicating host tissues. Only the adrenocortical hormones, sex hormones, and asparaginase have demonstrated a predictable selective killing power of tumor cells based on metabolically exploitable differences between neoplastic and normal tissue. The glucocorticoids exert "lympholytic" effect that can repeatedly induce remission of acute lymphoblastic leukemia, especially in combination with vincristine. Myopathies, psychosis, hypertension and osteoporosis are important side effects of long-term administration. The estrogenic steroids have been used since the early 1940s for prostatic carcinoma and shortly thereafter, estrogens were found useful in postmenopausal patients with breast cancer. Androgens are used principally in the treatment of disseminated breast especially in pre and perimenopausal women. Antiestrogens (nafoxidine and tamoxifen [Nolvadex]) are a new class of nonsteroidal agents that block estrogen receptor sites on tumor cells nad antagonize estrogen stimulation of hormone-dependent tumors such as breast and possibly renal carcinoma. Antiandrogens include cyproterone acetate, and flutamide. These drugs may be of benefit in advanced prostatic carcinoma no longer responsive to hormonal manipulations that were effective in the past. No major toxicities have been reported (Spivack '88: 406).

Drugs Useful in Urological Malignancy

Agent	Route	Toxicity	Usual Adult Dose
Hormones			
Glucocorticoids	Orally (IV and IM available	Sodium retention, potassium wasting, hyperglycemia, peptic ulcer, immunosuppression, hypertension, osteoporosis	Prednisone: 1-2 mg/kg/d (<6 weeks), then minimal required daily dosage
Estrogens	Orally	Sodium retention, feminization, uterine bleeding, nausea and vomiting	Diethylstilbestrol: 2.5 – 5 mg/d for prostate. Ethinyl estradiol: 1 mg/d
Progestogens	Orally, IM	Sodium retention	Hydroxyprogesterone: 1 g 2-3 times weekly IM. Medroxyprogesterone: 200-600 mg orally twice weekly
Androgens	Oraly, IM	Sodium retention, masculinization, cholestatic jaundice with oral preparations	Testosterone propionate: 100 mg 2-3 times weekly. Fluoxymesterone: 10-40 mg/d orally. Calusterone" 200 mg/d orally
Antihormones			
Antiestrogens Tamoxifen (Nolvadex)	Orally	Nausea, hot flashes	20-60 mg/d
Nafoxidine	Orally	Nausea, dermatitis, rarely tumor flare	60-180 mg/d
Antiandrogens Flutamide	Orally	Gynecomastia; loss of male body hair	750 mg-1.5 g/d
Cyproterone acetate	Orally	Fluid retention	200-300 mg/d
Hormone-alkylator complex Estramustine phosphate (Emcyt)	Orally	Nausea and vomiting, phlebitis, mild marrow depression	15 mg/kg/ as single dose
Alkylators			
Mechlorethaine (nitrogen mustard, HN2 Mustargen)	IV, intracavitary	Nausea and vomiting, marrow depression, ulcer if extravasated, hypogonadism, fetal anomalies, alopecia	0.4 mg/kg IV as single dose every 4-6 weeks; 0.4 mg/kg by intracavitary injection
Cyclophosphamide (Cytoxan)	IV, orally	Nausea and vomiting, marrow depression, alopecia, hemorrhagic cystitis	40-60 mg/kg IV every 3-5 weeks; 5 mg/kg/d orally for 10 days, then 1-3 mg/kg/d as

			maintenance
Chlorambucil (Leukaran)	Orally	Marrow depression, gastroenteritis	0.1-0.2 mg/kg/d
Melphalan (phenylalanine mustard, Alkeran)	Orally	Marrow depression (occasionally prolonged), gastroenteritis	0.25 mg/kg/d orally for 4 days every 6 weeks; 2-4 mg/d as maintenance
Thiotepa	IV, intracavitary	Marrow depression	0.8 mg/kg IV as single dose every 4-6 weeks; 0.8 mg/kg by intracavitary injection
Nitrosoureas			
Carmustine (BCNU), lomustine (CCNU), methyl-CCNU	BCNU, IV; CCNU and methyl-CCNU, orally	Nausea and vomiting, prolonged marrow depression, local phlebitis	BCNU: 75-100 mg^2 IV daily for 2 days every 4-6 weeks. CCNU: 130 mg/m^2 orally every 6 weeks. Methyl-CCNU: 200 mg/m^2 orally every 6 weeks
Structural analogs			
Methotrexate (amethopterin)	Orally, IV intrathecally	Ulerative mucositis, gastroenteritis, dermatitis, marrow depression, hepatitis, abortion	20-40 mg IV twice weekly' 5-15 mg intrathecally weekly. 2.5-5 mg/d orally. Low dose 2.5-5 mg/week orally.
Fluorouracil (5-FU) Adrucil)	IV	Atrophic dermatitis, gastroenteritis, mucositis, marrow depression, meuritis	15-20 mg/kg IV weekly for at least 6 weeks
Dacarbazine	IV	Gastroenteritis, marrow depression, hepatitis, phlebitis	150-250 mg/m^2/d IV for 5 days every 4-6 weeks
Cytotoxic antibiotics			
Dactinomycin (actinomycin D, Cosmegen)	IV	Nausea and vomiting, stomatitis, gastroenteritis, prcitis, marrow depression, ulcer if extravasated, alopecia, radiation potentiator	0.01 mg/kg/d for 5 days every 4-6 weeks.
Doxorubicin (Adriamycin)	IV	Alopecia, marrow depression, myocardiopathies, ulcer if extravasated; stomatitis	1 mg/kg/wk; total cumulative dose should not exceed 550 mg/m^2
Mithramycin	IV	Marrow depression,	0.05 mg/kg IV every

(Mithracin)		nausea and vomiting, complex coagulopathies, hepatotoxicity	other day to toxicity or 8 doses per course
Bleomycin (Blenoxane)	IV, IM, subcut	Allergic dermatitis, pulmonary fibrosis, fever, mucositis	15 mg twice weekly, total cumulative dosage should not exceed 300 mg
Vinca alkaloids			
Vinblastine (Velban)	IV	Marrow depression, alopecia, ulcer if extravasated, nausea and vomiting, neuropathy	0.1-0.2 mg/kg IV weekly
Vincristine (Oncovin)	IV	Alopecia,neuropathy (peripheral and autonomic), ulcer if extravasated, rarely, marrow depression	1.5 mg/m^2 weekly or less No individual dose should exceed 2 mg
Miscellaneous agents			
Litotane (o,p'-DDD, Lysodren)	Orally	Gastroenteritis, dermatitis, CNS abnormalities	5-12 g/d orally
Aminoglutethide (Cytardren)	Orally	Gatroenteritis, dermatitis, somnolence	1-15 g/d orally in 3-4 divided doses
Inorganic metallic salt			
Cisplatin (Platinol)	IV with mannitol diuresis	Nausea and vomiting, bone marrow depression, hephrotoxicity, ototoxicity	1 mg/kg every 3 weeks IV, or 80 mg/m^2 IV every 3 weeks. Use lower dose when renal function impaired
Podophyllotoxin derivative			
Etoposide (VP-16-213, VePesid)	IV, orally	Marrow depression, nausea and vomiting, hypotension, alopecia	50-100 mg/m2/d IV for 5 days; orally at approximately double the IV dose

Source: Spivack '88: Table 19-3: 407-408

Chemotherapy of specific urologic cancers varies. In **adrenal cortical carcinoma** mitotane (o.p'-DDD, Lysodren) is often used to decrease corticosteroids excretion and produce tumor regression in 35% of patients. Aminoglutethimide (Cytadren) is also used decrease corticosteroid excretion when mitotane fails to control the disease, but does not reduce tumor bulk. **Metastatic renal cell carcinom**a is not highly susceptible to cytotoxic chemotherapy, although favorable responses are reported in the treatment of pulmonary metastases with vinblastine (Velban), 0.1-0.2 mg/kg intravenously weekly and with nitrosoureas such as lomustine (CCNU), 130 mg/m^2 orally every 6 weeks. A 25% remission rate was repoted in one

study of 135 patients treated with vinblastine, whereas nitorsourea produced remissions in only 9% of 79 patients. Alpha-interferon have induced tumor regression in patients with metastatic renal cell carcinoma more consistently than any other hormonal or chemotherapeutic agent, with a major response rate in the order of 15%. Nephrectomy to remove primaryneoplasm is not likely to be of significant benefit for disseminated disease. Nephrectomy alone cures 20% of children with localized **Wilms' tumor**; the addition of radiation therapy to the tumor bed after nephrectomy increases the cure rate to 47%, and the addition of multiple courses of dactinomycin as adjucant treatment has increased the overall cure rate to 80%. The combination of dactinomycin, 15 mg/kg IV daily for 5 days followed by multiple courses at 6 weeks and 3, 7, 9, 12, and 15 months thereafter and vincristine, 1.5 mg/m^2 IV weekly for 6 weeks followed by 2 doses (4 days apart) of 1.5 mg/m^2 IV, repeated every 3 months for 15 months, may be more effective. No single dose of vincristine should exceed 2 mg. Up to two-thirds of patients with **multiple small superficial papillary tumors** show a favorable response to thiotepa, 60 mg instilled into the bladder in 60 mL of sterile water and retained for 2 hours. One-third of patients may achieve a complete remission, which can be maintained with 30 to 60 mg instillations every 4-6 weeks. Adverse effets include marrow suppression and cystitis. Doxorubicin produced a response rate of 23% with objective regression of metastases within 1 mont and lasting up to 5 months. Cisplatin had a response rate of 40%. Combined regimens of cyclophosphamide, doxorubicin, and cisplatin are more effective than single agents.

Bladder sarcomas may respond temporarily to combination chemotherapy with doxorubicin and dacarbazine in up to 40%. Twenty percent of children with meastatic rhabdomyosarcomas of the urinary tract are curable with combined therapy with 3 drugs (dactinomycin, vincristine and cyclophosphamide) in conjunction with radiation therapy. Drugs are given in 3 month cycles for 1-2 years, vincristine, 2 mg/m2 IV weekly for 12 weeks (maximum, 2 mg/dose)); dactinomycin, 0.075 mg/kg/course IV over 5 days (maximum, 0.5 mg/d) every 3 months for 5 courses, and cyclophosphamide, 2.5 mg/kg orally daily for 2 years. Antiandrogens (cyproterone acetate and flutamide and estramustine (Emcyt)) can be effective in prostatic carcinoma. Estramustine has had a response rate of 38% in over 200 European patients with advanced prostatic carcinoma. Oral estamustine yielded a 22% reponse rate. Respone rate of approximately 35% are reported for fluorouracil, cyclophosphamide, and doxorubicin as single agents. Nonseminoatmous testicular carciomas have been treated successfully with varying combiantions of bleomycin, vinblastine and cisplatin with an overall 75% response rate and 45% complete remission rate, to a regimen of vinblastine, 0.2 mg/kg IV daily on days 1 and 2; bleomuycin, 30 units infused in 1000 mL of 5% glucose and water over 24 hours on day 2 and for 5 additional days. Courses are repeated every 3-4 weeks for 3 or 4 cycles depending on toxicity. Side effets include severe leukopenia (80%), thrombocytopenia (40%) and stomatitis (100%). Median duration of response was 34 weeks. A triple combination of vinblastine, 0.2 mg/kg IV on days 1 and 2 every 3 weeks; bleomycin, 30 units IV weekly for 12 weeks; and cisplatin, 20 mg/m^2 IV daily on days 1-5 every 3 weeks; met with 100% success in 20 patients, 15 of whom achieved complete remission with a median duration of 9 months. Mithramycin has been a useful single agent, with a 36% response rate when used in embryonal carcinoma, or in various combinations; and doxorubicin a 20% response rate. Combination regimens can achieve significant disease control for relatively long durations and can be curative in some patients, but they may also carry the risk of major toxicity (Spivack '88: 414-417).

21. Renal disease

Human **kidneys** serves to convert more than 1700 liters of blood per day into about 1 liter of a highly specialized concentrated fluid called urine. In so doing the kidney excretes the waste products of metabolism, precisely regulates the body's concentration of water and salt, maintains the appropriate acid balance of plasma, and serves as an endocrine organ, secreting such hormones as erythropoietin, renin and prostaglandins. Renal disease is responsible for a great deal of morbidity by, fortunately, are not equally major causes of mortality. Approximately 20% of patients who visit a primary physician's office have urologic problems. Approximately 45,000 deaths are attributed yearly to renal disease in the United States, in contrast to about 650,000 to heart disease, 560,000 to cancer, and 145,000 to stroke. Millions of people are affected annually by nonfatal kidney diseases, most notably infections of the kidney or lower urinary tract, kidney stones and urinary obstruction. Twenty percent of all women suffer from infections of the urinary tract or kidney at some time in their lives, and as many as 5% of the U.S. population develops renal stones. Modern treatment, notably dialysis and transplantation, keep many patients alive who earlier would have died of renal failure. People with even mild chronic kidney disease have a greatly enhanced risk for cardiovascular disease. The study of kidney disease is facilitated by dividing them up in those that affect the four basic morphologic components: glomeruli, tubules, interstitium and blood vessels. Most glomerular disease are immunologically mediated, whereas tubular and interstitial disorders are frequently caused by toxic or infectious agents. Damage to one kidney invariably affects the other. Disease primarily in the blood vessels, for example, inevitably affects all the structures that depend on this blood supply. Severe glomerular damage impairs the flow through the peritubular vascular system and also delivers potentially toxic products to tubules; conversely, tubular destruction, by increasing intraglomerular pressure, may induce glomerular injury. Whatever its origin there is a tendency for all forms of chronic kidney disease ultimately to destroy all four components of the kidney, culminating in chronic renal failure and what has been called end-stage kidneys. The functional reserve of the kidney is large and much damage may occur before there is evident functional impairment (Saunders-Elsevier; Alpers '10: 906).

The medical renal disease are those that involve principally the parenchyma of the kidneys. Hematuria, proteinuria, pyuria, oliguria, polyuria, pain, renal insufficiency with azotemia, acidosis, anemia, electrolyte abnormalities, hypertension, headache, and ocular involvement may occur in a wide variety of disorders affecting any portion of the parenchyma of the kidney, its blood vessels, or the excretory tract. **Urinalysis** is the essential part of the investigation. **Proteinuria** of any significant degree (2-4+) is suggestive of renal disease (parenchymal involvement). Proteinuria of 1+ in a dilute urine may indicate a significantly great protein loss. Proteinuria may indicate pathological disease such as: glomerulonephritis, subacute or chronic nephritis, nephrotic syndrome, autoimmue disease, diabetic nephropathy, myeloma of the kidney, amyloid kidney and polycystic kidney disease. **Red cells** in the urine indicate extravasation of blood anywhere along the urinary tract and the occurrence of **red cells in casts** proves the renal origin of the bleeding. Formation of typical red cell casts by erythrocytes is indicative of glomerulitis. **Fatty casts** and oval fat bodies in tubule cells occur in degenerative diseases of the kidney such as nephrosis, glomerulonephritis, autoimmune disease, amyloidosis, and damage due to such toxins as mercury). The presence of **abnormal urinary chemical constituent**s may be the only indication of metabolic disorders involving the kidneys, including: diabetes mellitus, renal glycosuria, aminoacidurias (including cystinuria), oxaluria, gout, hyperparathyroidism, hemochromatosis, hemoglobinuria, and myoglobinuria (Krupp '88: 514), 515).

Oliguria means "too little" urine volume in response to the body's excretory needs. Oliguria is present when the daily urine volume is not sufficient to remove the endogenous solute loads that are the end products of metabolism. No precise figure for 24-hour urine volume can be used in defining oliguria, since urine volumes normally vary with fluid intake and the concentrating ability of the kidney. If the kidney can concentrate urine in a normal fashion to a specific gravity of 1.035, oliguria is present at urine volumes under 400 mL/d. On the other hand, if the kidney concentration is impaired and the patient can achieve a specific gravity of only 1.010, oliguria is present at urine volumes under 1000-1500 mL/d. **Acute renal failure** is a condition in which the glomerular filtration rate is abruptly reduced, causing a sudden retention of endogenous metabolites (urea, potassium, phosphate, sulfate, creatinine) that are normally cleared by the kidneys The urine volume is usually low (under 400 mL/d), however may be normal. Prompt differentiation of the cause is important in determining appropriate therapy. Pre-renal renal failure is reversible if treated promptly , but a delay in therapy may allow it to progress int a fixed, nonspecific form of intrinsic renal failure (e.g., acute tubular necrosis). The other causes of acute renal failure are classified on the basis of their involvement with vascular lesions, intrarenal disorders or postrenal disorders. Rapid intravenous administration of 300-500 mL of physiologic saline or 125 mL of 20% mannitok (25g/125mL) is the usual initial treatment. Urine output is measured over 1-3 hours. A urine volume of more than 50 mL/h is considered a favorable response that warrants continued intravenous infusion with physiologic solutions to restore plasma volume and correct dehydration Therapy is directed toward eradication of infection, removal of antigen, elimination of toxic materials and drugs, suppression of autoimmune mechanisms, removal of autoimmune antibodies, or a reduction in effector-inflammatory responses (Amend et al '88: 526-528).

An increasing number of **drugs are known to be nephrotoxic**. First reported after the use of sulfonamides, acute tubulointerstitial nephritis and renal papillary necrosis most frequently occurs with synthetic penicillins (methicillin, ampicillin) other synthetic antibiotics (rifampin), diuretics (thiazides), allopurinol, cimetidine, aristolochic acid found in some herbal remedies, NSAIDs, analgesics mixtures including phenacetin, aspirin, caffeine, acetaminophen and codeine. Selective COX-2 inhibitors, while sparing the gastrointestinal tract, affect the kidneys. Acute uric acid nephropathy can be caused by the precipitation of uric acid crystals in the renal tubes particularly in individuals with leukemias and lymphomas who are undergoing chemotherapy whereas the drugs induce death of tumor cels and uric acid is produced as released nucleic acids are broken down. Gouty nephropathy is often precipitated by the consumption of moonshine whiskey contaminated with lead. Papillary necrosis is readily induced experimentally by a mixture of aspirin and phenacetin, usually combined with water depletion. The disease begins about 15 days (2-40) after exposure to the drug and characterized by fever, eosinophilia, a rash in 25% of patients and renal abnormalities in the form of hematuria, mild proteinuria and lukocyturia (often including eosinophils). A rising serum creatinine level or acute renal failure with oliguria develops in about 50% of cases, particularly older patients. Withdrawal from the offending drug is followed by recovery, although it may take several month, and irreversible damage occurs occasionally in older subjects. While drugs are the leading cause of acute interstitial nephritis in 30-40% of patients no offending drug or mechanism can be found. Urinary tract infections complicate 50% of cases (Alper '10: 944-946).

Acute kidney injury (AKI) is a reversible renal lesion that causes 50% of case of acute renal failure in hospitalized patients and can be caused by ischemic or toxic tubular injury and acute renal failure or inflammatory reaction of the tubules and interstitium (tubulointerstitial nephritis). In AKI there is a rapid reduction of renal function and urine flow, falling within 24 hours to less than 400 mL per day. It can be caused by ischemia, direct toxic injury by drugs, such as

gentamicin and other antibiotics, poisons (heavy metals such as mercury), organic solvents (e.g. carbon tetrachloride), pancreatitis, radiocontrast dyes, myoglobin, hemoglobin, radiation or urinary obstruction by tumors, prostatic hypertrophy or blood clots. The clinical course of AKI is variable but he classic case may be divided into (1) initiation phase lasting about 36 hours dominated by the inciting medical, surgical or obstetric event with a slight decline in urine output and rise in BUN, declining GFR and blood flow explaining oliguria; (2) maintenance phase with sustained decreases in urine output to between 40 to 400 mL/day (oliguria), salt and water overload, rising BUN concentrations, hyperkalemia, metabolic acidosis and other manifestations of uremia. With appropriate attention to the balance of water and blood electrolytes, including dialysis, the patient can be supported through this oliguric crisis; and (3) the recovery phase has a steady increase in urine volume that may reach up to 3 L/day. The tubules are still damaged, so large amounts of water, sodium and potassium are lost in the flood of urine. Hypokalemia, rather than hyperkalemia becomes a clinical problem and there is a peculiar increased vulnerability to infection at this stage. Eventually, renal tubular function is restored and concentrating ability improves, BUN and creatinine levels return to normal. Tubular functional impairment may persist for months, but most patients who reach this phase recover completely. The prognosis of AKI depends on the clinical setting, recovery is expected with nephrotoxic AKI when the toxin has not caused serious damage to other organs, such as the liver or heart. With current supportive care, 95% recover but with shock related to sepsis, extensive burns, or other causes of multi-organ failure, the mortality rate can rise to more than 50%. Up to 50% of patients with AKI do not have oliguria and instead have increased urine volumes and tend to follow a more benign clinical course. (Alper '10: 935-938).

The clinical manifestations of renal disease can be grouped into well defined syndromes. **Azotemia** is a biochemical abnormality that refers to an elevation of the blood urea nitrogen (BUN) and creatinine levels, and is related largely to a decreased glomerular filtration rate (GFR). Azotemia is a consequence of many renal disorders, but also arises from extrarenal disorders. Prerenal azotemia is encountered when there is hyperfusion of the kidneys (e.g. hemorrhage, shock, volume depletion and congestive heart failure that impairs renal function in the absence of parenchymal damage. Postrenal azotemia is seen whenever urine flow is obstructed beyond the level of the kidneys. Relief of the obstruction is followed by correction of the azotemia. Uremia is characterized by a host of metabolic and endocrine alterations resulting from renal damage. Nephritic syndrome onset present grossly visible hematuria (red blood cells in urine), mild to moderate proteinuria (>3.5 gm/day), hypoalbuminemia (plasma albumin <3 gm/dL), severe edema, hyperlipidemia and lipiduria (lipid in the urine) is due to glomerular disease classically acute poststreptococcal glomerulonephritis. Glomerular disease is often associated with such systemic disorders as diabetes mellitus, SLE, vasculitis, amyloidosis and endocarditis. Rapidly progressive glomerulonephritis includes a rapid decline (hours to days) in GFR) (Alpers '10: 906-907). The glomerular filtration barrier allows discrimination among various protein molecules, depending on their size (the large, the less permeable) and charge (the more cationic, the more permeable). Most cases of human glomerulonephritis are a consequence of deposits of discrete immune complexes. Microbial antigens that have been implicated are bacterial products (streptococci), appearing 1 to 4 weeks post-streptococcal infection of the pharynx or skin, but only certain strains of groups A β-hemolytic streptococci are nephritogenic, as well as the surface antigen of hepatitis B and C virus antigens, and antigens of *Treponema pallidum*, *Plasmodium falciparum* and several other viruses. More than 95% of children and 60% of adults recover but fewer than 1% of children and 40% of adults become severely oliguric, and develop a rapidly progressive glomerulonephritis; prolonged and persistent heavy proteinuria and abnormal GFR mark patients with an unfavorable prognosis (Alpers '10: 940, 941, 907, 910, 914, 919).

Acute **renal failure** is dominated by oliguria or anuria (reduced or no urine flow), and recent onset of azotemia that can result from glomerular, interstitial or vascular injury or acute tubular injury. Chronic renal failure is characterized by prolonged symptoms and signs of uremia, it is the end result of all chronic renal parenchymal diseases. Renal tubular defects are dominated by polyuria (excessive urine formation), nocturia and electrolyte disorders (e.g. metabolic acidosis). Defects in specific tubular functions can be inherited (e.g., familial nephrogenic diabetes, cystinuria, renal tubular acidosis) or acquired (e.g. lead nephropathy). Urinary tract infection is characterized as bacteriuria and pyuria (bacteria and leukocytes in the urine). The infection may be symptomatic or asymptomatic and may affect the kidney (pyelonephritis) or the bladder (cystitis). Nephrolithiasis (renal stones) manifest as severe spasms of pain (renal colic) and hematuria, often with recurrent stone formation. Urinary tract obstruction and renal tumors have varied clinical manifestations based on the specific anatomic location and nature of the lesion. Nephrotic patients are particularly vulnerable to infection especially staphylococcal and pneumococcal. Thrombotic and thromboembolic complications are also common due in part to loss of endogenous anticoagulants (e.g. antithrombin III) and antiplasmins in the urine. Renal vein thrombosis may result (Alpers '10: 907-908, 922).

About 10% of all people are born with potentially significant malformations of the urinary system. Renal dysplasias and hypoplasias account for 20% of chronic renal failure in children. Congenital renal disease can be hereditary but is most often the result of an acquired developmental defect that arises during gestation. Genetic abnormalities may also cause enzymatic or metabolic defects in tubular transport and renal tubular acidosis. All except horseshoe kidney are uncommon. **Horseshoe kidney** is caused by fusion of the upper or lower poles of the kidneys produces a horsehoe-shaped structure that is found in 1 in 500 to 1,000 autopsies. Ninety percent of such kidneys are fused at the lower pole and 10% are fused at the upper pole. Agenesis of the kidney can be bilateral, which is incompatible with life, usually encountered in stillborn infants, and is often associated with other congenital disorders and leads to early death. Unilateral agenesis is compatible with normal life if no other abnormalities exist. The opposite kidney is usually enlarged as a result of compensatory hypertrophy. Some patients eventually develop progressive glomerular sclerosis in the remaining kidney. **Hypoplasia** refers to a failure of the kidneys to develop to a normal size. This anomaly may occur bilaterally, resulting in renal failure in early childhood, but it is more commonly encountered as a unilateral defect. Most cases probably represent acquired scarring but a truly hypoplastic kidney shows no scars and has a reduced number of renal lobes and pyramids, usually six or fewer. In one form of hypoplastic kidney, oligomeganephronia, the kidney is small with fewer nephrons that are markedly hypertrophied. **Ectopic kidneys** lie either just above the pelvic brim or within the pelvis. They are usually normal or slightly small in size but otherwise not remarkable, because of their abnormal position, kinking or tortuosity of the ureters may cause some obstruction to urinary flow, which predisposes to bacterial infection. **Multicystic renal dysplasia** is characterized by the persistence in the kidney of abnormal structures-cartilage, undifferentiated mesenchyme and immature collecting ductures, and by abnormal lobar organization. Most cases are associated with ureteropelvic obstruction, ureteral agenesis or atresis and other anomalies of the lower urinary tract. Dysplasia, enlargement of the kidney, can be unilateral or bilateral and is almost always cystic. When unilateral surgical nephrectomy is performed, when bilateral renal failure may ultimately result (Alper '10: 954-956).

Cystic diseases of the kidney may be hereditary, developmental or acquired disorders. Besides Multicystic renal dysplasia, explained above, polycystic kidney disease is a hereditary disorder. **Polycystic kidney disease** can be autosomal-dominant (adult) polycystic disease (ADPKD) or

autosomal-recessive (childhood) polycystic disease (ARPKD). **ADPKD** is characterized by multiple expanding cysts of both kidneys that ultimately destroy the renal parenchyma and cause renal failure. It is a common condition affecting roughly 1 of every 400 to 1000 live births and accounting for 5-10% of cases of chronic renal failure requiring transplantation or dialysis. The likelihood of developing renal failure with a PKD1 mutation is less than 5% by 40 years of age, rising to more than 35% by 50, more than 70% at 60 and m ore than 95% by 70. With a PKD2 mutation the odds of renal failure are less than 5% by 50, 15% at 60, and about 45% at 70. Progression is accelerated in blacks (largely correlated with the sickle cell trait), in males, and in the presence of hypertension. Individuals with PKD tend to have external congenital anomalies and about 40% have one to several cysts in the liver (polycystic liver disease) that are usually asymptomatic. Cysts are derived from biliary epithelium. Cysts occur much less frequently in the spleen, pancreas, and lungs. Intracranial berry aneurysms arise in the circle of Willis, and subarachnoid hemorrhages from these account for death in about 4-10% of individuals. Mitral valve prolapse and other cardiac valvular anomalies occur in 20-25% of patients, but most are asymptomatic. Patients may survive for many years with azotemia slowly progressing to uremia. Ultimately, about 40% of adult patients die of coronary or hypertensive heart disease, 25% of infection, 15% of a ruptured berry aneurysm or hypertensive intracerebral hemorrhage, and the rest of other causes. ARPKD is genetically distinct. Patients who survive infancy may develop a peculiar type of congenital hepatic fibrosis. In older children the hepatic disease is the predominant clinical concern. Such patients may develop portal hypertension with splenomegaly (Alper '10: 956- 959).

The three major types of **medullary cystic disease** are medullary sponge kidney, a relatively common and unusually innocuous structural change, and nephronophthisis and adult-onset medullary cystic disease, which are almost always associated with renal dysfunction. Medullary sponge kidney is restricted to lesions consisting of multiple cystic dilations of the collecting ducts in the medulla. The condition occurs in adults and is usually discovered radiographcially. The papillary ducts in the medulla are dilated, and small cysts may be present. The cysts are lined by cuboidal epithelium or occasionally by transitional epithelium. **Nephronophthisis** and Adult-onset medullary cystic disease is a group of progressive renal disorders. The common characteristic is the presence of a variable number of cysts in the medulla, usually concentrated at the cortico-medullary junction, cortical tubulointerstitial damage is the cause of the eventual renal insufficiency. Some forms are inherited as autosomal recessive traits and usually become manifest in childhood or adolescence. As a group, the nephronophthisis complex is now thought to be the most common genetic cause of end-stage renal disease in children and young adults. **Adult-onset medullary cystic disease** has an autosomal dominant pattern of transmission and is now considered a distinct entity. Affected children present first with polyuria and polydipsia, reflecting a defect in the concentrating ability of the renal tubules. Sodium wasting and tubular acidosis are also prominent. The kidneys are small and show cysts in the medulla and small cysts in the cortex. The expected course is progression to terminal renal failure during a period of 5 to 10 years (Alper '10: 959, 960).

Pyelonephritis is a renal disorder affecting the tubules, interstitium and renal pelvis and is one of the most common diseases of the kidney. It can be acute renal lesion caused by bacterial infection. Chronic pyelonephritis is more complex, bacterial infection plays a dominant role, but other factors such vesicoureteral reflux, where the reflux of urine allows bacteria to ascend the ureter and obstruction by a tumor or enlarged prostate are involved. Pyelonephritis is a serious complication of urinary tract infections that affect the bladder (cystitis). The dominant etiologic agents, accounting for more than 85% of cases of urinary tract infection are the gram-negative bacilli that are normal inhabitants of the intestinal tract, most commonly *Escherichia coli*,

followed by *Proteus*, *Klebsiella* and *Enterobacter*. *Streptococcus feacalis*, also of enteric origin, *staphylocooci* and virtually every other bacterial and fungal agent, (e.g. *Candida*) can also cause lower urinary tract and renal infection that destroys the glomeruli (Alper '10: 939). In chronic interstitial nephritis there is infiltration with predominantly mononuclear leukocytes, prominent interstitial fibrosis and widespread tubular atrophy. Defects in tubular function may cause impaired ability to concentrate urine, evidenced by polyuria or nocturia, salt wasting, diminished ability to excrete acids (metabolic acidosis), and isolated defects in tubular reabsorption or secretion. In immunocompromised persons, particularly those with transplanted organs, viruses such as Polyomavirus, cytomegalovirus and adenovirus can also cause renal infection. In most patients with urinary tract infections, the infecting organisms are derived from the patient's own fecal flora that has reached the kidney through the bloodstream (hematogenous infections) or from the lower urinary tract (ascending infection) the most common cause of clinical pyelonephritis. Chronic pyelonephritis at one time accounted for 10-20% of patients in renal transplant or dialysis units, until predisposing conditions such as reflux became better recognized.

In some patients with **rapidly progressive (crescentic) glomerulonephritis**, exhibiting hematuria with red blood cell casts in the urine, variable hypertension and edema, antibodies produce the clinical picture of pulmonary hemorrhage associated with renal failure known as **Goodpasture syndrome** treated with plasmapheresis to remove the pathogenic circulating antibodies and immunosuppression. Exposure to viruses and hydrocarbon solvents has been implicated. Crescentic glomuleronephritis can also be caused by immune complex deposition or pauci-immune type with circulating anti-neutrophil cytoplasmic antibodies (ANCAs). 1 to 7% of patients treated for rheumathoid arthritis with drugs such as penicillamine, captopril, gold, develop **membranous glomerulopathy**. Underlying malignant tumors are present in as many as 5-10% of adults with membranous glomerulopathy that can be caused by chronic hepatitis B or C, syphilis, schistosomiasis, malaria, Systemic Lupus Erythomatous (SLE), or autoimmune disorders such as thyroiditis but in 85% of patients no associated condition is discovered and the condition is considered idiopathic. Although proteinuria persists in more than 60% of patients, only about 10% die or progress to renal failure within 10 years. **Minimal-change disease** can be caused by non-steroidal anti-inflammatory drugs (NSAIDs), and although there are no immune deposits, tends to respond well to corticosteroids and other immunosuppressive therapies (Alpers '10: 920, 922, 925).

Focal segmental glomerulonephrosis is characterized by sclerosis of some but not all, glomeruli and can be a primary disease or secondary disease due to HIV infection, sickle-cell disease, massive obesity, scarring and accounts for 10-35% of cases of nephrotic syndrome in children and adults in the United States particularly in Hispanic and African-American patients, there is a poor response to corticosteroid therapy, and 50% develop end-state renal disease in 10 years. 20% of patients follow an unusually rapid course, with intractable massive proteinuria ending in renal failure within 2 years. Recurrences are seen in 25% to 50% of patients receiving allografts. **Membranoproliterative glomerulonephritis** (MPGN) accounts for 10-20% of cases of nephrotic syndrome in children and young adults. Glomerular immune deposits are thought to derive from infections by hepatitis B and C viruses. About 50% develop chronic renal failure within 10 years. Treatment with steroids, immunosuppressive agents and antiplatelet drugs have not proved to be effective, There is a high incidence of recurrence in transplant recipients, particularly in dense deposit disease recurrence happens in 90% of patients although renal failure in the allograft is much less common. Secondary MPGN can result from SLE, hepatitis B and C, cryoglobulinemia, endocarditis, infected ventriculoatrial shunts, chronic visceral abscesses, HIV infection, schostosomiasis, α_1-Antitrypsin deficiency, malignant diseases such as chronic

lymphocytic leukemia and lymphoma and hereditary deficiencies of complement regulatory proteins (Alpers '10: 920, 922, 925).

IgA Nephropathy (**Berger Disease**) has prominent IgA deposits that occur with increased frequency with Henoch-Schönlein purpura, gluten enteropathy (celiac disease) and liver disease. The disease affects people of any age, but older children and young adults are most commonly affected. The hematuria typically lasts for several days and then subsides, only to return every few months. Many patients maintain normal renal function for decades. Slow progression to chronic renal failure occurs in 15-40% of cases over a period of 20 years. Recurrence of IgA deposits in transplanted kidneys is frequent and 15% develop another progressive disease. **Alport Syndrome** is a hereditary nephritis that is manifest by hematuria with progression to chronic renal failure, accompanies by nerve deafness and various eye disorders, including lens dislocation, posterior cataracts and corneal dystrophy. The disease is inherited as an X-linked trait in 85% of cases with males expressing the full syndrome and females as carriers limited to hematuria although autosomal recessive and autosomal dominant pedigrees exist. Symptoms appear at ages 5 to 20 years, and the onset of overt renal failure is between the ages of 20 and 50 years in men. **Thin basement membrane lesion** (Benign Familial Hematuria) is a fairly common hereditary entity manifested clinically by familial asymptomatic hematuria and diffuse thinning of the GBM to between 150 and 250 nm (compared with 300-400 nm in normal adults) renal function is normal and prognosis is excellent but most patients are heterozygous for the defective gene and may be carriers, homozygotes or compound heterozygotes may progress to renal failure (Alpers '10: 929-933). **Sickle cell nephropathy** can occur in homozygous people with the disease or heterozygous people with the trait. The most common clinical abnormalities are hematuria and diminished concentrating ability (hyposthenuria). Patchy papillary necrosis may occur associated with cortical scarring. Mild to moderate proteinuria is also common, occurring in about 30% of patients.

Disorders associated with **hypercalcemia**, such as hyperparathyroidism, multiple myeloma, vitamin D intoxication, metastatic cancer, or excess calcium intake (milk-alkali syndrome) may induce the formation of calcium stones and deposition of calcium in the kidney (nephrocalcinosis) which can lead to chronic tubulointerstitial disease and renal insufficiency. The earliest functional defect is an inability to concentrate the urine. Other tubular defects, such as tubular acidosis and salt-losing nephritis, may also occur. Extensive accumulations of calcium phosphate crystals can occur in patients consuming high doses of oral phosphate solutions in preparation for colonoscopy, presenting as renal insufficiency several weeks after exposure. **Nonrenal malignant tumors**, particularly those of hematopoietic origin, affect the kidneys in several ways. The most common involvements are tubulointerstitial, caused by complications of the tumor (hypercalcemia, hyperuricemia, obstruction of ureters) or therapy (irradiation, hyperuricemia, chemotherapy, injections in immunosuppressed patients). As the survival rate of persons with malignant neoplasms increases, so do these renal complications. Overt renal insufficiency occurs in half of those with multiple myeloma and related lymphoplasmacytic disorders. The main cause of renal dysfunction is related to the **Bence Jones (light-chain) proteinuria**. Amyloidosis formed from free light chains occur in 6-24% of individuals with myeloma. Light-chain deposition disease can cause glomerulopathy or tubulointerstitial nephritis. Hypercalcemia and hyperuricemia are often present in these patients. In the most common form, chronic renal failure develops insidiously and usually progresses slowly during a period of several months to years. Another form occurs suddenly and is manifested by acute renal failure with oliguria. Precipitating factors in these patients include dehydration, hypercalcemia, acute infection and treatment with nephrotoxic antibiotics, mistakenly used to treat myeloma of fungal origin (Alper '10: 947, 948).

Hypertension affects about 50 million Americans. In most patients, the cause if unknown, and the disease is termed **essential hypertension**. Renal disease is fund to be the cause in 5-15% of patients with hypertension, who are said to have **renal hypertension**. Renal hypertension may be vascular in nature, may be related to renal parenchymal disease, or may result form a combination of these two processes. The renin-angiotension-aldosterone system is an integrated hormonal cascade that simultaneously controls blood pressure and sodium and potassium balance and influences regional blood flow Renin is a proteolytic enzyme produced in the juxtaglomerular cells of the afferent arterioles. It acts on renin substrate (angiotensinogen), an α-2 globulin produced in the liver, to form the decapeptide angiotensin I. Converting enzyme, found in the lung and kidney, cleaves 2 amino acids from angiotensinI to form the octapeptide angiotensin II, a potent arterial vasoconstrictor. Angiotensin II also stimulates the zona glomerulosa of the adrenal gland to secrete aldosterone. Elevation of blood pressure and restoration of sodium balance inhibit further renin secretion. Frequent causes of hypersecretion of renin include sodium depletion, hemorrhage, shock, congestive heart failure and renal artery stenosis. Plasma renin activity is closely related to the patients sodium intake and urinary sodium excretion, ie. Sodium balance. Management of patients with renovascular hypertension using conventional antihypertensive drugs has been been difficult. Morbidity and mortality rates were shown to be significantly greater in the medically treated group Cure or improvement of hypertension was achieved in 90% of the surgically treated patients, whereas adequate control was attained in fewer than 50% of patients medically treated. The operative mortality rate is significant – in the range of 2-9%. The development of drugs such as captopril and beta-blockers has made medical management of hypertension more effective than surgery. Patients with stenotic renal artery can be treated with percutaneous transluminal balloon dilation. Hypertension has been cured or improved in over 90% of carefully selected patients treated surgically with mortality rates less than 2% (Sosa & Vaughan '88:625-635).

Nearly all diseases of the kidney involve the renal blood vessels secondarily. Hypertension is intimately linked to the kidneys because kidney disease can be both the cause and consequence of increased blood pressure. There are benign and malignant **nephrosclerosis** and renal artery stenosis, lesions associated with hypertension and sundry lesions involving mostly smaller vessels of the kidney. Benign **n**ephrosclerosis is associated with the sclerosis of renal arterioles and small arteries causing focal ischemia of parenchyma supplied by vessels with thickened walls and narrowed lumens. Nephrosclerosis at autopsy is associated with increasing age, more frequent in blacks than whites, and may be seen in the absence of hypertension. Kidneys are often moderately reduced in size, with average weights of 110 to 130 gm. It is unusual for uncomplicated benign nephrosclerosis to cause renal insufficiency or uremia. Although there is usually a moderate reduction in renal blood flow, the GFR is normal or only slightly reduced and occasionally there is mild proteinuria. Hypertension and diabetes mellitus, however, increase the incidence and severity of the lesions.

Malignant nephrosclerosis is the form of renal disease associated with the malignant or accelerated phase of hypertension. It is relatively uncommon, occurring in 1-5% of all people with elevated blood pressure. In its pure form is usually affects younger individuals and occurs more often in men and in blacks. The turn for the worse seems to result from some sort of vascular damage to the kidneys. Fibrinoid necrosis of the arterioles and small arteries cause the kidneys to become markedly ischemic, and patients with malignant hypertension have markedly elevated levels of plasma renin which causes angiotensin II to cause intrarenal vasoconstriction. Aldosterone levels are also elevated, and salt retention contributes to the elevation of blood pressure. The consequences of the markedly elevated blood pressure on the blood vessels

throughout the body are known as malignant arteriosclerosis and the renal disorder is malignant nephrosclerosis. The full blown syndrome is characterized by a systolic pressure greater than 200 mm Hg and diastolic pressures greater than 120 mm Hg, papilledema, retinal hemorrhages, encephalopathy, cardiovascular abnormalities and renal failure. Early symptoms are related to increased intracranial pressure and include headaches, nausea, vomiting and visual impairment, particularly scotomas or spots before the eyes. Hypertensive crisis is sometimes encountered, characterized by loss of consciousness or convulsions. Soon however, renal failure makes its appearance. The syndrome is a true medical emergency requiring the institution of aggressive and prompt antihypertensive therapy to prevent the development of irreversible renal lesions. Before the introduction of current antihypertensive drugs, e.g. captopril and beta-blockers, malignant hypertension was associated with a 50% mortality rate within 3 months of onset, progressing to 90% within a year. At present, however, 75% of patients survive 5 years, and 50% survive with restoration of pre-crisis renal function (Alper '10: 949-950).

Unilateral renal artery stenosis is a relatively uncommon cause of hypertension, responsible for 2-5% of cases, but it is important because it represents a potentially curable form of hypertension with surgical treatment. 70% of cases of renal artery stenosis involve an occlusion by an atheromatous plaque at the origin of the renal artery, that are more common in men, the remaining 30% are caused by fibromuscular dysplasia of the renal artery, which are more common in women. The hypertensive effect is, at least initially, due to stimulation of renin secreting cells of the juxtaglomerular apparatus and the subsequent production of vasoconstrictor angiotensin II. Many patients with renovascular hypertension have elevated plasma or renal vein renin levels, and almost all show a reduction of blood pressure when given drugs that block the activity of angiotensin II. Unilateral renal renin hypersecretion can be normalized after renal revascularization, usually resulting in a decrease of blood pressure. Other factors, however, may contribute to the maintenance of renovascular hypertension after the renin-angiotensin system has initiated it, including sodium retention and possibly loss of nitric oxide. **Bilateral renal artery disease**, usually diagnosed definitively by arteriography, seems to be a fairly common cause of chronic ischemia with renal insufficiency in older individuals, sometimes in the absence of hypertension, that is reversible with surgical revascularization.
Atheroembolic renal disease involving embolization of fragments of atheromatous plaques from the aorta or renal artery into intraparenchymal renal vessels occurs in elderly patients with severe atherosclerosis, especially after surgery on the abdominal aorta, aortography, or intra-aortic cannulization. These emboli can be recognized in the lumens and walls of arcuate and interlobular arteries by their content of cholesterol crystals, which appear as rhomboid clefts. Frequently they have no clinical significance, however, acute renal failure may develop in elderly patients in whom renal function is already compromised, principally after abdominal surgery or atherosclerotic aneurysms.

Diffuse cortical necrosis is an uncommon condition that occurs most frequently after obstetric emergency, such as abrupti placentae (premature separation of the acenta), septic shock, or extensive surgery, giving rise to sudden anuria, terminating rapidly in uremic death. When bilateral and symmetric, it is fatal in the absence of supportive therapy, unilateral or patchy involvement is compatible with survival. Renal infarcts are predisposed by the extensive blood flow to the kidneys (one fourth of the cardiac output), and end-organ nature of the arterial blood supply. Most infarcts are due to embolism. A major source of such emboli is mural thrombosis of the left atrium and ventricle as a result of myocardial infarction. Vegetative endocarditis, aortic aneurysms and aortic atherosclerosis are less frequent sources of emboli. Most renal infarcts are of the white anemic variety. They may be solitary lesions or may be multiple and bilateral. Within 24 hours infarcts become pale, yellow-white areas tat may contain small

irregular foci of hemorrhagic discoloration, usually ringed by a zone of intense hyperemia. Many renal infarcts are clinically silent. Sometimes pain with tenderness occurs. Large infarcts of one kidney are probably associated with narrowing of the renal artery or one of its major branches, which in turn may be a cause of hypertension (Alper '10: 953-955).

22. Kidney failure, dialysis and transplant

Renal failure may classified as acute or chronic depending on the rapidity of onset and the subsequent course of azotemia. The general incidence of chronic renal failure in the USA, defined as "people who can benefit from hemodialysis or renal transplantation" is 50 per million population per year. More than 95,000 patients are being treated with either dialysis or transplantation, each year by 1988. A variety of disorders are associated with end stage renal disease Either a primary renal process (e.g., glomerulonephritis, pyelonephritis, congenital hypoplasia) or a secondary one (e.g., a kidney affected by a systemic process such as diabetes mellitus or lupus erythematosus) may be responsible. Minor physiologic alterations secondary to dehydration, infection or hypertension often "tip the scale" and put a borderline patients into uncompensated clinical uremia. Severe abnormalities in serum electrolytes and mineral metabolism become manifest when the GFR drops below 30 mL/min and metabolic acidosis manifests. Hyperkalemia is not usually seen unless the GFR is below 5 mL/min or there is a predisposition to an increase in serum potassium Conservative management includes restriction of dietary protein (0.5 g/kg/f), potassium and phosphorus, as well as close sodium balance in diet so that patients do not retain sodium or become sodium depleted. Use of bicarbonate can be helpful when moderate academia occurs Fresh blood transfusions may be helpful. Prevention of possible uremic osteodystrophy requires close attention to calcium and phosphorus balance; phosphate-retaining antacids and administration of calcium or vitamin D may be needed to maintain the balance. However, extreme care must be paid to this management, because if the Ca x P produce is greater than 65 mg/dL, metastatic calcifications can occur (Amend & Vincente '88: 530, 531).

Oliguria means "too little" urine volume in response to the body's excretory needs. Oliguria is present when the daily urine volume is not sufficient to remove the endogenous solute loads that are the end products of metabolism. No precise figure for 24-hour urine volume can be used in defining oliguria, since urine volumes normally vary with fluid intake and the concentrating ability of the kidney. If the kidney can concentrate urine in a normal fashion to a specific gravity of 1.035, oliguria is present at urine volumes under 400 mL/d. On the other hand, if the kidney concentration is impaired and the patient can achieve a specific gravity of only 1.010, oliguria is present at urine volumes under 1000-1500 mL/d (Amend et al '88: 526-528). **Azotemia** is a biochemical abnormality that refers to an elevation of the blood urea nitrogen (BUN) and creatinine levels, and is related largely to a decreased glomerular filtration rate (GFR). Azotemia is a consequence of many renal disorders, but also arises from extrarenal disorders. Prerenal azotemia is encountered when there is hyperfusion of the kidneys (e.g. hemorrhage, shock, volume depletion and congestive heart failure that impairs renal function in the absence of parenchymal damage. Postrenal azotemia is seen whenever urine flow is obstructed beyond the level of the kidneys. Relief of the obstruction is followed by correction of the azotemia (Alpers '10: 906-907).

Acute renal failure is a condition in which the glomerular filtration rate is abruptly reduced, causing a sudden retention of endogenous metabolites (urea, potassium, phosphate, sulfate, creatinine) that are normally cleared by the kidneys. Acute renal failure is dominated by oliguria or anuria (reduced or no urine flow), and recent onset of azotemia that can result from

glomerular, interstitial or vascular injury or acute tubular injury. The urine volume is usually low (under 400 mL/d), however may be normal. Prompt differentiation of the cause is important in determining appropriate therapy. Pre-renal renal failure is reversible if treated promptly , but a delay in therapy may allow it to progress int a fixed, nonspecific form of intrinsic renal failure (e.g., acute tubular necrosis). The other causes of acute renal failure are classified on the basis of their involvement with vascular lesions, intrarenal disorders or postrenal disorders. Rapid intravenous administration of 300-500 mL of physiologic saline or 125 mL of 20% mannitok (25g/125mL) is the usual initial treatment. Urine output is measured over 1-3 hours. A urine volume of more than 50 mL/h is considered a favorable response that warrants continued intravenous infusion with physiologic solutions to restore plasma volume and correct dehydration Therapy is directed toward eradication of infection, removal of antigen, elimination of toxic materials and drugs, suppression of autoimmune mechanisms, removal of autoimmune antibodies, or a reduction in effector-inflammatory responses (Amend et al '88: 526-528).

Chronic renal failure is characterized by prolonged symptoms and signs of uremia, it is the end result of all chronic renal parenchymal diseases. **Uremia** is characterized by a host of metabolic and endocrine alterations resulting from renal damage. **Nephritic syndrome** onset present grossly visible hematuria (red blood cells in urine), mild to moderate proteinuria (>3.5 gm/day), hypoalbuminemia (plasma albumin <3 gm/dL), severe edema, hyperlipidemia and lipiduria (lipid in the urine) is due to glomerular disease classically acute poststreptococcal glomerulonephritis. **Glomerular disease** is often associated with such systemic disorders as diabetes mellitus, SLE, vasculitis, amyloidosis and endocarditis. **Rapidly progressive glomerulonephritis** includes a rapid decline (hours to days) in GFR). Reduced clearance of certain solutes principally excreted by the kidney results in their retention in the body fluids. The most commonly used indicators of renal failure are blood urea nitrogen and serum creatinine. However, marked elevation of blood urea nitrogen can be due to nonrenal causes such as prerenal azotemia, gastrointestinal hemorrhage, or high protein intake. The clearance of creatinine can be used as a reasonable measure of glomerular filtration rate (GFR) (Alpers '10: 906-907).

Chronic renal failure progresses through four stages that merge into one another. In stage 1 there is a **diminished renal reserve** the GFR is about 50% of normal. Serum BUN and creatinine values are normal, and the patient is asymptomatic. However, they are more susceptible to developing azotemia with an additional renal insult. Stage 2 is known as **renal insufficiency** the GFR is 20-50% of normal. Azotemia appears, usually associated with anemia and hypertension. Polyuria and nocturia can occur as a result of decreased concentrating ability. Stage 3 **chronic renal failure**, GFR is less than 20-25% of normal. The kidneys cannot regulate volume and solute composition, and patients develop edemia, metabolic acidosis, and hyperkalemia. Overt uremia may ensue, with neurologic, gastrointestinal and cardiovascular complications. Stage 4 **end-stage renal disease** GFR is less than 5% of normal; this is the terminal stage of uremia. The major characteristic of normal glomerular filtration are an extraordinarily high permeability to water and small solutes, and impermeability to proteins, such as molecules of the size of albumin (~3.6 nm radius; 70 kilodaltons [kD] molecular weight or larger (Alpers '10: 907, 910).

In the early 1960s came the development of **hemodialysis**, a method of removing waste products from the blood when the kidneys are unable to perform this function, to sustain the lives of patients with end-stage kidney disease. As a result of this treatment advance, these patients were able to survive the underlying disease, but their damaged kidneys could no longer make erythropoietin, leaving them severely anemic and in desperate need of Epo therapy. In 1983, scientists discovered a method for mass producing a synthetic version of the hormone. Experiments were conducted to test the safety and effectiveness of the new drug, **Epo**, for

treating anemia in patients with kidney failure. The results of these early clinical trials were dramatic. Patients who had been dependent on frequent blood transfusions were able to increase their red blood cell levels to near-normal within just a few weeks of starting therapy. Patients' appetites returned, and they resumed their active lives. It was the convergence of two technologies – long-term dialysis and molecular biology – that set the stage for anemia management in this group of patients. Since then, millions of patients worldwide have benefited from Epo therapy (Adamsom '08).

Chronic periotoneal dialysis is used electively, either intermittent thrice-weekly treatment (IPPD) or chronic ambulatory peritoneal dialysis (CAPD) is possible. With the latter, the patient performs 3-5 daily exchanges using 1-2 L of dialysate at each exchange. Bacterial contamination and peritonitis are becoming less common with improvements in technology. Chronic hemodialysis using semipermeable dialysis membranes is now widely performed. Access to the vascular system is by means of Scribner shunts, arteriovenous fistulas and grafts . The actual dialyzer may be of a parallel plate, coil or hollow fiber type. Body solutes and excessive body fluids can be easily cleared by using dialysate fluids of known chemical composition. Newer high efficiency membranes are serving to reduce dialysis treatment time. Treatment is intermittent – usually 3-5 hours 3 times weekly. It may be given in a kidney center, a satellite unit or the home. Home dialysis is optimal., but only 30% of dialysis patients meet the medical and training requirements for this type of therapy. Common problems with either type of chronic dialysis include infection, bone symptoms, technical accidents, persistent anemia, and psychologic disorders. Atherosclerosis often occurs with long-term treatment. Yearly costs range from an average of $15,000 for patients who receive dialysis at home to as much as $30,000-$50,,000 for patients treated at dialysis centers, but much of this is absorbed by Medicare. The mortality rates are 8-10% per year once maintenance dialysis therapy is instituted (Amend & Vincenti '88: 530-532).

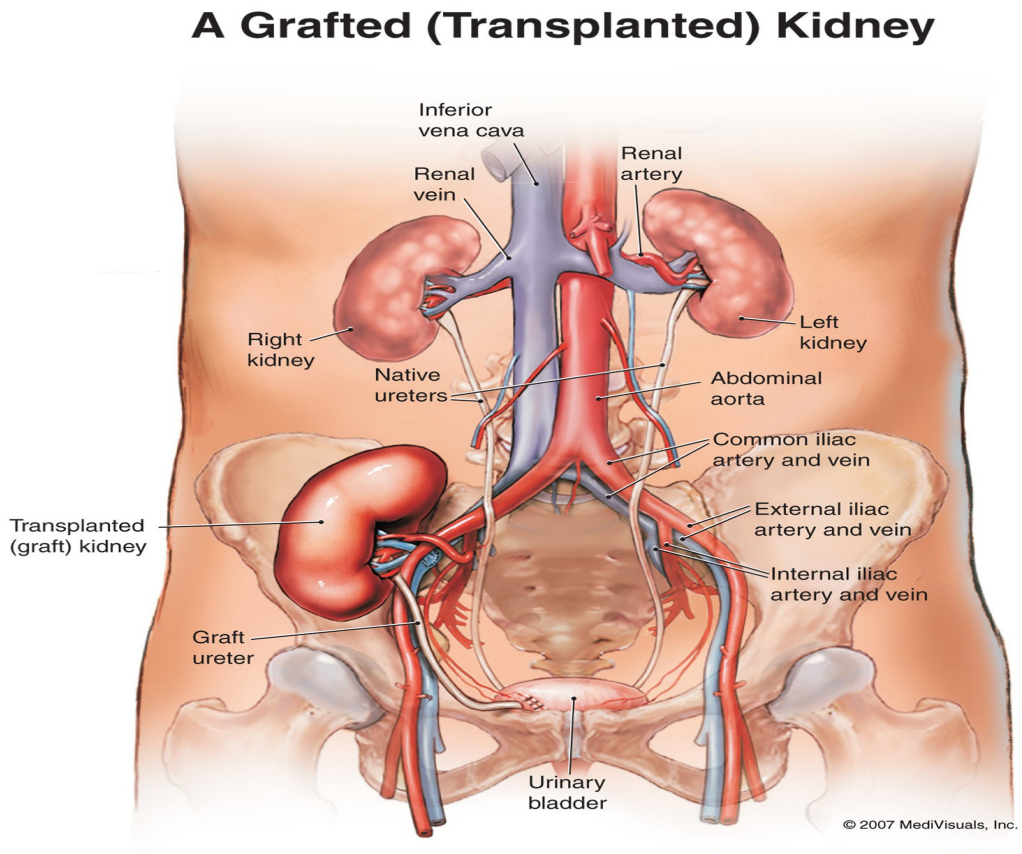
The kidneys from patients with end-stage renal disease who have undergone prolonged dialysis sometimes show numerous cortical and medullary cysts, a condition known as **acquired (dialysis associated) cystic disease**. The cysts measure 0.5 to 2 cm in diameter, contain clear fluid, are lined by either hyperplastic or flattened tubular epithelium, and often contain calcium oxalate crystals. The probably form as a result of obstruction of tubules by interstitial fibrosis or by oxalate crystals. Most are asymptomatic, but sometimes the cysts bleed, causing hematuria. The most ominous complication is the development of renal cell carcinoma in the walls of these cysts occuring in 7% of dialyzed patients observed for 10 years. Simple cysts may occur as multiple or single, usually cortical, cystic spaces that vary widely in diameter. They are commonly 1 to 5 cm but may reach 10 cm or more in size. They are translucent, lined by a gray, glistening, smooth membrane, and filed with clear fluid. Simple cysts are a common postmortem finding without clinical significance. The main importance of cysts lies in their differentiation from kidney tumors when they are discovered either incidentally or because of hemorrhage and pain. Radiologic studies show that in contrast to renal tumors, renal cysts have smooth contours, are almost always avascular, and give fluid rather than solid signals on ultrasonography (Alper '10: 960).

After immunosuppression techniques and genetic matching were developed, **renal homotransplantations** became an acceptable alternative to maintenance hemodialysis. Improved transplantation results are now noted due to the development of newer immunosuppressant drugs (cyclosporine and antilymphocyte preparations). Diet can be less restrictive. The disadvantages include bone marrow suppression, susceptibility to infection, cushingoid body habitus, and the psychologic uncertaining of the homograft's future. Most of

the disadvantages are related to the medicines (azathioprine and corticosterois) given to counteract the rejection. Later problems with transplantation include recurrent disease in the transplanted kidney (Amend et al '88: 532). Renal transplantation is an effective form of therapy for patients with end stage renal disease. More than 2800 **renal transplants** have been performed at the University of California, San Francisco (UCSF) by 1988. The principal indication for renal transplantation is end stage renal failure. Patients with active infections or primary oxalosis are not accepted for transplantation. Approximately 90% of patients now receive transplants with their own kidneys left in situe. The indications for preliminary nephrectomy are anatomic abnormalities, severe hypertension, some cases of polycystic renal disease. Some transplant centers have performed **splenectomy** before transplantation, but there is still not clear evidence that it modifies the immunologic reaction. In addition, there is evidence the patients who have undergone splenectomy are predisposed to pneumococcal and other infections (Salvatierra & Feduska '88: 533, 534, 536).

The kidney to be transplanted can be obtained from either a living related donor or a cadaver donor. **Living related donors** are usually siblings or parents, but in some cases, more distant relative may be accepted. Histocompatibility is assess by determination of human leukocyte antigens (HLA) to establish the inheritance pattern in a family group. The best donor-recipient combinations share all HLA antigens The prognosis for long term graft survival is about 90%. **Cadaver kidneys** are not acceptable from newborns or those over age 55, preexisting renal disease or neoplastic disease. Blood transfusions prior to transplantation enhance graft survival. Preservation of the cadaver kidney prior to transplantation can be accomplished by hypothermic storage (up to 24 hours) or by pulsatile perfusion (up to 3 days). When perfusion preservation was started immediately after nephrectomuy, the postoperative dialysis rates following transplantation has been 20% and an average of only 2 or 3 dialysis treatments was required for each patient. One year cadaver graft survival rates of greater than 80% are regularly achieved with conventional immunosuppression (Salvatierra & Feduska '88: 533, 534, 536).

The surgical technique of **renal transplantation** involves vascular anastomoses and establishment of urinary tract continuity. In adults the kidney is laced through an oblique lower abdominal incision and the common iliac and internal iliac (hypgastric) arteries are mobilized. The iliac veins are similarly mobilized ot hath an end-to-side renal vein-to-iliac vein anastomosis can be performs. When multiple arteries are present in cadaver donors, the kidneys are transplanted with anastomosis of a Carrel patch of aorta to the common iliac artery. In small children, a midline abdominal incision is used and the cecum and ascending colon are mobilized, exposing the aorta and vena cava. An end-to-side anastomosis of the renal vessels to the vena cava and aorta is then easily accomplished. Arterial anastomosis is performed by using a Carel patch of donor aorta, and whenever possible a Carel patch of the vena is used for the venous anastomosis. Urinary tract continuity can be established by pyeloureterostomy, ureteroureterostomy, or ureteroneocystostomy. Ureteroneocystostomy has an incidence rate of primary ureteral leaks of less than 1%. Foley catheter drainage is maintained for 1 week, because of the impaired wound healing associated with immunosuppressive therapy. Intravenous fluids are given immediately after the operation at a rate to maintain a good diuresis (Salvatierra & Faduka '88: 535-537).



Renal failure following transplantation can be difficult when urinary output suddenly decreases shortly after and transplantation or when **rejection** is superimposed upon acute tubular necrosis. Hyperacute rejection is mediated by humoral antibodies. It occurs in patients who have preexisting circulating cytotoxic antibodies that react with the donor kidney. Acute rejection generally presents during the first several months following transplantation. This type of rejection is usually characterized by fever, oliguria, weight gain, tenderness and enlargement of the graft. Treatment has traditionally been by increasing the dosage of corticosteroids, but the use of antithymocyte globulin or monoclonal antibodies has also proved very effective at reversing rejection. Chronic rejection is a late cause of renal deterioration over several years after inception of impaired renal function. The principal drugs used in conventional immunosuppression are prednisone and azathioprine or (Imuran) an antimetabolite, or cyclosporine, are used in combination. After a policy of low-dose immunosuppressive therapy was adopted in 1972, the cumulative patient mortality rate has been reduced to 2% at 1 year and 3% at 2 years for living related transplants and 4% and 6% for cadaver transplants. Living related transplantations should achieve greater than 90% graft survival at 2 years with conventional immunosuppression. The survival rate of cadaver grafts has been about 60% at 1 year and 55% at 2 years with conventional immunosuppression and with refined immunosuppression cadaver graft survival rates are approximately 80% at 1 year and 75% at 2 years (Salvatierra & Faduka '88: 535-537).

V. Abdominal Medicine

1. Diagnosis

Approximately 20% of patients who visit a primary physician's office have urologic problems (Alpers '10: 906). Gastrointestinal (GI) disease accounts for about 10% of general practitioner consultations, 8.5% of prescriptions and 8.3% of the cost of inpatient treatment. The GI is responsible 8.8% of days of certified incapacity to work and 10% of all deaths (Lewis and Elvin-Lewis ’77: 272). Chronic abdominal disease is often first noted as **colic** that is intolerably painful with exercise, forcing the patient to curtail their athletic endeavor. Because of the complicated overlapping functions of the abdominal organs, lymphatic, biliary, urinary and digestive system clinical diagnosis begins by pinpointing the part of the abdomen where pain if felt, e.g. upper right quadrant pain (liver, gallbladder), epigastric pain (transverse colon, duodenum, stomach), left upper quadrant pain (pancreas, spleen), bladder pain, or flank pain (kidneys) (Beckmann et al '02: 91, 92). The adult bladder holds about 400 mL of urine and the kidneys produce 1 liter of urine a day (McAninch '88: 34). Each 24 hours about 100-200 grams of stool is evacuated (Jones et al '85: 301). The more fruit and vegetables eaten, the more feces excreted per bowel movement. Increasing the proportion of that food group can raise the weight of a bowel movement from the average 3 ½ to 7 ounces (100 to 200 grams) to as much as 178 or 18 ounces (500 grams) per day (Enders '15: 70, 71). Complete blood counts (CBC) can be useful (Williams '88: 55-56).

Abdominal pain can be of two kinds – visceral and parietal. The abdominal viscera are insensitive to handling and cutting, but obstruction, causing distension, triggers stretch receptors, traction on mesenteries is painful, acid gastric juice stimulates pain receptors in the base of gastric and duodenal ulcers. The level at which pain is felt depends on the site being stimulated. Thus esophagitis causes substernal pain. The pain of an ulcer in the stomach or duodenum, or a stone in the biliary tree, is felt high in the epigastrium. Obstructive appendicitis due to a fecolith impacted near the base causes quite severe pain around the umbilicus, whilst an obstructing carcinoma in the sigmoid colon will produce recurrent pain across the lower abdomen. The timing of abdominal pain is very important. The patient who perforates a peptic ulcer or who suffers embolism of the mesenteric artery may be literally caught in the act of physical activity. The pain of a duodenal ulcer is typically related to hunger, so it often waken the patient at night and is relieved by a drink of milk or bicarbonate of soda, relapse tends to occur in spring and autumn. The pain of acute bowel obstruction is typically colicky, rising to a peak of severity and then fading away, to be followed in a few minutes by another spasm. However, so-called biliary and ureteric colic are usually steady pains, maintained over several hours often of great severity. The pain of peptic ulcer is a duller, boring type of pain, but very persistent and repetitive. Almost everyone with an acute abdominal condition loses any desire to eat (Jones et al '85: 32-34).

Visceral pain may be referred to other sites it is characteristic of a stone impacted in the biliary tract for pain to be felt first below the xiphoid process and then for it to spread along the costal margin through to the back, around the angle of the right scapula. When visceral pain arises from the paired renal tracts, the pain is felt on the affected side. A stone in the renal pelvis causes aching or colicky pain in the loin or, if the stone impacts lower in the ureter, the pain is felt low in the iliac fossa or in the testicle of labia. Acute retention of urine produces intense pain felt directly over the distended bladder. Totally different from visceral pain is the pain which is experienced when the **parietal peritoneum**, which lines the abdominal wall is subjected to irritation. When, for instance, acute appendicitis has developed sufficiently to cause

inflammation in the abdominal wall peritoneum overlying it, this is felt as a steady aching pain well localized to the inflamed area. Movement of coughing conspicuously aggravates this type of pain. The irritation of the parietal peritoneum also sets up a reflex protective spasm in the overlying abdominal muscles which can be recognized, on palpation, as either a stiffening or complete rigidity of the abdominal wall. This rigidity is classically seen when a duodenal ulcer perforates and the contents of the stomach flow out over the peritoneal cavity causing immediate severe generalized abdominal pain for the chemical assault on the peritoneum lining the abdominal wall, and the whole abdominal musculature also immediately tightens up. Blood, such as that from a ruptured bleeding ectopic pregnancy in the fallopian tubes can also irritate the parietal peritoneum (Jones et al '85: 32-34).

According to government statistics, 60 to 70 million Americans, 20 percent to 24 percent of the population suffer from **digestive diseases**. Each year, problems with the digestive tract prompt 45 million doctor visits and send 14 million to the hospital, millions more wind up at their local pharmacy, where shelves are stocked with products that promise relief for gas, indigestion, diarrhea, or constipation. Gastrointestinal disease accounts for about 10% of all illness, as well as 10% of general practitioner consultations, 8.5% of prescriptions and 8.3% of the cost of inpatient treatment. It is responsible 8.8% of days of certified incapacity to work and 10% of all deaths. Gastroenterology began to emerge as a specialty in Britain in the 1930s and 40s, launched by such pioneers as Arthur Hurst and John Ryle at Guy's Hospital London and Sir Francis Avery Jones who, at the Central Middlesex Hospital, showed the advantages of a combined medical and surgical gastrointestinal unit, and the valuable epidemiological studies which can be made in a district general hospital. Gastroenterology is now a vigorous independent discipline which embraces many specialties and new technology such as fibre-optic endoscopy and endoscopic catheterization and incision of the ampulla of Vater, colonic polypectomy, coagulation of bleeding points in the stomach and duodenum and such scanning techniques as ultrasound, isotopic and computerized axial tomography (Jones et al '85: xvi). Alimentary tract disease is astonishingly common throughout the world. In the tropics, intestinal parasites are widespread; it has been calculated that about 1000 million people harbor roundworms and 500 million suffer from hookworm. Ten per cent of the world's population has amoebiasis: in Egypt, this infestation affects half the population. In Britain, gastroenterological disorders make up 11% of GP's work, and their treatment costs equal those of the whole maternity services. Colo-rectal cancer, diverticular disease and acute appendicitis are almost entirely found among the residents of Western-style civilization and refined diet. Post-mortem studies show that 35% of British citizens over 60 years of age have diverticula but probably on 10% of actual diverticulitis, in contrast, only five out of 3000 Bantu post-mortems showed colonic diverticula in autopsies, although in the Bantu, with an extremely simple diet of milled grain, 20% cancers are liver cancer, 85% in the gold mines, compared to 0.2%-1% of cancer in Western nations (Gerson '96). Other diseases, such as peptic ulcer, have much more complicated origins, being either gastric and duodenal ulcers. In Western Europe, North America, Australia and New Zealand acute appendicitis is the commonest abdominal surgical emergency. Before the routine appendectomy three out of four patients died from a perforated appendix (Jones et al '85: 24, 28, 25).

Fecal samples can be useful diagnostic tools, particularly in the search for harmful colonization of the gut by bacteria, protozoa and worms. About 1.5 liters of liquid chime passes through the ileocaecal valve each 24 hours, but only about 100-200 grams of stool is evacuated, of which 60-80% is water. Transit through the small bowel takes 4-5 hours but on average it takes a further 12-18 hours for feces to travel from caecum to rectum, about 24 hours in total. Whereas peristaltic activity is more-or-less constant in the small bowel, two separate types of movement

can be distinguished in the colon. Segmentation produces mixing of the contents, whereas propulsion is a mass movement which on three or four occasions in the day (generally after a meal) propels feces down the colon. On a typical western diet a daily stool weight in excess of 300 g would be considered pathological unless exceptional quantities of dietary fibre were being eaten. Only 1 in 100 Western citizens have fewer than three bowel movements a week or more than three per day (Jones et al '85: 301). Feces are three-quarters water. Around 3 ½ ounces (100 milliliters) of fluid are lost everyday. During a passage though the digestive system, some 10 quarts (9.8 liters) are reabsorbed. Whatever fluid is left in the feces belongs there. This optimal water content makes our feces soft enough to ensure metabolic waste products an be transported out of the body safely. A third of the solid components are bacteria, that have died or otherwise are exiting the digestive system. Another third is made up of indigestible vegetable fiber. The more fruit and vegetables eaten, the more feces excreted per bowel movement. Increasing the proportion of that food group can raise the weight of a bowel movement from the average 3 ½ to 7 ounces (100 to 200 grams) to as much as 178 or 18 ounces (500 grams) per day. The remaining third is made up of substances the body wants to get rid of, such as the remains of medicines, food coloring or cholesterol (Enders '15: 70, 71).

Bristol Stool Scale

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on the surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cute edges
Type 6	Fluffy pieces with ragged edges; mushy stool
Type 7	Watery, no solid pieces, entirely liquid

Source: Newman ’11: 45

The **Bristol stool scale** was first published in 1997 by Dr. Ken Heaton at the University of Bristol in the United Kingdom. The scale classifies the consistency of feces into seven groups. A healthy digestive system, producing fees with the optimum water content, will produce types 3 or 4. The other types are less than ideal. Type 1 separate hard lumps, like nuts (hard to pass. Type 2 sausage shaped, but lumpy. Type 3 Like a sausage but with cracks on its surface. Type 4 like a sausage or snake, smooth and soft. Type 5 Soft blobs with clear-cut edges (passed easily). Type 6 fluffy pieces with ragged edges, a mushy stool. Type 7 watery, no solid pieces, entirely liquid. The type a person's feces belong to can be an indication of how long indigestible particles take to pass through their gut. Type 1 digestive remains take around one hundred ours t pass through the system (constipation). In Type 7 they pass through in just ten hours (diarrhea). Type 4 is considered ideal, because it has the optimum ratio between fluid and solid content. Those who find types 3 or 4 may also want to observe how quickly their feces sink in water. Ideally, they should not plummet straight to the bottom, as this would indicate the possibility that they still contain nutrients that have not been digested properly. Feces that sink slowly contain bubbles of gas that keep them afloat in water. These gas bubbles are produced by gut bacteria that mostly perform useful services, so this is a good sign, as long as it is not accompanied by flatulence (Enders '15: 73-75).

The natural **color of human feces** ranges from brown to yellowish-brown, even when not eating anything of these colors. The same is true of urine, it always tends towards yellow. This is due to freshly manufactured blood. The body creates about 2.4 million new blood corpuscles a day.

But the same number are broken down every day too. In that process, the red pigment they contain is first turned green, then yellow. The same process occurs during the various stages of bruise on the skin. A small portion of this yellow pigment is excreted in the urine. Most of it, though, passes through the liver and into the gut. There, bacteria change its color once again – this time turning it brown. Light brown to yellow feces can be the result of a harmless disorder, affecting about 8 percent of the world's population, called Gilbert's syndrome (or Gilbert-Meulengracht syndrome). In this condition, of the enzymes involved in the breakdown of blood works at only 30 percent of its normal efficiency. This means less pigment finds its way to the gut. This enzyme defect is not harmful. The only effect is a reduced tolerance for acetaminophen, that should be avoided. Another possible cause of yellowish feces is problems with bacteria in the gut. If they are not working as they should, the familiar brown pigment will not be produced. Antibiotics or diarrhea can cause such an alteration in fecal color. Light brown to gray feces can result if the connection between the liver and the gut is blocked by a kink in the tubes or by pressure (usually behind the gall bladder), no blood pigment an make it into the feces. Blocked connections are never good, and those who notice a gray tint to their fees should consult their doctor. Black or red feces is caused by black congealed blood or red fresh blood. The color is not caused by the pigment, but by the presence of entire blood corpuscles. For those with hemorrhoids, a small amount of bright red blood in the stool is not reason to worry. However, anything darker in color than fresh, bright red blood should be checked by a doctor, unless the reddish color is caused by eating a large amount of beetroot (Enders '15: 71-73).

Stool specimens should be promptly sent to the laboratory. **Apt Test** (Downey Test, Qualitative Fetal hemoglobin Stool Test, Stool for Swallowed Blood) is that there should be no newborn blood present although maternal blood is present. The Apt Test is a screening test to indicate if blood present in the stool or amniotic fluid of a newborn is fetal blood or swallowed maternal blood. Fetal hemoglobin is resistant to alkali denaturalizaton, adult hemoglobin (hemoglobin A) is not. When sodium hydroxide is added to the blood, maternal blood will dissolve, leaving only a brown hematin stain. Newborn blood (containing hydroxide-resistant hemoglobin) will not dissolve, and red blood will remain in the specimen. This test can be performed on stool, a stool-stained diaper, amniotic fluid or vomitus. A newborn usually defecates maternal blood I he first 3 to 5 days of life. If maternal nipple disease exists, the blood in the stool of a newborn can persist. Fetal blood is an indication of disease within the gastrointestinal tract of the newborn and must be evaluated immediately. **Fecal Fat** (Fat Absorption, Quantitative Stool Fat Determination) normal finding is Fat: 2-6gm/24 hr or 7-21 mmol/day (SI units). Retention coefficient: >95%. This test is performed to confirm the diagnosis of steatorrhea. Steatorrhea is suspected when the child with cystic fibrosis has large greasy, and foul smelling stools. Determining an abnormally high fecal fat content confirms the diagnosis. The fecal fat test measures the fat content in the stool (Pagana, '06: 902).

Stool for Occult Blood (Stool for OB) normal finding is no occult blood within stool. This test is part of the evaluation for abdominal pain. It is also a part of routine colorectal cancer screening of asymptomatic individual older than age 50 years. Normally only minimal quantities of blood are passed into the gastrointestinal (GI) tract. Usually this bleeding is not significant enough to cause a positive result in stool for OB testing. This test can etet OB when as little as 5 mL of blood is lost per day. Tumors of the intestine grow into the lumen and are subjected to repeated trauma by the fecal stream. Eventually the friable tumor ulcerates and bleeding occurs. Most often bleeding is so slight that gross blood is not seen in the stool. The blood can be detected only by chemical assay. Benign and malignant GI tumors, ulcers, inflammatory bowel disease, arteriovenous malformations, diverticulosis, and hematobilia (hemobilia) can all cause OB within the stool. Vigorous exercise can create OB within the stool. Many drugs and

ingestion of red meats (such as beef and pork) may cause a false-positive OB stool test (red meats contain animal hemoglobin). The more sensitive the test, the more false-positive results will be obtained. Four positive test results out of six specimens constitute further study. Patients with chronic and prolonged OB loss in the stool may have iron-deficiency anemia. Bleeding gums following a dental procedure may affect results. Ingestion of red meat within 3 days before testing may affect results. Ingestion of fish, turnips, and horseradish may affect results. Drugs that may cause GI bleeding include anticoagulants, aspirin, colchicine iron preparations (large doses), non-steroidal anti-arthritics, and steroids. Drugs that may cause false-positive results include colchicine, iron, oxidizing drugs (e.g. iodine ,bromides boric acid), and rauwolfia derivatives Drugs that may cause false-negative results include vitamin C (Pagana '06: 906-907). Metronidazole is helpful for healing ulcers.

Clostridial Toxin Assay (*Clostridium difficile*, Antibiotic-Associated Colitis Assay; Pseudomembranous Colitis Toxic Assay, C. diff.) normal finding is negative, no Clostridium toxins identified. Clostridium difficile bacterial infection of the intestine may occur in patients who are immuno-compromised or taking broad-spectrum antibiotics. Overgrowth of antibiotic resistant *C. difficile* cause diarrhea that is usually watery and voluminous. Abdominal cramps, fever and leukocytosis are noted in most patients. Symptoms usually begin 4 to 10 days after the initiation of antibiotic therapy. This toxin identified by stool immunoassay techniques. Stool cultures for *C. difficile* can be performed. Management of this antibiotic associated colitis, includes immediate cessation of tee broad-spectrum antibiotics, replacement of electrolytes and fluids, and institution of metronidazole antibiotic therapy (Pagana '06: 899 – 901). **Stool Culture** (Stool for Culture and Sensitivity [Stool C&S], Stool for Ova and Parasites normal finding is normal intestinal flora. Stool cultures are indicated in patients who have urelenting diarrhea, fever and abdominal bloating. Normally stool contain many bacteria and fungi. The more common bacteria include *Enterococcus*, *Esherichia coli*, *Proteus*, *Pseudomonas*, *Staphylococcus aureus*, *Candida albicans*, Bacteroides and Clostridium. Bacteria are indigenous to the bowel, however, several bacteria act as pathogens within the bowel. These include *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, pathogenic *E. coli*, *Clostridium* and *Staphylococcus*. Parasites also may affect the stool. Common parasites are *Ascaris* (hookworm). *Strongyloids* (tapeworm, and *Giardia* (protozoans). *Helicobacter pylori* can be found in the stool indicates an increased risk of peptic ulcer disease and gastritis. Infections of the bowel from bacteria, virus, or parasites usually present as acute diarrhea, excessive flatulence, abdominal discomfort, and fever. This may progress to toxic megacolon. Some enteric pathogens may take as long as six weeks to isolate. The clinical significance of test results indicate Bacterial enterocolitis, Protozoa enterocolitis, Parasitic enterocolitis. Treatment of infection must be prompt, especially in children, who can rapidly become septic (Pagana '06: 899-904). Sample slides of pathogenic microorganisms are not readily available on the Internet. Metronidazole is effective for the treatment of bacterial and protozoal infections of the abdomen, ulcers and joints.

Diarrhea can be caused by particles of any kind, living, organic or inorganic, in drinking and cooking water, are noxious. Bottled water cannot contain more than 250 parts per million (ppm). Brackish water >500 ppm – <1,000 ppm salt water, causes loose stool and diarrhea, and salt water >1,000 ppm is a deadly poison. Genuinely brackish water from sea level sources invariably causes morning mush, the excretion of all discomforting colon contents in a shapeless diarrhea, punctually every morning, leaving the patient relieved, but anxious about calcium loss. The moldy white bread at sea level also hurts tooth calcification. Other municipalities, regions and sources, may also have notoriously discolored, turbid, or foul smelling water, all, or some, of the time. The mushy morning bowel movement continues until the indigestible particles in the digestive tract are completely flushed out with clean, pure, filtered water, without particles,

discoloration or infection, dispensed for 40 cents a gallon in 2019, outside many grocery stores. Filtration can reduce particles, including bacteria and rust, but not all chemicals and toxins, by 90-99%. There are special techniques for treating specific water quality issues, like turbidity, cloudiness, hardness and microbes, as well as maximum tolerable limits, and zero tolerance for certain chemicals. Well-water should be professionally tested before being treated for residential use as drinking, cooking and bathing water. Hard water does not enable soap to form a nice lather. Bad water is not the only cause of mushy stool and diarrhea, ie. dirty dish towel, overeating, especially fruit or vegetables at night, inadequate fiber, such as vegetable soup without bread and butter, or milk without granola, or one-pot-rice and vegetables, rather than rice and stir-fry, iron deficiency anemia, zinc or vitamin B_{12} deficiency. Waterborne pathogens and excessive levels of certain toxic chemicals can cause much more serious disease, not always including diarrhea, and even death. Do not drink water served at restaurants or by hosts, as a rule, unless they use effective water treatment technology and the water appears to be free of particles, discoloration or aroma. Do not drink from public drinking fountains, if suffering from diarrhea or mushy stool, or if the it appears to be defective or contaminated. The patient must ensure all drinking and cooking water is filtered and uncontaminated at the point-of-use.

Diarrhea can be caused by malabsorption, infection, with bacteria, protozoa or parasites, or deficiency in iron, vitamin B_{12} or zinc. Constipation is the more common disorder with the American diet resulting in colitis, hepatoxicity, atherosclerosis, arthritis and cancer. Iron deficiency anemia is the most common cause of diarrhea worldwide, affecting about one in seven people who don't get enough iron. Too little of this mineral makes it hard for red blood cells to ferry oxygen from lungs to tissues. Iron-poor blood causes one to be pale, fatigued, and mentally dull. Lack of iron stunts the growth and development of children and can damage long-term thinking skills. Iron deficiency isn't major problem in the United States, due to meat and iron fortified grain and other products. Thin vegans are frequently deficient in iron unless they eat green leafy vegetables, such as kale or nettles, every meal. The body carefully regulate the amount of iron absorbed from grains, fruits vegetables, and supplements. The iron from meat is much better absorbed than that from vegetable sources, and can lead to an over-accumulation of this mineral (Willet '01: 177, 169, 170).

Some 2 billion people around the world are subject to **deficiencies in micronutrients**. The presence of pallor, subcutaneous edema, skin lesions, muscle wasting and chronic diarrhea are general clinical signs of malnutrition. Patients with kwashiorkor will have edema, muscle wasting, psychomotor change, dyspigmentation of hair, ascites, liver enlargement and parotid gland hypertrophy. Marasmic patients demonstrate wasting of muscle and fat, but when stressed, also develop signs and symptoms seen with kwashiorkor. Vitamin deficiencies occur common in association with protein-calorie malnutrition (Thom & Daly '90: 499). The five vitamins that many people don't get enough of in their diets are folic acid, vitamins B_6, B_{12}, D and E (Willet '01: 177). Assessment of **nutritional state** lies in search for the subtle signs of deficiency and toxicity. 'Height for age' is an indication of stunting in growing children whereas 'weight for height' reflects adiposity or wasting from disease. Dementia encephalopathy can be caused by thiamine, nicotinamide and pyridoxine deficiency. Poor hair and hair loss can be caused by protein, zinc and copper deficiency during general severe illness. Visual failure (diminished dark adaptation) and xerophthalmia (dry eyes) can be caused by vitamin A and riboflavin deficiency. Pallor (anaemia) can be caused by iron, vitamin B_{12}, folic acid, zinc, copper, pyridoxine and protein deficiency. Stomatitis gingivitis can be caused by vitamin C deficiency. Glossitis can be caused by iron, riboflavin, nicotinamide and zinc deficiency. Goiter can be caused by iodine deficiency. Leuconychia (white nails) can be caused by protein deficiency. Fungal infections of the hands can be caused by calcium deficiency. Koilonychia (Spoon-shaped

nails) can be caused by iron and zinc deficiency. Skin ulceration can be caused by deficiency in essential fatty acids and zinc. Dermatitis – scaly, pigmented and erythematous – can be caused by nicotinamide, riboflavin, vitamin A and essential fatty acids deficiency. Muscle wasting can be caused by protein calorie deficiency. Muscle weakness can be caused by calcium, protein, magnesium and potassium deficiency. Liver enlargement can be caused by protein calorie deficiency. Ascites and edema can be caused by protein deficiency. 'Curly hairs' perifollicular hemorrhages and bruising can be caused by vitamin C deficiency. Peripheral neuropathy can be caused by thiamine, pyridoxine and nicotinamide deficiency. Swollen painful joints can be caused by vitamin C deficiency. Ataxia can be caused by vitamin B_{12} and vitamin E deficiency. Hypogonadism, weight loss and muscle weakness may be helped with multivitamins (Jones et al '85: 2, 3).

Symptoms of Vitamin and Mineral Deficiencies

Site	Sign or Symptom	Deficiency
Hair	Dryness	Zinc
	Alopecia	Zinc
	Easy pluckability	Vitamins E and A
	Corkscrew hair	Vitamin C
	Color change	Biotin
Nails	Dystrophic	Iron
Skin	Hyperpigmentation	Niacin
	Erythema	NIcain
	Scrotal dermatitis	Niacin
	Follicular keratosis	Vitamin A
	Acneiform lesions	Vitamin A
	Xerosis	Vitamin A, linoleic acid
	Ecchymosis	Vitamins C and K
	Petechiae	Vitamins C and K
	Nasolabial seborrhea	Vitamin B_6
Eyes	Angular palpebritis	Vitamin B_2
	Bitot's spots	Vitamin A
	Conjunctival keratosis	Vitamin A
	Keratomoalacia	Vitamin A
Mouth	Glossitis	Vitamin B_{12}, niacin, folate
	Angular stomatitis	Vitamin B_2
	Cheilosis	Vitamin B_2
	Magenta tongue	Vitamin B_2
	Scarlet, raw tongue	Niacin
	Atrophic papillae	Niacin
	Swollen, bleeding gums	Vitamin C
Neurologic	Peripheral neuropathy	Thiamine, niacin, B_6
	Wernicke's encephalopathy	Thiamine
	Encephalopathy (Pellagra)	Niacin
	"Burning feet" syndrome	Patothenic acid
	Loss of deep tendon reflexes	Thiamine, vitamin B_1 & B_{12}
Musculoskeletal	Osteomalacia	Vitamin D
	Joint pain	Vitamin C
	Tender muscles	Thiamine

Hematologic	Hemolytic anemia Macrocyctic anemia Microcytic anemia Coagulopathy Thrombocytopenia	Vitmain E Vitamin B_{12}, folate Vitamin B_6, iron, copper Vitamin K Linoleic acid
Visceral	Congestive heart failure Diarrhea Goiter Hepatosplenomegaly	Thiamine Iron, folate, zinc, niacin Iodine Zinc

Source: Thom & Daly '90: Table 59-5, Pg. 499

Deficiencies of most essential nutrients collectively and individually impair cell growth and division . This can be readily detected by assessing cell-mediated immunity. The peripheral lymphocyte count falls in malnutrition ($<1.2x10^9$/l) and the in-vitro lymphoblast response to a mitogen such as phytohaemagglutinin is impaired. Biochemical investigation of 'nutrient status' can be performed, but some are not available routinely in most laboratories. Serum assays are available for the estimation of most of the fat and water soluble vitamins. Serum folate levels should be performed on plasma specimens taken after fasting, otherwise red-cell folate estimations are more reliable. Plasma or serum fatty acid profiles will enable estimation of the triene-etraene ratio as an index of essential fatty acid deficiency. Vitamin K is assessed by measurement of the prothrombin time. Vitamin C status can be determined by measuring its content in leucocytes. Plasma concentrations of zinc, copper and iron can be measured but are unreliable. Leucocyte zinc concentrations may be a better criterion of tissue zinc depletion. Plasma iron-binding capacity, transferrin concentration, or ferritin levels are of value in measuring iron status. A reduced plasma transferrin level (<20 g/l) is also a sensitive index of protein malnutrition. Plasma albumin level below 35 g/l suggests protein deficiency (Jones et al '85: 3, 4).

In order to be diagnosed with **Irritable Bowel syndrome** (IBS), patients need to meet the Rome III criteria: Recurrent abdominal pain or discomfort has occurred at least 3 days a month in the past 3 months, and symptoms began at least 6 months prior to diagnosis and is associated with two or more of the following: (1) Improvement with defecation (bowel movement), (2) Onset of pain associated with a change in frequency of stool (3) onset associated with a change in form (appearance of stool). IBS typically begins with abdominal pain. Despite the intensity, severity and duration of the pain, it improves with defecation; in fact, it often disappears entirely with the passage of a bowel movement. Pain almost never occurs while the patient is asleep. During the painful episodes, the stools look different but there is never blood in the bowel movements (Newman ’11: 15, 24, 25).

When first described in 1932, **Crohn’s disease** was thought to be limited to the terminal ileum. When fully developed, Crohn's disease is characterized pathologically by (1) sharply delimited and typically transmural involvement of the bowel by an inflammatory process with mucosal damage, (2) the presence of noncaseating granulomas, (3) fissuring and formation of fistulas, and (4) systemic manifestation in some patients (Crawford ’94: 801-803). Crohn’s disease is hard to diagnose. Most physicians will use a combination of blood tests, endoscopies, K-rays, CAT scans or ultrasounds, and biopsies to help get a clear picture of the disease (Black ’10: 28, 29). **Ulcerative colitis** typically presents as a relapsing disorder marked by attack of bloody mucoid diarrhea that may persist for days, weeks or months and then subside, only to recur after an asymptomatic interval of months, years or decades. Bloody diarrhea containing stringy mucus, accompanied by lower abdominal pain and cramps usually relieved by defecation, is the first

manifestation of the disease. Flare-ups when they occur, may be precipitated by emotional or physical stress and rarely concurrent intraluminal growth of enterotoxin-forming *C. dificile* (Crawford '94: 806).

Numerous tests of **small bowel function** have been devised and used. Some common tests (1) fecal fat analysis is determined on a 3-day collection of stool while the patient is on a normal ward diet, i.e at least 100 g/day of fat. Normal excretion is less than 54 mmoles/3 days (18 mmol/day). **Butter fat absorption test** is performed on a fasting blood sample (t=0) after which the patient ingests a standard test meal (o.t g butter/kg body weight spread on toast). Further blood samples are taken at 90 minutes, 120 minutes and 150 minutes. A quantitative assessment of the serum chylomicrons provides a measure of fat absorption. **D-xylose absorption tests** carbohydrate absorption. D-xylose is a pentose sugar which is normally absorbed rapidly from the small intestine, only slightly metabolized by the body, and excreted rapidly in the urine, and can be used to test monosaccharide absorption. The patient fasts overnight, empties the bladder in the morning, and drinks 250 ml water containing 25 g xylose. The xylose excreted in the urine in the next 5 hours is measured. Normal persons should excrete more than 40 mmol/l in 5 hours. Children should be given a lower dose, e.g. 0.5 g/kg. Normally, after a 25 mg dose, a serum value at 1 hour of at least 2.5 mmol/l should be obtained. **Intestinal lactase deficiency** can be assessed by giving 50 g lactose orally in 250 ml water and measuring plasma glucose levels at ½ - hourly intervals for 2 hours. In subjects with normal lactase activity, the plasma glucose should increase by at least 1.1 mmol/l. A normal glucose tolerance test with abnormal lactose tolerance test is suggestive of intestinal lactase deficiency. Similar tests can be performed with sucrose, maltose or isomaltose to test for other disaccharidase deficiencies. For the water-soluble vitamins, the most commonly used test is the Schilling test for vitamin B^{12} absorption. In this test a small (0.5-2µg) dose of ^{57}Co-labeled vitamin B^{12} is given orally, followed 1-3 hours later by a large (1000µg) intramuscular injection of unlabeled vitamin B^{12} to saturate the liver store and ensure that all the orally administered dose absorbed will be excreted and not stored. The radioactivity in the urine excreted in 24 hours is measured. The proportion excreted in the urine is normally more than 12% of the given dose. Pernicious anaemia may be distinguished from other causes of vitamin B^{12} malabsorption by repeating the tests with ^{57}Co-lablled vitamin B^{12} coupled to Intrinsic Factor. By using two separable isotopes of radio-cobalt, both parts of the test can be performed simultaneously.

Of the several conditions resulting in reduced functional **bile-salt** concentrations, the one most easily investigated is the presence of bacterial colonization in the intestine. Radiolabelled glycocholic acid (labeled with ^{14}C in the glycine side-chain) is administered orally; samples of expired air are collected at hourly intervals for 5 hours and the $^{14}Co_2$ measured. Excessive bile salt deconjugation is shown by increased amounts of radioactivity in the first 3-4 samples. The Hydrogen breath test is a non-invasive investigation that may useful in the detection of acquired and inborn (e.g. disaccharidase deficiency) sugar malabsorption. Hydrogen is one of the gases produced in the intestinal lumen by the bactrial breakdown of carbohydrates. These bacteria are usually only present in the colon and, as most carbohydrates are absorbed from the small intestine, little hydrogen is produced by healthy people. However, when there is malabsorption of any sugar, the colonic production of hydrogen is increased, and after diffusion to the blood stream it appears on the expired air where it can be easily and cheaply detected by a hydrogen gas-sensing polarographic cell. Barium contrast either by drinking or injection via duodenal intubation can be used to show general nonspecific abnormalities suggestive of malabsorption: clumping and flocculation of barium, dilatation and effacement of the normal feathery pattern, structural changes in the wall of the small bowel such as strictures, diverticula, polyps, tumors and infiltration. Mucosal biopsy of jejunum and ileum can be difficult due to inaccessibility.

The distal duodenum can be biopsied under vision with standard endoscopes. Blind biopsy can be achieved by a variety of mechanical devices, e.g. the multiple biopsy tube devised by Rubin, the pneumatic capsule devised by Crosby and Krugler and the Watson modification of this (Jones et al '85: 122-126).

Disruption of bile formation becomes clinically evident as yellow discoloration of the skin and sclerae (jaundice of icterus) owing to retention of pigmented bilirubin, and as cholestasis, defined as retention of not only bilirubin but also other solutes eliminated in bile. **Bilirubin** is the end product of heme degradation. The majority of daily production (0.2 to 0.3 gm) is derived from breakdown of senesescent erythrocyte, especially in the spleen, liver and bone marrow. Bilirubin found outside the liver is bound to albumin because bilirubin is virtually insoluble in aqueous solutions at physiologic pH. The brilliant yellow color of bilirubin makes it an easily identified component of hepatic bile formation. Most bilirubin glucuronides are decongjugated by bacterial beta-glucuronidases and degraded to colorless urobilinogens that are largely excreted in the feces. Bilirubin metabolism and excretion, are however, but one cog in the hepatic machinery rthat secretes 12 to 36 gm of bile acids into bile per day, mostly taurine and glycine conjugates of cholic and chenodeoxycholic acid. **Clinical jaundice** appears when bilirubin is elevated in blood and is deposited in tissues. Cholestasis refers to bile secretory failure which is accompanied by the accumulation in blood of substances normally excreted in bile (bilirubin, bile salts and cholesterol). Normal blood levels of bilirubin are less than 1.2 mg/dl. Jaundice becomes evident when bilirubin levels rise above 2.0 to 2.5 mg/dl; levels as high as 30 to 40mg/dl can occur with severe disease. Jaundice occurs when bilirubin production exceeds hepatic clearance capacity. Extrahepatic biliary obstruction is frequently amenable to surgical alleviation because it is most often produced by impaction of a gallstone in the common bile duct or ampulla of Vater (adults) or by extrahepatic biliary atresia (infants). In contrast, cholestasis resulting from disease of the intrahepatic biliary tree or hepatocellular secretory failure (collectively terms intrahepatic cholestasis) cannot be benefited by surgery (short of transplantation) and the patient's condition may be worsened by an operative procedure. There is thus considerable urgency in making a correct diagnosis of the cause of jaundice and cholestasis (Crawford '94: 838-839).

Liver function tests are several, but they tend to only be sensitive in advance stages of liver failure. **Transaminases** (aminotransferases) reflect liver and other tissue damage especially in cardiac and skeletal muscle. Alanine transaminase (ALT; serum glutamic pyruvic transaminase, SGPT) is more specifically related to liver damage, but it is not more sensitive than aspartate transaminase (AST; serum glutamic oxaloacetic transaminase, SGOT) and the latter is more generally used. Very high levels (over 1000 units) are found in hepatic necrosis, e.g. severe hepatitis. Numerous other enzymes e.g. lactic dehydrogenase, ornithine carbamoyl transferase) are not widely applicable. **LDH isoenzymes** are highly specific. Gamma glutamyl transpeptidase (GGT) is an enzyme of induction, it is a sensitive enzyme widely used as a screening test and, in conjunction with alkaline phosphatase, to establish the hepatic origin of the later, with which it rises in concert. Some drugs, and particularly alcohol, cause modest to major rises in GGT (50-500 units). **Alkaline phosphatase** (AP) is an important duct enzyme of several origins but is normally mostly derived from biliary ductular epithelium. Modest rises (up to twice normal) are common, they often reflect liver damage but may be difficult to interpret. Elevation sin excess of 2-3 times normal occur in biliary tract obstruction. Space-occupying lesions can cause levels of AP in excess of 6 times normal. Mild elevations of **bilirubin** (up to 4-5 time normal) may reflect increased production (haemolysis), impaired transport of conjugation (e.g. Gilbert's disease) or mild cellular damage. Significant rises reflect a failure of excretion. Almost all will be conjugated bilirubin and will be soluble in water and excreted in

urine. High bilirubin levels occur in drug-induced and cholestatic viral hepatitis. In established liver disease high levels of bilirubin and jaundice denote a poor prognosis. **Albumin** tends to be low where protein synthesis is impaired or protein lost, e.g. cirrhosis, malignant disease or severe infection. **Prothrombin time** (PT) is a sensitive and useful indicator of hepatic function. In simple obstructive jaundice, prolongation may be rapidly reversed with parenteral vitamin K. In drug damage and hepatitis a lengthening or very prolonged PT suggests a poor prognosis. There are many viral markers but the single most important is **hepatitis B surface antigen**. A positive alpha-feto-protein test strongly suggests primary hepatoma. Mitochondrial antibodies are useful for primary biliary cirrhosis (positive in 98% cases). Smooth muscle antibodies suggest chronic active hepatitis, but are not specific. Ultimately a histological diagnosis should be made in most cases (with the exception of gallstone disease and the relief of extrahepatic obstruction) (Jones et al '85: 175-178).

The diagnosis of **acute pancreatitis** should be suspected in all patients admitted with acute upper abdominal pain and it is customary to estimate the **serum amylase** in all such patients. The normal level is 70-300 international units/l, and values above 1200 units strongly support the diagnosis. A urinary amylase level in excess of 3000 units/l (normal 300-1500) is a valuable confirmation of the diagnosis. Severe pancreatitis is present if any three of the following measurements are positive: (1) WBC> 15,000/mm^3, (2) glucose > 10 mmol/l (no diabetic history), (3) urea > 16 mmol/l (no improvement on i.v. fluids, (4) PaO^2 < 60 mmHg (8 kPa), (5) calcium < 2.0 mmol/l, (6) albumin < 32 g/l), (7) lactic dehydrogenase > 600 units/l, (8) aspartate transaminase > 200 units/l. The differential diagnosis of sudden severe epigastric pain is acute pancreatitis, spontaneous rupture of the esophagus, perforated peptic ulcer, acute cholcystitis, high para-colic acute appendicitis, myocardial infarction, pneumonia and pleurisy, traumatic rupture of spleen or liver, or high jejunal strangulating obstruction. In 70% of patients acute pancreatitis runs a benign course. Gradual restoration or diet to normal, the avoidance of alcohol and early surgical removal of gallstones results in survival of 99% of patients, however a severe attack carries a mortality rate of 20%. Respiratory failure is the major hazard and the cause of 65% of deaths (Jones et al '85: 104-106).

The number of new cases of **Diabetes mellitus** has nearly doubled in the past fifteen years since the atypical antipsychotic Olanzapine (Zyprexa), known to cause both diabetes and fatal diabetic episodes when mixed with alcohol, hit the market for depressed and increasingly obese people in 1994 (Sanders ’12). On some Native American reservations 60% of the population has diabetes. In the United States an estimated 23.6 million children and adults, 7.8% of the population, have diabetes. While an estimated 17.9 million have been diagnosed with diabetes, 5.7 million people (or nearly one quarter) are unaware that they have the disease and another 57 million have pre-diabetes. An estimated 177 million people are affected by diabetes world-wide, the majority by type 2 diabetes. Two-thirds live in the developing world. The rate of new cases of diabetes has increased by about 90 percent in the United States over the past decade. From 1995 to 1997, newly diagnosed cases of diabetes were at 4.8 per 1,000 annually. Between 2005 and 2007, that number rose to 9.1 per 1,000 people. An estimated 90 percent to 95 percent of the new cases are type 2 diabetes. Diabetes and pre-diabetes have skyrocketed among the nation’s youth, jumping from 9 percent of the adolescent population in 2000 to 23 percent in 2008. An estimated 50 percent of Type 1 juvenile onset diabetics die within 20 years of diagnosis. With an annual toll of more than 144,000 deaths diabetes mellitus is the seventh leading cause of death in the United States. It is estimated that 2 to 3% of the adult population had diabetes mellitus in 1994 (Crawford and Cotran ’94: 909, 910) rising to 7% in 2010.

Chronic hyperglycemia is a major contributing factor towards almost all possible complications with diabetes including kidney failure, blindness, diabetic neuropathy, and heart problems. Two kinds of **home blood glucose monitoring** exist. The first type uses a reagent strip. The second type uses a reagent strip and glucose meter. Use of the glucose meter has become more common due to higher reliability than strips alone. Glucose and ketoacidosis can also be measured in the urine but no longer has a significant role in home testing. **Ketoacidosis** is a serious but preventable complication from inadequate treatment of diabetes. This dangerous condition is identified by testing for urinary ketones. People with diabetes should visit their health care professional every three months to monitor their **hemoglobin A1c** levels and to discuss their treatment plan. **Reagent strips** are saturated with glucose oxidase, an enzyme that interacts with glucose. When a drop of blood is placed on the strip, the glucose oxidase chemically reacts with the blood glucose. The resultant reaction changes the color of the strip. The higher the glucose level, the greater the reaction, so the more dramatic the color change. The blood glucose level can be determined by comparing the color of the strip with a color chart. For accurate results, test strips should be stored at room temperature and away from moisture. To protect the strips from moisture, bottles should be closed after use. The disadvantage of reagent strips alone is that they do not give an exact glucose measurement. They are accurate enough, however, to alert patients to seriously high or low levels of glucose. Examples of reagent strips available over–the–counter (OTC) are Chemstrip bG and Glucostix.

To determine a more accurate blood glucose level, the reagent strip must be combined with a **blood glucose meter**, which involves taking a small lancet to poke a finger. Usually, this testing is performed just off to the side of the finger's tip, although some meters do allow testing at other sites, such as the forearm. Then, a small quantity of blood is placed on a testing strip that has been inserted into a meter that reports the glucose value. The meter reads the blood glucose level from the reagent strip. Results obtained using a glucose meter are more accurate than those obtained without the meter (that is, with reagent strips alone). However, the results using a home meter vary as much as 20% from the more accurate measurements in a hospital or clinical laboratory. Portable meters are accurate enough, however, for home monitoring and self-adjustment of insulin doses. It is important to know that reagent strips are calibrated for specific meters. Most meters need to be calibrated once a new box of test strips is used. Inappropriate calibration will lead to errors in glucose readings. Using incompatible strips and meters will give unreliable glucose readings. Errors can also be caused when: meters are improperly calibrated; the meter is dirty; the battery in the meter is dead; reagent strips are stored improperly; the reagent strips have expired; not enough blood is applied to the reagent strip; blood is not left on the reagent strip long enough, or is left too long, before reading; the test is performed under the wrong conditions of temperature and humidity; or patients are dehydrated. The following general guidelines for normal blood glucose ranges in nondiabetics are from the American Diabetes Association. However, there are variations to these guidelines. For example, young children, those who are newly diagnosed, or are beginning insulin pump therapy may have slightly different target ranges. There are also tests for gestational diabetes in pregnant women.

Diabetes Tests

Morning Fasting Glucose Ranges	Indication
From 70 to 99 mg/dL, or 3.9 to 5.5. mmol/L	Normal glucose tolerance, not diabetic
From 100 to 125 mg/dL, or 5.6 to 6.9 mmol/L	Impaired fasting glucose (IGF) or Pre-diabetes

126 mg/dL or higher, or 7.0 or higher	Diabetes
2 Hours after drinking 75 grams of oral glucose tolerance test (except during pregnancy)	**Indication**
Less than 140, or 7.8 mmol/L	Normal glucose tolerance, not diabetic
From 140 to 200 mg/dL, or 7.8 to 11.1 mmol/L	Impaired glucose tolerance (IGT), or Pre-diabetes
Over 200 mg/dL, or 11.1 or higher on more than one occasion	Diabetes
Ketone testing	**Indication**
Below 0.6 mmol/L	Normal
Between 06 to 1.5 mmol/L	May develop into a problem
Above 1.5 mmol/L	Greater risk of ketoacidosis
Above 3.0 mmol/L	Emergency room
Hemoglobin A1c test (HbA1c)	**Indication**
Below 5.7%	Normal

Source: American Diabetes Association 2018

Urinary glucose only estimates blood glucose values roughly, and it provides no information at all unless there is glucose in the urine. Glucose appears in the urine when the blood glucose level is over 180 mg/dL, well above the target for most patients. Below that level, urinary glucose is usually negative. Urinary glucose levels should not be confused with checking urinary microalbumin and protein levels. These tests are performed in the doctor's office at least annually, provide necessary information about kidney function. There are two types of urine glucose tests. Both types rely on a chemical reaction that produces a color change. These tests use either tablets or strips. Generally, the test strip or tablet is placed in urine. The resulting color change is matched against a color chart provided by the manufacturer, which shows the different colors produced by different levels of glucose. The first type, called the copper reduction test, uses cupric sulfate (for example, Clinitest). In the presence of glucose, cupric sulfate (which is blue) changes to cuprous oxide (green to orange). The reaction should be observed closely and the manufacturer's instructions closely followed. The copper reduction tests can react with substances other than glucose in the urine, leading to false positive results. This means the test erroneously shows glucose when it is not present. Examples of these other substances include aspirin, penicillin, isoniazid (Nydrazid, Laniazid), vitamin C, and cephalosporin-type antibiotics. Tablets and solutions utilizing copper reduction may damage the skin and are poisonous if ingested. They should be handled carefully and kept out of the reach of children. The second type of urine glucose test, called the glucose oxidase test, uses the chemical toluidine and the enzyme glucose oxidase (for example, Clinistix). Glucose oxidase converts the glucose in urine to gluconic acid and hydrogen peroxide. The interaction of the hydrogen peroxide with the toluidine causes a change in color. False negative results (meaning the test shows no glucose when glucose really is present) may occur in patients taking vitamin C, aspirin, iron supplements, levodopa (Sinemet), and tetracycline-type antibiotics. Glucose oxidase tests are more convenient to use and less expensive than copper reduction tests. The strips should be kept

away from moisture. Blood glucose levels higher than normal, but lower than diabetic ranges, classify a person as having impaired glucose tolerance. To see how a person reacts to a glucose load an oral glucose tolerance test (OGTT) may be given to check blood glucose levels 2 hours after being given 75 grams of glucose to drink. If two or more tests show blood glucose higher than the normal ranges above, gestational diabetes will be diagnosed. A 75-gram glucose load may be used but may not be as reliable as the 100-gram glucose test. Blood is not drawn at the 3-hour mark if the 75 gram test is done. Both IFG and impaired glucose tolerance (IGT) are associated with an increase risk in developing type 2 diabetes and lifestyle changes, including weight loss and an exercise program, as well as possible oral medications such as Glucophage are sometimes indicated.

Ketone testing is an important part of monitoring in type 1 diabetes. It is a tool that is often also used in pregnancies that are complicated by diabetes. If the reading is below 0.6 mmol/L you are in the normal range. If the number is between 0.6 to 1.5 mmol/L is in this range ketones are present in the blood, which may develop into a problem if not treated. Readings above 1.5 mmol/L indicate a greater risk for developing ketoacidosis (DKA). A healthcare provider should be consulted. Readings above 3.0 mmd/L may warrant a trip to the nearest emergency room for immediate treatment. Ketones are formed when one fasts (for example, sleeping overnight) or when there is a profound lack of insulin. When the body produces an insufficient amount of insulin, the cells are unable to remove glucose from the blood, and the level of glucose in the blood rises. Rising blood glucose level causes more urination and dehydration. In addition, ketones are produced by the liver due to low insulin levels. The presence of ketones signals a condition in diabetics called ketoacidosis. Ketoacidosis signifies that the cells are not getting enough insulin. Severe diabetic ketoacidosis is a medical emergency, since it can result in loss of consciousness and even death. There is a correlation between high blood glucose levels, dehydration, and ketones. The higher the glucose level, the more likely that ketones will be made. Therefore, patients with diabetes with blood glucose levels over 240 mg/dL should test promptly for urinary ketones. Patients with type 1 diabetes should test for ketones during any acute illness and during severe stress. Also, urinary ketones should be checked if any symptoms of ketoacidosis occur (such as nausea, vomiting, abdominal pain).

Ketones can normally be found in the urine. For example, after an overnight fast, ketones can be seen in up to 30% of people without diabetes. However, these levels of ketone production are usually below the threshold of measurement by the ketone test strips. The strips can also give false positive results when patients are on drugs such as captopril (Capoten). False-negative readings may be seen if the test strips are old, exposed to air, or if the urine is very acidic (such as after drinking a lot of orange juice, which is also high in vitamin C). These tests are based on the color change that occurs when ketones react with sodium nitroprusside or similar compounds. The tests are performed in a manner similar to that of urinary glucose testing. Different tests detect the three types of ketones (acetoacetic acid, acetone, and ß-hydroxybutyric acid). For example, Acetest only detects acetoacetic acid and acetone, but not ß-hydroxybutyric acid. Ketostix detects only acetoacetic acid, which can produce false-negative results if only acetone and ß-hydroxybutyric acid are present in the urine. Ketone tests are supplied as strips or tablets. The American Diabetes Association advises that ketone testing materials be available in the office setting and that physicians should prefer using blood ketone measurements over urine ketone measurements if possible. Home testing for blood ketones is also available, though not often used due to higher cost of the test strips (Ferry ’14). Most people can tell if they are ‘ketotic’ by the foul smelling breath that occurs when the body runs out of nutrition and metabolizes its own tissue. Diabetic ketoacidosis (DKA) can eventually cause unconsciousness, from a combination of severe hyperglycemia, dehydration, shock, and exhaustion. Coma only occurs at an advanced stage, usually after 36 hours or more of worsening vomiting and

hyperventilation but can also occur much sooner for many reasons. Treatment of DKA consists of intravenous fluids to stabilize the circulation, and intravenous saline with potassium and other electrolytes to replace deficits. Insulin will also be given and the patient will need careful monitoring for complications.

The **hemoglobin A1c test** (HbA1c) is crucial to monitor blood glucose control in patients with diabetes. In brief, hemoglobin A1c refers to the final product of several chemical reactions that occur in the bloodstream as red blood cells are exposed to glucose. A red blood cell typically lives for about three months, so the HbA1c reading provides a report card averaging the prior three months blood sugar levels. The A1C test result is reported as a percentage. The higher the percentage, the higher a person's blood glucose levels have been. A normal A1C level is below 5.7 percent. Many different methods are available to determine the HbA1c level. Regardless, HbA1c level has been shown to predict the risk for developing complications of diabetes, much in the same way that cholesterol levels are predictive of heart disease. The HbA1c test should be performed routinely at three-month intervals in established patients with diabetes. The HbA1c can be tested when a new case of adult diabetes is suspected, although its use to diagnose borderline pediatric diabetes is still debatable. To measure HbA1c, blood obtained in the usual way (from a vein) and can be sent to a laboratory. Alternatively, many clinics specialized in diabetes care now have desktop HbA1c machines, which will read a simpler finger-stick blood sample within minutes. A few conditions can affect HbA1c measurements, most related to problems with red blood cells. For example, results may be falsely low if too few red cells are present (anemia). Falsely low readings can occur when red blood cells lose their proper shape (as with conditions like thalassemias, sickle cell disease, or spherocytosis). The HbA1c is a valuable tool to individualize patient care plans so that glycemic goals can be achieved (Ferry '14).

Urinalysis is one of the most useful screening tests available. The medical renal disease are those that involve principally the parenchyma of the kidneys. Hematuria, proteinuria, pyuria, oiguria, polyuria, pain, renal insufficiency with azotemia, acidosis, anemia, electrolyte abnormalities, hypertension, headache, and ocular involvement may occur in a wide variety of disorders affecting any portion of the parenchyma of the kidney, its blood vessels, or the excretory tract. Urinalysis is an essential investigation. **Proteinuria** of any significant degree (2-4+) is suggestive of renal disease (parenchymal involvement). Proteinuria of 1+ in a dilute urine may indicate a significantly great protein loss. Proteinuria may indicate pathological disease such as: glomerulonephritis, subacute or chronic nephritis, nephrotic syndrome, autoimmune disease, diabetic nephropathy, myeloma of the kidney, amyloid kidney and polycystic kidney disease. **Red cells** in the urine indicate extravasation of blood anywhere along the urinary tract and the occurrence of **red cells in casts** proves the renal origin of the bleeding. Formation of typical red cell casts by erythrocytes is indicative of glomerulitis. **Fatty casts** and oval fat bodies in tubule cells occur in degenerative diseases of the kidney such as nephrosis, glomerulonephritis, autoimmune disease, amyloidosis, and damage due to such toxins as mercury). The presence of **abnormal urinary chemical constituent**s may be the only indication of metabolic disorders involving the kidneys, including: diabetes mellitus, renal glycosuria, aminoacidurias (including cystinuria), oxaluria, gout, hyperparathyroidism, hemochromatosis, hemoglobinuria, and myoglobinuria (Krupp '88: 514), 515). Reasons for inadequate urinalysis include (1) improper collection, (2) failure to examine the specimen immediately, (3) incomplete examination, (4) inexperience of the examiner and (5) inadequate appreciation of the significance of findings.

Urinalysis

Test	Normal Findings	Test	Normal Findings
Appearance	clear	Bilirubin	none
Color	amber yellow	Urobilirubin	0.01-1 Ehrlich unit/mL
Odor	aromatic	Crystals	none
pH	4.6 – 8.0 (average 6.0)	Casts	none
Protein	0-8 mg/dL, 50-58 mg/24 hr (at rest), <250 mg /24 hr (during exercise)	Glucose	Random: none; 24 hour specimen: 50-300 mg/day or 0.3-1.7 mmol/day (SI units)
Specific Gravity	Adult: 1,005-1,030 (usually 1,010 – 1,025), Elderly: values decrease with age, Newborn: 1,001 – 1,020	Fresh specimen	none
Leukocyte enterase	negative	White blood cells	0-4 per low-power field
Nitrites	none	WBC casts	none
Ketones	none	Red Blood cells	<2, no casts

Source: Pagana '02: 1,007

With **diminished renal function**, the ability of the kidneys to concentrate urine lessens progressively until the specific gravity of the urine reaches 1.006-1.010. Patients uric acid stones rarely have a **urinary pH** over 6.5 (uric acid is soluble in alkaline urine). Patients with calcium stones, nephrocalcinosis, or both may have renal tubular acidosis and will be unable to acidify urine below pH 6.0. With urinary tract infections caused by urea splitting organisms (most commonly *Proteus* species), the urinary pH tends to be over 7.0. Urine obtained within 2 hours of a large meal or left standing at room temperature for several hours tends to be alkaline. Persistently elevated **protein levels** in the urine may indicate significant disease, e.g., glomerulopathy or cancer; proteinuria can be determined by the protein: creatinine ratio. The normal ratio is 0.2 mg or less of protein per milligram of creatinine and that a ratio of 3.5 or more represents significant proteinuria (more than 1 g of protein excreted every 24 hours). **Serum creatinine** levels will remain within the normal range (0.8-1.2 mg/dL in adults; 0.4-0.8 mg/dL in young children) until approximately 50% of renal function has been lost. Unlike most excretory products serum creatinine is not generally influenced by dietary intake or hydration status.

The endogenous **creatinine clearance test** is the most accurate and reliable measure of renal function available without resorting to infusion of exogenous substances such as inulin or radionuclides. Determination of creatinine clearance requires the collection of a times (usually 24 hour) urine specimen and a serum specimen. The clearance can then be calculated as follows: Clearance = UV/P where U= creatinine in urine (mg/dL); P=creatinine in plasma (mg/dL); V=mL or urine excreted per minute or per 24 hours. The resulting clearance is expressed in milliliters per minute, with 90-110 mL/min considered normal. Because muscle mass differs among individuals further has been achieved by using the following formula UV/P x 1.73 m^2/estimated surface area = corrected clearance. A corrected clearance level of 70-140 mL/min is considered normal. The **blood urea nitrogen** level is related to the glomerular filtration rate. Urea is the primary metabolite of protein catabolism and is excreted entirely by the kidneys. Blood urea nitrogen is influenced by dietary protein intake, hydration status ,gastrointestinal bleeding, urinary obstruction. Approximately two-thirds of renal function must be lost before a significant rise in blood urea nitrogen level will be evident. The **blood urea nitrogen: creatinine ratio** is normally 10:1 in dehydrated patients and those with bilateral urinary obstruction or urinary extravasation, the ratio may range from 20:1 to 40:1, and patients with advanced hepatic insufficiency and overhydrated patients may exhibit a lower than normal blood urea nitrogen level and blood urea nitrogen: creatinine ratio. Patients with renal insufficiency may develop extremely high blood urea nitrogen levels that can be partially controlled by a decrease in dietary protein. (Williams '88: 48, 54, 55).

Microscopic examination of the urinary sediment is an essential part of urinalysis. Early-morning urine is the best specimen if it can be examined within a few minutes of collection. In most cases, the sediment can be prepared as follows: (1) Centrifuge a 10-mL specimen at 2000 rpm for 5 minutes. (2) Decant the supernatant. (3) Suspend the sediment in the remaining 1 mL of urine by tapping the tube gently against a counter top. (4) Place 1 drop of the mixture on a microscopic slide, cover with a coverslip, and examine first under a low-power (10x and then under a high-power (40x) lens. **Bacteria** are more easily seen if the slide is stained with methylene blue, but staining is not essential. More than 5-8 **white blood cells** per high-power field is generally considered abnormal (pyuria) however 61% of those with pyuria had no bacterial growth from bladder urine obtained by catheterization or suprapubic aspiration. *Mycobacterium smegmatis*, a commensal organism, may be present in the urine (particularly in uncircumcised men). The presence of even a few red blood cells in the urine (**hematuria**) is abnormal, causes of hematuria include strenuous exercise (long-distance running), vaginal bleeding, and inflammations of organs near or directly adjoining the urinary tract, e.g. diverticulitis, appendicitis. **Epithelial cells** in the urinary sediment indicate contamination of the specimen from the distal urethra in males and the introitus in females. **Casts** are formed in the distal tubules and collecting ducts and, for the most part, are not seen in normal urinary sediment, they commonly signify intrinsic real disease. **Leukocyte casts** must be distinguished from **epithelial cell casts**, because the latter have little significance when present in small numbers. In renal transplant recipients, an increase in the number of epithelial cells or casts from the renal tubules may be an early indication of acute graft rejection. **Red blood cell casts** indicate underlying glomerulitis or vasculitis. **Hyaline casts** probably represent a mixture of mucus and globulin congealed in the tubules, in small numbers, they are not significant. Hyaline casts are commonly seen in urine specimens taken after exercise and in concentrated or highly acidic urine specimen. **Granular casts** most commonly represent disintegrated epithelial cells, leukocytes, or protein and indicate intrinsic renal tubular disease. The findings of **crystals** in the urine can be helpful but does not indicate disease Crystals form in normal urine below room temperature. Cystine, leucine, tyrosine, cholesterin, bilirubin, hematoidin and sulfonamide crystals are abnormal findings or varying importance . The presence of trichomonads or yeast

cells in the stained or unstained smear of sediment establishes diagnosis. A **presumptive diagnosis of bacterial infection** may be made on the basis of results of microscopic examination of the urinary sediment, should be confirmed by culture. The concept that urinary tract infection is present only when the urine specimen contains 10^5 or more bacteria per milliliter is not an absolute rule, a lower count does not exclude the possibility of an infection. It is not always necessary to identify the specific organism causing the infection, however, identification of the causative may be important. *Escherichia coli* causes 85% of routine urinary tract infections, often maltreated with Bactrim (trimethoprim-sulfamethoxazole)(Williams '88: 48-52) respond better to metronidazole (Flagyl ER).

Oliguria means "too little" urine volume in response to the body's excretory needs. Oliguria is present when the daily urine volume is not sufficient to remove the endogenous solute loads that are the end products of metabolism. No precise figure for 24-hour urine volume can be used in defining oliguria, since urine volumes normally vary with fluid intake and the concentrating ability of the kidney. If the kidney can concentrate urine in a normal fashion to a specific gravity of 1.035, oliguria is present at urine volumes under 400 mL/d. On the other hand, if the kidney concentration is impaired and the patient can achieve a specific gravity of only 1.010, oliguria is present at urine volumes under 1000-1500 mL/d. **Acute renal failure** is a condition in which the glomerular filtration rate is abruptly reduced, causing a sudden retention of endogenous metabolites (urea, potassium, phosphate, sulfate, creatinine) that are normally cleared by the kidneys The urine volume is usually low (under 400 mL/d), however may be normal. Prompt differentiation of the cause is important in determining appropriate therapy. Pre-renal renal failure is reversible if treated promptly , but a delay in therapy may allow it to progress int a fixed, nonspecific form of intrinsic renal failure (e.g., acute tubular necrosis). The other causes of acute renal failure are classified on the basis of their involvement with vascular lesions, intrarenal disorders or postrenal disorders. Rapid intravenous administration of 300-500 mL of physiologic saline or 125 mL of 20% mannitok (25g/125mL) is the usual initial treatment. Urine output is measured over 1-3 hours. A urine volume of more than 50 mL/h is considered a favorable response that warrants continued intravenous infusion with physiologic solutions to restore plasma volume and correct dehydration Therapy is directed toward eradication of infection, removal of antigen, elimination of toxic materials and drugs, suppression of autoimmune mechanisms, removal of autoimmune antibodies, or a reduction in effector-inflammatory responses (Amend et al '88: 526-528).

The clinical manifestations of renal disease can be grouped into well defined **renal syndromes**. Azotemia is a biochemical abnormality that refers to an elevation of the blood urea nitrogen (BUN) and creatinine levels, and is related largely to a decreased glomerular filtration rate (GFR). **Azotemia** is a consequence of many renal disorders, but also arises from extrarenal disorders. Prerenal azotemia is encountered when there is hyperfusion of the kidneys (e.g. hemorrhage, shock, volume depletion and congestive heart failure that impairs renal function in the absence of parenchymal damage. Postrenal azotemia is seen whenever urine flow is obstructed beyond the level of the kidneys. Relief of the obstruction is followed by correction of the azotemia. Uremia is characterized by a host of metabolic and endocrine alterations resulting from renal damage. Nephritic syndrome onset present grossly visible hematuria (red blood cells in urine), mild to moderate proteinuria (>3.5 gm/day), hypoalbuminemia (plasma albumin <3 gm/dL), severe edema, hyperlipidemia and lipiduria (lipid in the urine) is due to glomerular disease classically acute poststreptococcal glomerulonephritis. Glomerular disease is often associated with such systemic disorders as diabetes mellitus, SLE, vasculitis, amyloidosis and endocarditis. Rapidly progressive glomerulonephritis includes a rapid decline (hours to days) in GFR) (Alpers '10: 906-907). The glomerular filtration barrier allows discrimination among

various protein molecules, depending on their size (the large, the less permeable) and charge (the more cationic, the more permeable). Most cases of human glomerulonephritis are a consequence of deposits of discrete immune complexes. Microbial antigens that have been implicated are bacterial products (streptococci), appearing 1 to 4 weeks post-streptococcal infection of the pharynx or skin, but only certain strains of groups A β-hemolytic streptococci are nephritogenic, as well as the surface antigen of hepatitis B and C virus antigens, and antigens of *Treponema pallidum*, *Plasmodium falciparum* and several other viruses. More than 95% of children and 60% of adults recover but fewer than 1% of children and 40% of adults become severely oliguric, and develop a rapidly progressive glomerulonephritis; prolonged and persistent heavy proteinuria and abnormal GFR mark patients with an unfavorable prognosis (Alpers '10: 940, 941, 907, 910, 914, 919).

Acute **renal failure** is dominated by oliguria or anuria (reduced or no urine flow), and recent onset of azotemia that can result from glomerular, interstitial or vascular injury or acute tubular injury. Chronic renal failure is characterized by prolonged symptoms and signs of uremia, it is the end result of all chronic renal parenchymal diseases. Renal tubular defects are dominated by polyuria (excessive urine formation), nocturia and electrolyte disorders (e.g. metabolic acidosis). Defects in specific tubular functions can be inherited (e.g., familial nephrogenic diabetes, cystinuria, renal tubular acidosis) or acquired (e.g. lead nephropathy). **Urinary tract infection** is characterized as bacteriuria and pyuria (bacteria and leukocytes in the urine). The infection may be symptomatic or asymptomatic and may affect the kidney (pyelonephritis) or the bladder (cystitis). **Nephrolithiasis** (renal stones) manifest as severe spasms of pain (renal colic) and hematuria, often with recurrent stone formation. Urinary tract obstruction and renal tumors have varied clinical manifestations based on the specific anatomic location and nature of the lesion. Nephrotic patients are particularly vulnerable to infection especially staphylococcal and pneumococcal. Thrombotic and thromboembolic complications are also common due in part to loss of endogenous anticoagulants (e.g. antithrombin III) and antiplasmins in the urine. Renal vein thrombosis may result (Alpers '10: 907-908, 922).

Complete blood counts can be useful for diagnosing renal disease and blood loss from stomach and intestinal ulceration. Normochromic normocytic anemia is often seen with chronic renal insufficiency. Chronic blood loss from microscopic hematuria is usually not sufficient to cause anemia, although gross hematuria can be. A specific increase in the number of red blood cells, as manifested by elevated hemoglobin and hematocrit levels (erythrocytosis, not polycythemia) may be indicative of a paraneoplastic syndrome associated with renal cell cancer. The **white blood cell count** is usually nonspecific, although marked elevations may indicate an underlying leukemia that may be the cause of urologic symptoms. A **platelet count** important in patients receiving chemotherapy and those who have received extensive radiation therapy (Williams '88: 55-56).

Complete Blood Count

Test	Normal Finding
Red Blood Cells Count	RBC x 10^6 / microL or RBC x 10^{12} /L [SI units]. Adult/elderly: male: 4.7-6.1, female:4.2-5.4, Child: 2-8 weeks: 4.0-6.0, 2-6 months: 3.5-5.5, 6 months – 1 year: 3.5-5.2, 1-6 years: 4.0-5.5, 6-18 years: 4.0-5.5, Newborn: 4.8-7.1

Hemoglobin HgB, Hb	Male: 14-18 g/dL or 8.7-11.2 mmol/L (SI units) Female: 12-16/dL or 7.4-9.9 mmol/L, Pregnant female: >11 g/dL, Elderly: Values are slightly decreased, Children/adolescents: Newborn: 14-24 g/dL, 0-2 weeks: 12-20 g/dL, 2-6 months: 10-17 g/dL, 6 months – 1 year: 9.5-14 g/dL, 1-6 yars: 9.5-14 g/dL, 6-18 years: 0-5.5 g/dL
Hematocrit (Hct, Packed Red Blood Cell Volume, Packed Cell Volume (PCV)	Male: 42%-52% or 0.42-0.52 volume fraction (SI units), Female: 37%-47% or 0.37-0.47 volume fraction (SI units), Pregnant female:; >33%, Elderly: Values may be slightly decreased, Child/adolescent: Newborn: 44%-64%, 2-8 weeks: 39%-59%, 2-6 months: 35%-50%, 6 months-1 year: 29%-43%, 1-6 years: 30%-40%, 6-18 years 32%-44%
Red Blood Cell Indices	Mean Corpuscular Volume (MCV) Adult/elderly/child: 80-95 mm^3, Newborn: 96-108 mm^3, Mean Corpuscular Hemoglobin (MCH) Adult/elderly/child: 27-31 pg, Newborn: 32-34 pg, Mean Corpuscular Hemoglobin Concentration (MCHC) Adult/elderly/child: 32-36 g/dL (or 32%-36%), Newborn: 32-33 g/dL (32%-33%), Red Blood Cell Distribution Width (RDW) Adult: variation of 11%-14.5%
White Blood Cell Count and Differential	Total WBCs Adult/child>2 years: 5,000-10,000/mm^3 or 5-10 x 10^9/L (SI units), Child <2 years: 6,200-17,000/mm^3, Newborn: 9,000-30,000/mm^3 Differential Count % / Absolute (per mm^3) Neutrophils 55-70% / 2500-8000 Lymphocytes 20-40% / 1000-4000 Monocytes 2-8% / 100-700 Eosinophils 1-4% / 50-500 Basophils 0.5-1.0% / 25-100
Blood Smear (Peripheral blood smear, red blood cell morphology, RBC Smear)	Normal quantity of RBCs, white blood cells (WBCs), and platelets. Normal size, shape, and color of RBCs, Normal WBC differential count. With special stains infection, infestation, leukemia, and other diseases can be identified.
Platelet Count (Thrombocyte Count)	Adult/elderly: 150,000-400,000 mmol/mm^3 or 150-400 x -10^9/L (SI units), Child: 150,000-400,000/mm^3, Infant: 200,000-475,000 mm^3, Premature infant: 100,000-300,000/mm^3, Newborn: 150,000-300,000/mm^3
Mean Platelet Volume (MPV)	7.4-10.4 fL

Source: Pagana '02: 189, 446, 300, 296, 450, 537, 750, 409, 412

The determination of **prothrombin and bleeding time** (and perhaps partial thromboplastin time) is often a useful test of vitamin K deficiency, hemophilia and other clotting and bleeding disorders. **Serum sodium and potassium** determinations may be indicated in patients taking diuretics or digitalis preparations and in patients who have just undergone transurethral prostatectomy. **Serum calcium** determination are useful in patients with calcium urolithiasis. Elevated calcium levels are occasionally indicative or a paraneoplastic syndrome in patients with renal cell cancer. **Serum albumin** levels should be measured simultaneously with calcium levels in order to assess adequately the significance of the latter. **Serum acid phosphatase** is a useful marker of prostatic cancer, usually signifying metastatic disease when levels are consistently and significantly elevated. The enzymatic tests (particularly the thymolphthalein monophosphate method) are quite reliable, although prostatic infarction, recent prostatic massage, or hemolysis may cause false-positive. Alkaline phosphatase is a useful market of bone metastasis in prostatic cancer. **Serum parathyroid hormone** studies are useful in determining the presence of a parathyroid adenoma. **Serum renin** levels may be elevated in patients with renal hypertension, although many conditions can cause false-positive results. Studies of **adrenal steroid hormones** (e.g. aldosterone, cortisol, epinephrine, norepinephrine) are useful in determining adrenal function or the presence of adrenal tumors. Determination of serum levels of the beta-subunit of hCG and of alpha-fetoprotein are indispensable in staging and in treatment follow-up for testicular tumors. One of these tumor markers is usually elevated in 85% of patients with non-seminomatous testicular tumors and can predict the recrudescence of tumor several months before disease is clinically evident. **Serum testosterone** studies can help to establish the cause of impotence or infertility. The finding of elevated fasting **plasma glucose level** in patients with urologic disease can establish the diagnosis of diabetes mellitus and thus indicate a possible cause of renal insufficiency, neurovesical dysfunction, impotence, or recurrent urinary tract infection. **Serum uric acid levels** are often elevated in patients with uric acid stones. Elevated serum complement levels may be diagnostic of underlying glomerulopathies (Williams '88: 55-56). The **basic imaging mechanics** of radiography, ultrasonography, computerized tomography (CT scanning), and magnetic resonance (MR, nuclear magnetic resonance, NMR) tomography are converted electronically into digits corresponding to the reconverted analog images. Radiography (roentgenography) is the oldest method of urologic imaging, having been used to demonstrate radiopaque urinary calculi shortly after the discovery of x-rays by Wilhelm Röntgen in 1895. Newer imaging methods (e.g. scintigraphy, sonography, CT scan and MR are competing with, complementing and increasing replacing long-established uroradiographic techniques (Palubinskas '88:57).

Blood cholesterol levels can convince people to exercise and consume a plant-based diet. Cholesterol, triglycerides, saturated fats, trans-fatty acids, homocysteine and other harmful substances from food. Because fat is not soluble in water, and blood is mostly water, fat from food goes from the intestine to the liver in lymphatic fluid, and is then taken out of the blood by cells in the liver. It travels in the bloodstream in packages made up of an outer layer of protein, with fat in the center. These proteins are called lipoproteins (proteins that transport lipids) (Spence ’06: 80). It is estimated that 65 million American adults with high blood cholesterol need to make the therapeutic lifestyle changes (TLC) needed to lower their cholesterol and, with it, their risk for heart disease. To understand high blood cholesterol, it is important to know more about cholesterol. **Cholesterol** is a waxy, fat-like substance that is found in all cells of the body. Your body needs some cholesterol to work the right way. Your body makes all the cholesterol it needs. Cholesterol is also found in some of the foods you eat. Your body uses cholesterol to make hormones, vitamin D, and substances that help you digest foods. Blood is watery, and cholesterol is fatty. Just like oil and water, the two do not mix. To travel in the bloodstream, cholesterol is carried in small packages called **lipoproteins**. The small packages are made of fat

(lipid) on the inside and proteins on the outside. Two kinds of lipoproteins carry cholesterol throughout your body. It is important to have healthy levels of both: **Low-density lipoprotein** (LDL) cholesterol is sometimes called bad cholesterol. High LDL cholesterol leads to a buildup of cholesterol in arteries. The higher the LDL level in your blood, the greater chance you have of getting heart disease. **High-density lipoprotein** (HDL) cholesterol is sometimes called good cholesterol. HDL carries cholesterol from other parts of your body back to your liver. The liver removes the cholesterol from your body. The higher your HDL cholesterol level, the lower your chance of getting heart disease.

Lipid Profile

LDL Cholesterol Level	Category
Less than 100 mg/dL	Optimal
100 to 129 mg/dL	Near or above optimal
130 to 159 mg/dL	Borderline high
160 to 189 mg/dL	High
190 mg/dL and above	Very high
Triglyceride Level	Category
Less than 150 mg/dL	Normal
150–199 mg/dL	Borderline high
200–499 mg/dL	High
500 mg/dL and above	Very high

Credit: American Heart Association

The American Heart Association endorses the National Cholesterol Education Program (NCEP) guidelines for detection of high cholesterol. The Third Report of the Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) was released in 2001. It recommends that everyone age 20 and older have a fasting "**lipoprotein profile**" every five years. This test is done after a 9-12-hour fast without food, liquids or pills. If total cholesterol is 200 mg/dL or more, or HDL cholesterol is less than 40 mg/dL (for men) and less than 50 mg/dL (for women), a lipoprotein profile should be done to determine LDL cholesterol, triglyceride, homocysteine and C-reactive protein (CRP) levels. **Triglyceride** is the most common type of fat in the body. Many people who have heart disease or diabetes have high triglyceride levels. Normal triglyceride levels vary by age and sex. A high triglyceride level seems to speed up atherosclerosis, the buildup of fatty deposits in artery walls and atherosclerosis increases the risk for heart attack and stroke. Other potentially cartiotoxic lipoproteins can be detected, but are not necessary to confirm a diagnosis of hyperlipidemia. **C-**

reactive protein (CRP) has been known for many years as a non-specific test for inflammation that led to the discovery in the 21st century of the use of CRP as a marker of arteriosclerosis risk. **Homocysteine** is major cause of arteriosclerosis and some process intimately involved in the methionine/homocysteine metabolic interplay but other factors are likely to be involved (Graveline '04: 72, 59).

Neoplasms of the prostate gland, bladder and kidney are among the most common abnormal growth that afflict the human body. Tumors of the testis are highly malignant. Neoplasms of the ureter, urethra, penis scrotum epididymis and seminal vesicle are rare. Adrenal tumors may also occur. In the USA, adenocarcinoma accounts for 86% of all malignant tumors of the renal parenchyma and constitutes approximately 2% of all new cancers found each year. The greatest number of patients are in their 60s, and tumors develop 2-3 times more frequently in men than in women. The risk of developing renal cell carcinoma was found to be over 5 times higher in men who used any form of tobacco at all than in men who did not use tobacco (Johnson et al '88: 330). Tumor associated antigen exist in human tumors;.the most commonly employed tests measure afp and β-hCG. Both are onco-developmental antigens expressed by 60-80% of testicular cancers. Alpha-Fetoprotein (AFP) is a glycoprotein (MW 70,000) produced by the liver, yolk sac, and gastrointestinal tract of the fetus. In normal adults, levels of his markers are below 11 ng/ml. AFP levels are raised in most patients with hepatomas, in 75% of patient with non-seminomatous cancer of the testis, and occasionally in patients with gastrointestinal cancers of gastric, pancreatic, or biliary origin. Human chorionic gonadotropin (hCG) is a glycoprotein (MW 38,000) normally elevated in the first trimester of pregnancy. It is composed of α and β subunits. In normal adult males the level of β-hC is below 3 ng/mL. Its half-life is 2 day. It is elevated in 50-60% of non-seminomatous cancers of the testis and in 10% seminomatous tumors. Prostate-specific antigen (PSA) is a biologic marker for prostate cancer. It is a protein of MW 34,000 and has no subunits. Young males, with 2, usually have a much low score than older males, with 20, the higher scores are highly indicative of malignant prostatic disease (Nayaran '88: 321, 323).

2. Treatment

Stone Breaker™ (Chanca piedra) cures urinary and gallstones overnight. Ingredients: Stonebreaker herb (*Phyllanthus niruri*), Hydrangea root (*Hydrangea arborescens*), Celery seed (*Apium graveolens*), Burdock seed (*Arctium lappa*); and other Ingredients: certified organic grain alcohol & distilled water. Stonebreaker costs around $10 bottle. Caution: Do not take during pregnancy and keep out of reach of children. Shake well before taking 40 drops in a full cup of water, three times per day. Gastrointestinal disease is a common side effect of antibiotics and NSAIDs. **Metronidazole** (Flagyl ER), patented in 1960, longtime generic antibiotic, is uniquely useful in the treatment of diarrhea and intra-abdominal infections (including ulcers, peritonitis, intra-abdominal abscess, liver abscess), because it is effective against antibiotic resistant *Clostridium difficile* and *Helicobacter pylori* and is the only antibiotic that is well-tolerated by the gut. Caution: do not take in the first trimester of pregnancy because it may cause neural tube defects. Metronidazole is a broad spectrum antibiotic and antiprotozoal is useful in the treatment of bone and joint infections, vaginalis, endocarditis, non-gonococcal urethritis, rosacea, tetanus and trichomoniasis. Metronidazole possesses bactericidal, amebicidal, and trichomonacidal action and has direct anti-inflammatory effects and effects on neutrophil motility, lymphocyte transformation, and some aspects of cell-mediated immunity. Spectrum of activity includes most obligately anaerobic bacteria and many protozoa. Inactive against fungi and viruses and most aerobic or facultatively anaerobic bacteria. Gram-positive anaerobes: *Clostridium*, *C. difficile*, *C. perfringens*, *Eubacterium*, *Peptococcus*, and *Peptostreptococcus*. Gram-negative anaerobes: Active against *Bacteroides fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*, *B. ureolyticus*, *Fusobacterium*, *Prevotella bivia*, *P. buccae*, *P. disiens*, *P. intermedia*, *P. melaninogenica*, *P. oralis*, *Porphyromonas*, and *Veillonella*. Active against *Helicobacter pylori*, *Entamoeba histolytica*, *Trichomonas vaginalis*, *Giardia lamblia*, and *Balantidium coli.* Acts principally against the trophozoite forms of *E. histolytica* and has limited activity against the encysted form. Resistance has been reported in some *Bacteroides* and *T. vaginalis* (Lewis and Elvin-Lewis ’77: 292). Metronidazole must be prescribed to prevent deaths from *E. coli*, *Salmonella* and before fecal transplant, rather than some new antibiotic that has wormed its way into the literature. Doxycycline to treat Methicillin resistant *Staphylococcus aureus* and Ampicillin for pneumonia and meningitis are the only other antibiotic

Anthelmintics eliminate parasitic worms. Most of the worms that affect man live unobtrusively in the intestine and do little to impair the health of the heir host. The common helminths, with an indication of the most effective drugs administered for treatment are roundworms or trematodes *Ascaris* by piperazines, *Trichinella* by prednisone, *Trichuris* or whipworms and *Strongyloides* by thiabandazole, hookworms by tetrachloroethylene, *Enterobius* or pinworms by bacitracin, tapeworms or cestodes *Taenia* spp. by niclosamide or dichlorophen and trematodes or flukes (schistosomiasis by antimony). An anthelmintic drug must have a wide margin of safety between its toxicity to the worm and its toxic side effects to the host. To be effective they should orally active, produce results in a single dose, and be cheap. Schistosome and soil-transmitted helminth (roundworms, hookworms and whipworms) infections are among the most common infections in developing countries and can cause internal bleeding, leading to anemia. They can also cause malabsorption of nutrients, diarrhea and vomiting, and loss of appetite, further damaging nutritional status. Children infected with soil-transmitted helminths benefit significantly from anthelminthic treatment, in terms of reduction of worm burden and weight and height gain. Preventive chemotherapy (deworming), using annual or biannual single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for all young children (12–23 months of age), preschool (24–59 months of age), school-age children (5–12 years) and non-pregnant women (15-49) living in areas where the baseline

prevalence of any soil-transmitted infection is 20% or more among children, in order to reduce the worm burden of soil-transmitted helminths. Albendazole and mebendazole are well tolerated among children over 12 months of age, at appropriate doses, with only minor and transient side-effects reported. The most cost-effective approach to reach infected individuals is to treat the entire group at risk without individual diagnosis. Deliver deworming together with promotion of health and hygiene, to reduce transmission by encouraging healthy behaviors, such as hand-washing, use of footwear and proper disposal of feces. Take extra care and precaution in ensuring that women receiving anthelminthic medicines are not pregnant. Albendazole and mebendazole are well tolerated, with no adverse events in pregnant women and their fetuses when given after the first trimester of pregnancy. Anthelminthic medicines must not be given during the first trimester. Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for pregnant women, after the first trimester, living in areas where both: (i) the baseline prevalence of hookworm and/or *T. trichiura* infection is 20% or higher among pregnant women, and (ii) anemia is a severe public health problem, in order to reduce the worm burden of soil-transmitted helminths (WHO '19).

Gastrointestinal Medicine

Medicine	**Trade Name**
Aminosalicylates (ulcerative colitis, proctitis and Crohn's disease anti-inflammatory)	Sulfasalazine (Azulfidine), Azathioprine (Imuran, Azasan), Mesalamine (Asacol, Canasa, Rowasa), Olsalazine (Dipentum), Balsalazide (Colazal), Prednisone (Deltasone, Meticorten, Liquid Pred, Orasone, Prednicen-M, Prednicot)
Anthelminthics	Preventive chemotherapy (deworming), using annual or biannual single-dose albendazole (400 mg)b or mebendazole (500 mg), is recommended as a public health intervention. Roundworms or trematodes (Ascaris by piperazimes, Trichinella by prednisone), Trichuris or whipworms and Strongyloides by thiabandazole, hookworms by tetrachloroethylene, Enterobius or pinworms by bacitracin), tapeworms or cestodes (*Taenia* spp. by niclosamide or dichlorophen) and trematodes or flukes (schistosomiasis by antimony). Amebiasis by metronidazole.
Antibiotic (for all abdominal organ infections, infectious gastroenteritis, ulcers and joints)	Metronidazole (Flagyl ER)
Anti-cholinergenic (Anti-vomiting)	Phenothiazines (chlorpromazine, peperazine), othopramides (metoclopramide); Aristolochiaceae, *Aristolochia serpentine* (Virginia snakeroot), Nyrtaceae, *Eugenia caryophyllata* (clove tree). Lamiaceae, *Menthe piperita* (peppermint), *Monarda puncata* (horsemint), Rosaceae, *Rubus* spp. (blackberry and thimbleberry)
Anti-diarrheal	Imodium (loperamide)
Anti-emetic (anti vomiting and nausea)	5-HT_3 receptor antagonists, Dolasetron (Anzemet), Granisetron (Kytril, Sancuso), Ondansetron Zofran), Tropisetron (Setrovel, Navoban), Palonosetron (Aloxi) Aprepitant (Emend), NK1 Receptor antagonist and Casopitant Investigational NK1 receptor antagonist.

	Antihistamines (H_1 histamine receptor antagonists), opioid nausea, such as Cyclizine, Diphenhydramine (Benadryl), Dimenhydrinate (Gravol, Dramamine), Doxylamine, Meclozine (Bonine, Antivert), Promethazine (Pentazine, Phenergan, Promacot), Cannabinoids are used in patients with cachexia, cytotoxic nausea, and vomiting.
Antifungal	topical clotrimazole (Fungoid Solution, Gyne-Lotrimin, Lotrimin, Lotrisone, Mycelex), topical nystatin (Mycostatin, Mykacet, Nystat-Rx, Nystop, Pedi-Dri), topical ketoconazole (Extina, Nizoral, Nizoral A-D, Xolegel), fluconazole (Diflucan), ketoconazole, amphotericin B, OTC anti-candida
Anti-ulcer	*Glycyrrhiza glabra* root (common licorice native to Eurasia) carbenoxolone sodium and deglycyrrhizinized licorice, can on the average reduce the size of an ulcer by 70 to 90% after one month of treatment. Aluminum salts (e.g. aluminum hydroxide gel, BPC). For nausea and vomiting metroclopramide or domperidone intramuscularly. For the specific healing of gastric ulcer colloidal bismuth (De-Nol); carbenoxolone (Biogastrone), (Tagamet) 200 mg, ranitidine (Zantac). For the specific healing of duodenal ulcer cimetidine (Tagamet), (Zantac); colloidal bismuth (De-Nol); Maalox. Metronidazole is uniquely effective antibiotic against *Helicobacter pylori*, and is good at healing internal abdominal ulceration.
AIDS	efavirenz/emtricitabine/ tenofovir (Atripla)
Contraceptives	
Diabetes	Insulin injection Humulin, Humulin 70/30, Humulin 70/30 Pen, Humulin 50/50, Humulin L, Humulin N, Humulin R, Humulin U Ultralente, Novolin, Novolin 70/30, Novolin 70/30 Innolet, Novolin 70/30 PenFill, Novolin N, Novolin R). Sulfonylureas, Chlorpropamide (Diabinese) is the only first-generation sulfonylurea still in use today. The second generation sulfonylureas are used in smaller doses than the first-generation drugs. There are three second-generation drugs: glipizide (Glucotrol and Glucotrol XL), glyburide (Micronase, Glynase, and Diabeta), and glimepiride (Amaryl); Meglitinides, Repaglinide (Prandin) and nateglinide (Starlix); Biguanides, Metformin (Glucophage); Thiazolidinediones, Rosiglitazone (Avandia) and pioglitazone (ACTOS); Alpha-glucosidase inhibitors, Acarbose (Precose) and meglitol (Glyset); DPP-4 inhibitors, Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin (Nesina)
Emetic (induce vomiting)	ipecac
Gallstones and Urinary Stones	Stonebreaker (*Chianca piedra*)
Hepatitis	Pegylated interferon alfa-2b (Pegasys), Nucleoside/nucleotide analogues (NAs) such as adefovir (Hepsera), entecavir (Baraclude), lamivudine (Epivir-HBV, Heptovir, Heptodin), telbivudine (Tyzeka) and tenofovir (Viread)
Hemorrhoids	Preparation H. Ointment made from *Hamamelis virginiana* (witch hazel) and other herbs
Immunosuppressives	Tacrolimus, cyclosporine; adjunctive maintenance mycophenolate

(anti-rejection)	mofetil, aathiprine. Acute rejection is managed with infusion of either muromonab-CD3 (OKT#) or an interleukin-2 receptor blocker (e.g. basiliximab)
Urinary retention	Phenoxybenzamine, Cyproterone acetate

Antibiotics are indeed wonder drugs, essential to combat disease. But like any other medication, they have unintended side effects. Some of these side effects are temporary and relatively minor (for example yeast infection), others last longer and are of greater concern, such as diarrhea due to *Clostridium difficile* overgrowth. The enzyme needed to digest oxalate isn't made by the human body, but by bacteria in microflora, most notably the probiotic *Oxalobacter formigenes*, which normally lives in our gut. If the oxalate isn't broken down in the intestinal tract, the kidneys must try to filter it out, and if oxalate levels become high, stones may form in the kidneys (Elvin-Lewis '77: 315-316). But most significant of all are effects on the immune system, which are far more serious and may last for a lifetime. Fortunately, most, if not all, antibiotics side-effects can be prevented by consuming probiotics during and after treatment (Huffnagle '07: 48, 49). Constipation, diarrhea, and heartburn are common side effects of medication. To restore the normal intestinal flora following administration of antibacterial drugs, which often results in diarrhea, lactobacillus cultures (*L. acidophilus, L. bulgaricus*) are available for oral therapy. Prolonged use of any antidiarrheal agent is discouraged (Lewis and Elvin-Lewis '77: 284).

Helping Medication and Probiotics Work Together

Type of Drug	What's the Issue	What to Do
Antibiotic	Kills probiotic bacteria, such as *Lactobacillus and Bifidobacterium*, as well as targeted bacteria. Not: probiotic yeasts, such as *Saccharamuces boulardii*, are not affected by antibiotics	Consume probiotic bacteria at least two hours after taking antibiotics. A probiotic yeast can be taken at the same time as antibiotics.
Systemic oral antifungal medications (e.g. fluconazole, nystatin)	Kills probiotic yeast, such as *Saccharomyces boulardii*, as well as harmful yeasts. Note: probiotic bacteria, such as *Lactobacillus* and *Bifidobacterium* are not affected by antifungal medications.	Take probiotic yeast at least two hours after taking antifungal drugs. Probiotic bacteria can be consumed at the same tiem as antifungals.
Antacids and acid blockers, such as Tagamet	Counters desirable presence of acid in the stomach and the beginning of the small intestine, acid controls growth of harmful bacteria, creating a selective advantage for probiotic bacteria.	If you must take these medications, increase the dose or frequency of probiotics. Gradually work up to double the usual amount of probiotic for as long as the medication is needed.
Nonsteroidal anti-inflamatory drugs, such as aspirin	Can block production of stomach acid, this acid	"

	normally gives probiotic bacteria a competitive advantage.	
Laxatives and any drug that lists diarrhea as a side effect	Speeds emptying of intestinal contents, including probiotic bacteria.	“
Muscle relaxants or any drug that lists constipation as a side effect	Decreases peristalsis, which slows emptying of intestinal contents, allowing competing bacteria to proliferate.	“

Source: Huffnagle ’07: 326

Acidophilus supplementation proves beneficial in irritable bowel sufferers at decreasing diarrhea and reestablishing proper flora balance. A different probiotic *Faecalibacterium prausnitzii* was studied in France for the Treatment of Crohn’s disease and proved beneficial in reducing inflammation in the colon. *Sachharomyces boulardi* is a very important probiotic to use in times of excess yeast of chronic fungal infections. Many specialized tests can be used to check for unwanted fungi and yeasts are found using saccharomyces can help by settling into the areas within the gastrointestinal tract that are normally inhabited by yeast and fungus species. Same with the use of the bacterial probiotic crowding out pathogenic bacteria, probiotic yeast can move into and compete for survival within the GI tract with pathogenic or overpopulated yeasts and fungi. If yeast infections or fungi overgrowth are strong only supplementing with saccharomyces may not be effective (Black ’10: 150, 151).

Age-related changes in the microflora make us more susceptible to *Clostridium difficile*, which causes diarrhea. This bacterium is normally present in the GI tract, but its numbers are kep in check by friendly bacteria. Probiotics such as *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* Iyo have proven very effective at treating diarrhea caused by *C. difficile*. As women go through menopause, their vaginal microflora changes. The population of *E. coli* increases, while the probiotic *Lactobacilli* decline and women become more vulnerable to vaginal infections after menopause. Aging has the potential to tip the microfloral balance away from probiotics, and consequently the balance of regulatory versus helper T cells. As a result, the immune system will regulate itself less effectively, leading to increased inflammation in the body. Research suggests that probiotics can help counter the physically damaging effects of stress, including effects on the gut and immune system. In a study of 68 infants whose bouts of crying lasted for three or more hours daily, three or more days per week, over a period of more than than three weeks. Half of the babies received drops containing the probiotic *Lactobacillus reuteri*, the rest received simethicone, the standard treatment for cholic. After four weeks the conventionally treated infants were still crying for an average of 2 hours and 27 minutes per day and those who received *L. reuteri* drops were down to an average of just 17 minutes of crying per day, which is well within the range of normal. Over the years, the composition of gut microflora changes. In midlife there is a decrease in the members of the probiotic *Bifidobacterium* genus and an increase in *E. coli* and *Clostridia*. *E. coli* can perform useful functions in the gut, they help compete against harmful microbes, they make certain vitamins that we absorb. On the other hand, if they leave the GI tract, they can cause disease. Many species of *Clostridia* are bad news. If their numbers get out of hand, they can cause serious illnesses. Members of the *Clostridium* genus are responsible for tetanus, botulism, and gangrene, as well as antibiotic-associated colitis (Huffnagle ’07: 94, 102, 104, 105).

An **emetic,** such as syrup of ipecac, is a substance that induces vomiting when administered orally or by injection. An emetic is used medically where a substance has been ingested and must be expelled from the body immediately (for this reason, many toxic and easily digestible products such as rat poison contain an emetic). Inducing vomiting can remove the substance before it is absorbed into the body. Ipecac abuse can cause detrimental health effects. Emesis has suffered a decline in popularity during the past century. Its use now is restricted to two main areas of treatment, ridding the stomach of irritant and poisonous substances, and using the unpleasantness of vomiting in aversion therapy. Emesis is of particular value in young children for the treatment of acute poisoning (Elvin-Lewis '77: 279, 280. 277-279). Vomiting is a common symptom having many causes inside and outside the gastrointestinal tract. One of the most direct ways to prevent vomiting is to inhibit the hyperactivity of the vomiting center by using anticholinergic drugs. An **antiemetic** is a drug that is effective against vomiting and nausea. Antiemetics are typically used to treat motion sickness and the side-effects of medications such as opioids and chemotherapy. Antiemetics act by inhibiting the receptor sites associated with emesis. Hence, anticholinergics, antihistamines, dopamine antagonists, serotonin antagonists, and cannabinoids are used as anti-emetics. One of the most direct ways for pharmaceutical medicine to prevent vomiting is to inhibit the hyperactivity of the vomiting center by using anticholinergic drugs. Antihistamines such as Dramamine or hydramine have mild antiemetic effects. Two synthetic compounds are the phenothiazines (chlorpromazine, piperazine) and othopramides (metoclopramide), they work in three minutes (Elvin-Lewis '77: 279, 280. 277-279). Antiemetics include: 5-HT_3 receptor antagonists – these block serotonin receptors in the central nervous system and gastrointestinal tract. As such, they can be used to treat post-operative and cytotoxic drug nausea & vomiting. However, they can also cause constipation or diarrhea, dry mouth, and fatigue. Dolasetron (Anzemet) - can be administered in tablet form or in an injection. Granisetron (Kytril, Sancuso) - can be administered in tablet (Kytril), oral solution (Kytril), injection D(Kytril), or in a single transdermal patch to the upper arm (SANCUSO). Ondansetron (Zofran) - administered in an oral tablet form, orally dissolving tablet form, orally dissolving film, or in an IV/IM injection. Tropisetron (Setrovel, Navoban) - can be administered in oral capsules or in injection form. Palonosetron (Aloxi) - can be administered in an injection or in oral capsules. NK1 receptor antagonists are Aprepitant (Emend) Commercially available NK1 Receptor antagonist and Casopitant Investigational NK1 receptor antagonist. Antihistamines (H_1 histamine receptor antagonists), effective in many conditions, including motion sickness, morning sickness in pregnancy, and to combat opioid nausea, such as Cyclizine, Diphenhydramine (Benadryl), Dimenhydrinate (Gravol, Dramamine), Doxylamine, Meclozine (Bonine, Antivert), Promethazine (Pentazine, Phenergan, Promacot) can be administered via a rectal suppository for adults and children over 2 years of age. **Cannabinoids** are used in patients with cachexia, cytotoxic nausea, and vomiting. These may cause changes in perception, dizziness, and loss of coordination. Cannabis - Medical marijuana, in the U.S., it is a Schedule I drug. Dronabinol (Marinol) – a Schedule III drug in the U.S. Some synthetic cannabinoids such as Nabilone (Cesamet) or the JWH series. Sativex is an oral spray containing THC and CBD. **Peppermint** is claimed to help nausea or stomach pain when added into a tea or peppermint candies. **Ginger** - contains 5HT3 antagonists gingerols and shogaols. To sooth the stomach there are Aristolochiaceae, *Aristolochia serpentine* (Virginia snakeroot), Nyrtaceae, *Eugenia caryophyllata* (clove tree). Lamiaceae, *menthe piperita* (peppermint), *Monarda puncata* (horsemint), Rosaceae, *Rubus* spp. (blackberry and thimbleberry) (Elvin-Lewis '77: 279, 280. 277-279).

Helicobacter pylori infection and **ulcer disease** is treated with the oral administration of 200 or 250 mg three or four times daily at meals and bedtime for fourteen days of metronidazole (Flagyl ER) (Berger '04: 62). The mere presence of *Helicobacter pylori* in the stomach is not enough to

cause ulcers. About 20 percent of Americans under the age of 40 and half over age 50 carry the bacteria, yet most don't develop the problem. We know that the immune system is involved, because ulcers result as an inflammatory response against *H. pylori*. Since high levels of *H. pylori* are required to develop an ulcer, laboratory experiments have established that numerous strains of *Lactobacillus*, including *L. acidophilus, L. johnsonii, L.salivarius*, and *L. casei,* can slow the growth of *H. pylori* in the petri dish, and sometimes even kill it. In the early 1980s, two Australian doctors, J. Robin Warren and Barry J. Marshall, isolated *Helicobacter pylori* from the stomachs of ulcer patients. But their suggestion that these bacteria actually caused the ulcers met with general disbelief for more than a decade. In frustration Dr. Marshall decided to improve the connection by infecting himself. After undergoing a preliminary examination to demonstrate that his stomach was healthy, he drank a pure culture of the bacteria. Five days later he developed severe gastrointestinal symptoms from gastritis, an inflammation of the stomach that is associated with ulcers. In 2005, Drs. Warren and Marshall shared a Nobel Prize for their discovery. *Lactobacillus* appears to inhibit *Helicobacter* growth. Mice fed *Lactobacillus* reduced the presence of *Helicobacter* by more than 99 percent. Subsequent research showed that ulcers could be permanently cured with the antibiotic metrodnidazole (Flagyl ER) that completely eradicates the *H. pylori*. The standard current treatment for those suffering from peptic ulcers is called "triple therapy" because it involves a combination of two antibiotics to kill *H. pylori*, plus a third medication to either decrease acid production in the stomach or to protect the stomach from the acids. The NIH claims it is more than 90 percent effective in patients with ulcers. In children, the success rate is lower, around 60 percent. Unfortunately, triple therapy may cause unpleasant side-effects, including nausea, diarrhea, abdominal pain, taste disturbances, headaches and body aches. In a Czech study 90 percent of those children whose triple therapy was supplemented by Actimel. Numerous studies have shown that probiotics, including *Lactobacillus rhamnosus GG*, *Saccharomyces boulardii*, mixed *Lactobacillus* species, and various strains of *Bifidobacterium*, reduced the unwanted symptoms accompanying triple treatment (Huffnagle '07: 123, 125, 124, 126).

In the absence of *H. pylori*, most but not all ulcers are caused by intolerance to anti-inflammatory drugs such a naproxen (Alleve) or ibuprofen (Advil). The key to treating these ulcers that are *H. pylori*- negative is to stop the anti-inflammatory and prescribe potent acid-suppressing medications, such as omeprazole, until the ulcer is healed. Then the anti-inflammatory drug may be restarted along with a gastro-protective agent such as the proton pump inhibitor (PPI) used to heal the ulcer (Newman '11: 102). Proton pump inhibitors (PPIs) are Prevacid (Lansoprazole), Prilosec (Omeprazole), Protonix (Pantoprazole) and Nexium (Esomeprazole Magnesium). Useful in the treatment of **gastro-esophageal reflux disease** (GERD) are antacids and the proton pump inhibitors (PPIs) Prilosec (Omeprazole) and Nexium (Esomeprazole Magnesium) as well as the antiemetic and gastroprokinetic agent Reglan (Metoclopramide). It may be necessary to modify the acid-base balance with antacids and bicarbonate. Essentially, small meals that are rich in vegetables and include modest servings of complex carbs and lean protein are usually best. A protein elimination diet is usually best (Berger '04: 142). Metronidazole is helpful for healing non-infectious ulcers.

The suggested plan for **management of peptic ulcer** include regular relaxed meals, no tobacco, alcohol, drugs (e.g. salicylates, other NSAIDs, or antibiotics other than metronidazole)). For symptomatic relief of pain, heartburn and discomfort is initially done with antacids with balanced magnesium/aluminum salts preparation. In patients with costive stools, magnesium salts (e.g. Mist, Magnesium Trisil. BPC) 10 ml three times daily 1 hour after food and at night. In patients with loose stools, aluminum salts (e.g. aluminum hydroxide gel, BPC) 10 ml three times daily 1 hour after food and at night. For nausea and vomiting metroclopramide 10 mg three

times daily orally or domperidone intramuscularly. For the specific healing of gastric ulcer colloidal bismuth (De-Nol) 5 ml in 15 ml water half-an-hour before meals and at night 4-6 weeks causes no significant side effects; carbenoxolone (Biogastrone) 100 mg three times daily one week, the 50 mg three times daily 5 weeks, watch for edema, blood pressure and hypokalemia; or cimetidine (Tagamet) 200 mg three times daily 400 mg nightly or ranitidine (Zantac) 150 mg twice daily 4-6 weeks, however as yet the role of H_2 receptor blockers has not been conclusively proven. For the specific healing of duodenal ulcer cimetidine (Tagamet) 200 mg three times daily 400 mg nightly or 400 mg twice daily 6-8 weeks or ranitidine (Zantac 150 mg twice daily 6-8 weeks; colloidal bismuth (De-Nol) 5 ml in 15 ml water or one tablet three times daily and at night 6-8 weeks; or 'high dose' antacid regimes, e.g. Maalox 10 l two-hourly and at night (Jones et al '85: 85). Metronidazole is highly curative of ulcers.

A **demulcent** is an herb that functions in providing a soothing film over a mucus membrane. For example, honey is often used as a demulcent for a sore throat, because it helps to coat the throat mucus membrane (Black ;10: 139, 143). Licorice has a long history in European domestic medicine for the treating of indigestion and for alleviating, or relieving, inflamed stomachs. Two derivatives of *Glycyrrhiza glabra* root (common licorice native to Eurasia) carbenoxolone sodium and deglycyrrhizinized licorice, can on the average reduce the size of an ulcer by 70 to 90% after one month of treatment. Healing occurs in patients who are not confined to bed, and many who continue to work during the treatment. Excessive secretion of hydrochloric acid or hyperacidity can lead to ulcerations of the stomach and duodenum. Common neutralizing agents for excessive acid may be prescribed: sodium bicarbonate, calcium carbonate, and magnesium hydroxide (milk of magnesia) are a few examples. A natural remedy used by North American Indians was hops (*Humulus lupulus*). Upset digestion (dyspepsia, heartburn) centers around a burning or tight feeling in the chest, belching and a cramped or bloated sensation in any part of the abdomen. Antacids and carminatives can alleviate this distress. A number of plants are used in folk medicine to relieve indigestion: Betulaceae, *Alnus rubra* (red alder), *A. rugosa* (hazel alder); Combretaceae, *Terminalia bellirica*, Rasaceae, *Rubus macropetalus* (dewberry); *Saxifragaceae*, *Hydrangea arborescens* (smooth hydrangea) (Lewis and Elvin-Lewis ’77: 6, 275, 272, 273). **Treatment of hemorrhoids** consists of obtaining easy bowel movement by the use of astringents, lotions and ointments manufactured from vegetable sources such as OTC Preparation H; Anacardiaceae, *Rhus glabra*, asteraceae, *Anaphalis margaritacea* (pearly everlasting), *Serretula tincotira* (centaury), Fabaceae, *Copaifera officinalis*, *C. reticulate*, Facaceae, *Quercus infectoria* (dyer’s oak) Hamamelidaceae, *Hamamelis virginiana* (witch hazel), *Oleaceae, Fraxinus* Americana (white ash), Rubiaceae, *Cinchona* spp., Simourabaceae, *Brucea javanic* and *B. sumatrana* (Lewis and Elvin-Lewis ’77: 293-294).

Anticholingergic/antispasmodic/antiparkinson’s drugs can be used to correct griping abdominal pain, often called colic, and other symptoms, including spasms of the stomach and intestines, spastic constipation, spasms of the bladder and urinary tract due to inflammation, pernicious vomiting of pregnancy, spasms of the biliary and pancreatic ducts, and excessive salivation, perspiration, and secretions of the nose, pharynx, and bronchi - dicycloverine and atropine sold as Benztropine (Cogentin), Ipratropium (Atrovent), Oxitropium (Oxivent), Tiotropium (Spiriva), Glycopyrrolate (Robinul), Oxybutinin (Ditropan, Driptane, Lyrinel XL), Tolterodine (Detrol, Detrusitol), Diphenhydramine (Benadryl, Sominex, Equate Sleep Aid, Advil PM, etc.) and Dimenhydrinate (Dramamine). In addition fainting due to heart block, arterial spasms, gangrenous conditions due to damaged and constricted blood vessels, and other important circulatory problems can be remedied by antispasmodic drugs. The most important antispasmodic is atropine, obtained from *Atropa belladonna*, *Hyoscyamus muticus*, *H. niger*,

Duboisia leichardtii, *D. moposroides*, and other solanaceaous species, or produced synthetically (Lewis and Elvin-Lewis '77: 276-277).

Infectious diarrhea, gastroenteritis, is an inflammation of the stomach and intestines, characterized by abdominal distress, nausea, vomiting and diarrhea definitively treated with **metronidazole**. Enteropathogenic strains of *Escherichia coli* are associated with infantile diarrhea and *Vibrio parahemolyticus* (Japanese raw-fish enteritis). One of the major causes of food poisoning is *Clostridium perfringens* and its toxins, *C. perfringens*, strain type F can produce a rare but more fatal type, *enteritis necroticans*. Other outbreaks of food poisoning have implicated *Bacillus cereus* and species of *Proteus*, *Klebsiella, Providencia* (Paracolon), *Citrobacter*, *Pseudomonas*, *Enterobacter*, and *Actinomyces*. When there is suppression of gut flora due to antibiotic therapy, overgrowth of organisms, such as *Staphylococcus aureus*. Or *Candida albicans*, *Streptococcus faecalis*, *Psuemonas aeroginosa*, and *Proeus mirabilis*, can result in enterocolitis or infection of the bowel wall. Enterocolitis may also be a manifestation of *Salmonella*, cholera, and *Shigella* infections. Cholera, a nonexudative form of acute diarrheal disease, is characterized by severe bloody diarrhea and dehydration due to the choleragen endotoxin associated with the etiologic agent, *Vibrio cholera*. This endotoxin, stimulates a prolonged increase in capillary permeability, inducing a basic lesion in the jejunal microcirculation with striking water and ion fluxes. Prognosis is excellent with current **electrolyte replacement therapy**, which involves infusing the patient with an alkaline saline solution in order to rehydrate him and to correct his acidosis. Once hydration has been achieved, tetracycline is used to reduce the number of organisms shed in the stool. Homeostasis is maintained by infusing solutions at a rate to match the measured stool volume (Elvin-Lewis '77: 288).

Antidiarrheal agents are used to treat diarrhea, an increase in the fluidity and frequency of stools, one of the most common disorders in man. The causes of diarrhea are numerous: acute diarrhea results from bacterial and viral enteritis, food and toxin poisoning, chemical poisoning, and gastrointestinal allergy, chronic diarrhea is caused by chronic intestinal infections, immunologic and metabolic abnormalities, environmental factors and the malabsorption syndrome (bile and pancreatic disorders, genetic abnormalities, etc.) Whenever possible, the cause should be eliminated or controlled. To restore the normal intestinal flora following administration of antibacterial drugs, which often results in diarrhea, lactobacillus cultres (*L. acidophilus, L. bulgaricus*) are available for oral therapy. Prolonged use of any antidiarrheal agent is discouraged (Elvin-Lewis '77: 284-287). If diarrhea is significant and no relief is obtained through the use of homeopathic remedies, then activated charcoal may be used. Charcoal is an excellent, easy-to-use supplement, but should only be used for a short period of time. If the need for charcoal extends past one or two weeks, consult a physician about the unrelenting diarrhea problems. Charcoal can be used as 204 capsules, 3 times per day during acute diarrhea. This amounts to about 500-1000 mg, 3 times per day. Do not exceed 3 grams daily (Black '10: 209). The traditional remedy for diarrhea, that is highly effective, is plain white rice. For patients losing a lot of fluid and electrolytes white rice water, cooked in three parts water, is indicated to be drunk until the appetite improves to the point the patient eats the plain white rice, which almost always ends violent diarrhea and vomiting immediately. Standard therapy for viral gastroenteritis involves drinking plenty of fluids and eating easy-to-digest foods. On average the duration of diarrhea in studies was reduced 13 hours, from 71 hours to 58 hours, in the group receiving probiotics. Studies have confirmed the efficacy of *L. rhamnosus GG* and demonstrated that *L. rhamnosus 19070-2* and *L. reuteri DSM 12246* also reduce the length and severity of viral gastroenteritis in children (Huffnagle '07: 126).

Treatment of *Candida* infections is primarily with the topical application of one of the the synthetic imidazoles. These agents give good cure rates after 3 to 7 days. Resistant strains of *C. tropicalis* or *T .glabrata* may respond to therapy with terconazole or gentian violet. Treatment with the oral agent fluconazole (Diflucan), 150 mg as a single dose, have become widely used. For recurrence or resistance ketoconazole 100 mg twice daily for 10 days can be effective. Victims of sexual assault often present with desquamative inflammatory vaginitis where there is a relative absence of lactobacili and overgrowth of gram-positive cocci, usually streptococci. Vaginal pH is greater than 4.5. Initial therapy is clindamycin cream 2% applied daily for 1 week Women suffer urinary tract infections roughly 10 times more often than men. Approximately 15% of women experience at least one urinary tract infection in their lifetime. Most urinary tract infections in women ascend from bacterial contamination of the urethra. Treatment is simple and generally successful. Hydration, urinary acidification (with ascorbic acid, ammonium chloride, or acidic fruit juices, and urinary analgesics (Pyridium (pheazopyridine hydrochloride) are helpful in most cases. Antibiotic therapy should be instituted. Nitrofurantoin (Macrodantin) produces good urinary antibiosis without undue alteration of other flora, although it is not effective against Proteus infections. Antibiotics such as ampicillin, tetracycline and trimethoprim-sulfamethoxazole (Septra, Bactrim) produce good coverage in the urinary tract but risk more alteration of vagina or intestinal flora. Vaginal yeast infections may result from these antibiotic treatments. When pyelonephritis is suspected, aggressive antibiotic therapy with cephalosporins such as Keflex (cephalexin) or Duricef (cefadroxil) is indicated. Patients who have been treated for urinary tract infections should have a follow urinalysis and culture done 10 to 14 days after the initial diagnosis (Beckman et al '02: 357-364, 393) and re-treated with metronidazole, 400 mg twice daily.

Aminosalicylates are used to treat ulcerative colitis, proctitis and Crohn's disease. Aminosalicylates are anti-inflammatory agents used to treat inflammatory bowel disease and some forms of arthritis. They work by inhibiting the production of cyclo-oxygenase and prostaglandin, thromboxane synthetase, platelet activating factor synthetase, and interleukin-1 by macrophages so reduces the acute inflammatory response in inflammatory bowel disease. Sulfasalazine (Azulfidine) works 40% to 80% of the time to make ulcerative colitis, Crohn's and irritable bowel symptoms better or keep them from coming back. But it cannot be used by people who are allergic to or cannot tolerate sulfa drugs. Mesalamine (Asacol, Canasa, Rowasa), Olsalazine (Dipentum), and Balsalazide (Colazal) do not contain sulfa (Friedman and Liechtenstein '6: 803-817). In the treatment of anto-immune and inflammatory diseases of the bowel and digestive tract, as well as allergic rhinitis and asthma, fast acting corticosteroids, such as **prednisone** (Deltasone, Meticorten, Liquid Pred, Orasone, Prednicen-M, Prednicot, Sterapred), are usually given for short periods of time to treat flare-ups. Side effects include, but are not limited to, weight gain, water retention, osteoporosis, diabetes, high blood pressure, increased susceptibility to infection due to immune suppression, cataracts, and psychosomatic disorders such as depression. **Immunomodulators** suppress the immune system slower than corticosteroids and have fewer side effects. TNF inhibitors, also known as biologics, are used to treat both Crohn's disease and ulcerative colitis. Biologics are proteins that block inflammation by affecting substances in the body such as pro-inflammatory cytokines. When remission is achieved drugs can be reduced, changed, or eliminated as long as symptoms stay under control (Black '10: 105, 106, 107) Medications, such as azathioprine (Azasan, Imuran) and 6-mercaptopurine (Purinethol), induce immunosuppression, to help prevent rejection in organ transplant recipients and as an oral anti-neoplastic chemotherapeutic agent, respectively.

Drug treatment of **irritable bowel disease** (IBD) employs corticosteroids, sulphasalazine (Salazopyrin, Asylufidine) and azathioprine (Imuran, Azasan). Oral prednisone is generally the

preferred corticosteroid, although hydrocortisone and ACTH may be given intravenously in severe attacks. Corticosteroids can also be given through the anal canal. In localized proctitis, prednisone suppositories are very useful, and in proctosigmoiditis prednisone 21-phosphate in water can be given as a retention enema, or administered as a foaming preparation. This local treatment can be used over quite long periods and side-effects are generally slight. Over the space of 20 years, about 20% of patients will show gradual proximal extension of the inflammation. Sulphasalazine (Salazopyrin) is a compound of sulphapyridine and 5- amino salicylic acid, which is split into its two components by bacterial action in the colon. It is now accepted that 5-amino salicylic acid is the active component. The drug is the mainstay of maintenance therapy in ulcerative colitis and many patients take it prophylactically over years. Unfortunately it is not so effective at preventing relapse in Crohn's disease. Side-effects are common, especially nausea and vomiting, but they are lessened with enteric-coated tablets. Other side-effets include skin rashes, headaches and rarely, blood dyscrasia. Oligospermia occurs, but is reversed if the drug continues. Azathiprine (Imuran) is of value in maintaining remission in chronic active CD. Some believe that it promotes the healing of fistulae. Side-effects, especially on hemopoiesis, can be severe, and it should only be used when other treatments are ineffective. Regular blood counts must be made. If colitis is active it is a serious mistake to give constipating drugs such as codeine phosphate or loperamide whereas there is a strong suspicion that they may precipitate toxic megacolon. However, after disease have been excised by right hemicolectomy, or colectomy and ileorectal anastomosis, these drugs are very helpful. After terminal ileal resection, cholestyramine may be useful. Sometimes lower abdominal pain is a feature of relapse and may be helped by antispasmodics such as mebeverine or propantheline (Jones et al '85: 234, 245, 240). Crohn’s disease has been effectively treated with 400 mg twice daily or 1 g daily of metronidazole (Flagyl ER).

Treatment for mild to moderate **ulcerative colitis** often begins with sulfasalazine (Azulfidine). Sulfasalazine (Azulfidine) works 40% to 80% of the time to make ulcerative colitis symptoms better or keep them from coming back. But it cannot be used by people who are allergic to or cannot tolerate sulfa drugs. Mesalamine (Asacol, Canasa, Rowasa), olsalazine (Dipentum), and balsalazide (Colazal) do not contain sulfa. So they may be used to treat mild to moderate ulcerative colitis if you cannot take sulfasalazine. Mesalamine enemas are effective in treating symptoms of mild to moderate distal (left-sided) ulcerative colitis and in maintaining remission. Mesalamine suppositories are preferred for people who have proctitis. The combination of a mesalamine pill (oral) and a mesalamine enema, foam, or suppository (topical) works better to treat left-sided colitis than either oral or topical mesalamine by itself (Friedman and Liechtenstein ‘6: 803-817). Patients with diverticular disease may respond to a high-fibre diet, the most popular way being to give wheat bran in one of its forms. Anti-cholinergic such as propantheline, or smooth muscle relaxants such as mebeverine, may be of value. If the pain is severe, analgesics may be required, but opiates (including codeine) should be avoided since these drugs increase intracolonic pressure and theoretically expose the patient to the risk of perforation of a diverticulum. Hospital treatment of infection, diverticulitis, involves intravenous gentamycin and metronidazole and analgesia for pain.

With regard to the digestive system, two families of **serotonin receptors** are extremely important: 5HT3 and 5-HT4. Alosetron is a 5-HT3 antagonist. This drug decreases the actions of this particular serotonin receptor and is effective in controlling diarrhea in IBS-D. It is perceived to be a somewhat dangerous drug, linked to cases of ischemic colitis (a bowel inflammation caused by too little blood flow) and in a very few cases, this was a fatal complication. Careful medical supervision helped make this drug effective. 5-HT4 Agonists (drugs that increase the action of this receptor) have found usefulness in IBS-C, but they also

present some difficulties and are not currently on the market in Canada or the United States. Several of these agents were on the market and have since been removed. The first was cisapride, which is quite effective in helping stomachs to empty. A few patients on this drug developed serious heart-rhythm disturbances, and there was even a rare death related to this agent. The most population drug in this family for treating IBS was tegaserod (Zelnorm), but the FDA felt the cardiac risks of this agent for a functional disease outweighed any potential benefit. Another drug in this category is prucalopride, now on the market in Europe and about to be launched in Canada and perhaps in the US. Prucalopride alters colonic motility patterns by stimulating serotonin 5-HT-4 receptors. It stimulates colonic mass movements, the main propulsive force in defecation. During the past 2 or 3 years there have been many favorable reports of this medication (Newman '11: 163).

Three groups of cells found in the bloodstream and in the intestinal tract have attracted much research interest of late – eosinophils, basophils and mast cells. Eosinophils are often seen in allergic situation or parasitic infestations. Basophils are white blood cells, which stain blue. Mast cells are tissue cells that are highly versatile producers of many really interesting chemicals and mediators, especially histamine, a mediator of inflammation. Mast cells are also in direct contact with the vagus nerves. Researchers have identified and characterized seven or more families of serotonin receptors and determining the effects of stimulating the receptors (agnoism) or inhibiting the receptors (antagonism). Numerous attempts have been made to use HT receptors for various manifestations of IBS and the hunt goes on. HT-1 is found in the central nervous system and in blood vessels. HT-2 is found in the GI tract and has a role in appetite, anxiety and gastrointestinal motility. The drug tegaserod is an HT-2 antagonist, that was at one time used to treat IBS-C, but had to be withdrawn from the market because of its cardiovascular side-effects. Alostron is an HT-3 antagonist and a wonderfully effective drug for IBS-D that had to be withdrawn from the market because of its side-effects. Because it worked so well and because so many IBS sufferers complained about its removal from the market, it was rereleased into the US market under rigid guidelines. There are many drugs within the family of HT-4 agonists that are of interest to gastroenterology, and this is quite an active field of investigation. One promising pharmaceutical product in this category is plucalopride, used for IBS-C is on the market in Europe and is soon to be released in Canada. There is little of interest to gastroenterology in the HT-5-7 families (Newman '11: 194, 195).

The **liver** aids in digestion, it is the largest gland in the body. The liver serves as a filter and clearing station for purifying blood, as a storage place for food (particularly sugar and vitamins) as a producer of various kinds of protein and antibodies, and as a remover of waste. Associated with the liver is the gallbladder, which stores bile. This substance is released into the intestine when a fatty meal is digested, the bile acids digest fat, and the bile salts help absorb fat and fat-soluble vitamins. Stonebreaker (Chanca piedra) cures urinary and gallstones overnight. *Hepatica nobilis* (Ranunculaceae) is reputed to cure all liver and bileous difficulties, as would the thallus of liverworts, a primitive group of nonvascular plants allied to mosses. The Houma Indians, boiled roots from *Solidago nemoralis* (goldenrod) for a tea to cure yellow jaundice. In the 19th century physicians used dandelion roots (*Taraxacum offinale*) and there is abundant evidence to show that the common dandelion supplies substances to the liver that the organ can utilize to enable it to perform its duties effectively. In England *Euonymus europaeus* was used for liver afflictions. Native American Indians used Rumex verticillatus (swamp dock) for jaundice, *Salix lucida* (red willow) for removing bile from the stomach, and *Zanthoxylum clava-herculis* (toothache tree) for obstructions of the liver. Fruit form *Emblica officinalis* in the *Euphorbiaceae*, which is very rich in vitamin C, is considered a good liver tonic in India (Elvin-Lewis '77: 288, 135, 289).

Alcoholic liver disease is the most prevalent form of liver disease in most Western countries. In the U.S. more than 10 million Americans are alcoholics, alcohol causes more than 200,000 deaths annually, the fifth leading cause of death and 25 to 30% of hospitalized patients have problems related to alcohol abuse. Short-term ingestion of up to 80 gm of ethanol per day (8 beers or 7 ounces of 80 proof liquor) generally produces mild, reversible hepatic changes, such as fatty liver. Daily ingestion of 160 gm or more of ethanol for 10 to 20 years is associated more consistently with severe injury; chronic intake of 80 to 160 gm/day is considered a borderline risk for severe injury. Only 10 to 15% of alcoholics however develop cirrhosis. Women tend to be more susceptible. Alcoholic hepatitis tends to appear relatively acutely, usually following a bout of heavy drinking. Each bout of hepatitis incurs about a 10 to 20% risk of death (Crawford '94: 857- 861). Alcohol withdrawal must be promptly diagnosed as being an acute cause of anxiety to the patient; untreated delirium tremens has a mortality of 15%. Commonly detoxification is accomplished with chlordiazeposide at a starting dose of 50 mg oraly every 6 hours with extra doses of 25 mg as needed to control symptoms. After an effective total daily dose has been reached, a taper of 10% total dose per day can be instituted. If parenteral administration is required, an equivalent dose of lorazepam can be used. In cases of hepatic dysfunction **oazepam** is the drug of choice. All suspected alcohol abusers should receive thiamine, 100 mg intramuscularly for 7 days (to help prevent Wernicki-Korsakoff encephalopathy) as well as folate, 1 mg daly, and multivitamins (Massie & Sinsheimer '90: 539). Metronidazole interacts badly with alcohol, but is otherwise the most effective antibiotic for the liver. Treatment of alcoholic liver disease should involve quitting drinking to effect a cure with medicines such as metronidazole.

When the liver does not work well toxins accumulate which may make the brain function abnormally, e.g cause encephalitis. Patients with liver disease may be confused, agitated or sleepy. One potential cause of this is accumulation of ammonia. **Lactulose** is sometimes used to help the body get rid of ammonia. Lactulose is given until the child has 3 or 4 loose stools per day. If the body gets rid of more ammonia, the child's mental state may improve. **Neomycin** is an oral antibiotic sometimes used to control the growth of ammonia-producing bacteria in the intestine. **NTBC** is a drug used to treat a metabolic liver disease called tyrosinemia. This drug, which was developed in Sweden, can reverse the liver failure that can be seen in infants with tyrosinemia. The drug does cause accumulations of tyrosine in the bloodstream. Patients are kept on a low protein diet so that tyrosine crystals do not accumulate in the eyes. Growth and development must be monitored carefully while on this drug. **Penicillamine** is a commonly used medicine for Wilson's disease. This drug chelates or binds with copper and leads to its secretion from the body. Patients on penicillamine are monitored since this drug can sometimes be tough on the kidneys or bone marrow. It can also affect wound healing. It is important to take penicillamine consistently, since patients with Wilson's disease who stop it have developed liver failure. Zinc therapy prevents the body from absorbing copper in Wilson's. Trientine, which removes copper from the body, is a third drug for Wilson's.

Monovalent Hepatitis A Vaccine (Havrix GSK) or (Vaqta Merck) can be used for the prevention of Hepatitis A, but if already infected wait a few months before being vaccinated. A Bivalent (Combination) Hepatitis A and Hepatitis B Vaccine (TWINRIX GSK) and Monovalent Hepatitis B Vaccine (Engerix-B; GSK) or Recombivax-HB; Merck) are also offered by health care professionals. Chronic viral hepatitis B is treated with Pegylated interferon alfa-2b (Pegasys), Nucleoside/nucleotide analogues (NAs) such as adefovir (Hepsera), entecavir (Baraclude), lamivudine (Epivir-HBV, Heptovir, Heptodin), telbivudine (Tyzeka) and tenofovir (Viread) (Sanders '11: 3). Ribavirin is an oral drug used for treatment of chronic hepatitis C.

This drug can cause anemia due to hemolysis, a process in which blood cells break down. Blood counts must be monitored during ribavirin therapy. Most importantly, ribavirin can cause severe damage to the developing fetus. It must not be taken by pregnant women and strict attention must be paid to birth control if a sexually active patient is taking ribavirin. Lamivudine is an oral drug used for treatment of chronic hepatitis B. It has very few side effects. Unfortunately, in a large fraction of treated patients the virus learns to mutate or change to avoid the drug's effects. Interferon injections are used for treatment of both chronic hepatitis B and hepatitis C, in different doses. As summarized in the section on viral hepatitis, interferon causes fevers, chills, and flu-like symptoms, especially with the first few doses. Drops in white blood cell counts can be seen and can require dose adjustment. Hepatitis C is treated with a combination of Pegylated interferon alfa-2b (Pegasys) and Ribavirin (Virazole), an antibiotic drug for certain viruses. By itself, ribavirin has little effect on HCV, but interferon increases its potency.

Primary carcinoma of the liver is much more common in colored races than in the white race, while malignancies in general are less frequent in colored people. Primary heptomas and 50 percent of primary cholangiomas are associated with cirrhosis. Teratomas of the liver are extremely rare. Primary cancer of the liver occurs much more frequently in the cirrhotic liver as compared with the normal liver that cirrhosis has been referred to as a precancerous lesion. There is no dispute that an adequate diet is essential in the treatment of liver disease. About 1:200 malignant tumors arise primarily in the liver. Most malignancies are metastatic in origin and are derived from the intestinal organs (Gerson '90: 68, 72), The following medicines are recommended to treat **hepatic itching**. Antihistamines hydroxyzine (Atarax) and diphenhydramine (Benadryl) are often the first drugs that are used. These may help the itching, usually by sedating the patient. Rifampin is an antibiotic which for some reason can also help itching. The patient should be monitored carefully since this drug can be hard on the liver. Ursodeoxycholic acid (Actigall or URSO) may also help itching by promoting bile flow. Questran is a material called a resin. This gritty substance binds bile salts in the stool, stimulating flow of bile from the liver. It should not be taken at the same time as certain other medicines such as URSO. **Prednisone** is a corticosteroid drug which is used to treat autoimmune hepatitis as well as to prevent rejection in liver transplant patients. Corticosteroids are normally made by the body in small amounts. Physicians may give these drugs in large amounts to suppress an overactive immune system. Prednisone causes bones to thin and may sometimes cause severe injury to bone. Prednisone can interfere with normal growth. Prednisone suppresses the immune system, making patients more susceptible to infection. Prednisone cannot be stopped suddenly since the adrenal glands, which normally make corticosteroids, may be suppressed. This can cause the patient to develop life-threatening adrenal insufficiency (the body goes into crisis due to lack of corticosteroids). Prednisone causes cosmetic changes such as weight gain, stretch marks and round, full cheeks. Facial acne may appear. Hypertension and cataracts are seen, mostly in adults, and mostly with prolonged treatment. Efforts are usually made to wean the dose down to the least amount that will keep the disease process under control. **Azathioprine** or Imuran (or a related drug called 6-MP or 6-mercaptopurine) may also be used to suppress the immune system, commonly in the context of autoimmune hepatitis. These drugs affect the DNA synthesis of rapidly dividing cells. Rarely, these drugs can cause hepatitis or pancreatitis. Low white counts are a more common problem, and blood work is monitored to assess this. An allergic reaction with fevers, rash, joint pains, gastrointestinal symptoms can develop 3 to 4 weeks after starting such a drug. Theoretically, since the drugs affect DNA repair, these drugs could be harmful to a developing infant, or even cause an increased risk of cancer. These are not common complications, although pregnancy should be undertaken with caution in patients on Imuran or 6-MP.

Gallstones afflict 10 to 20% of adults in developed countries. It is estimated that more than 20 million persons in the United States have gallstones, totaling some 25 to 50 tons in weight. About 1 million new patients annually are found to have gallstones, of whom approximately 600,000 undergo cholecystectomy. Nevertheless, the vast majority of gallstones (more than 80%) are "silent" and most individual remain free of biliary pain or stone complication for decades. In the West, about 80% of gallstones are cholesterol stones, containing more than 50% of crystalline cholesterol monohydrate. The remainder are composed predominantly of bilirubin calcium slats and are designated pigment stones. The prevalence of cholesterol gallstones approaches 75% in certain native American population: the Pima, Hopi and Navajo. Gallstones are more prevalent in industrialized societies. The prevalence of gallstones increases with age. In the United States less than 5 to 6% of the population under the age of 40 have stones, in contrast to 25 to 30% of those over age 80. The prevalence in which women is about twice as high as in men. Hypersecretion of biliary cholesterol appears to play the major role. Obesity and rapid weight loss are strongly associated with increased biliary cholesterol secretion. Infection of the biliary tract, as with *Escherichia coli*, *Ascaris lumbricoides*, or in Asia, by the liver fluke, *Opishtochis sinensis*, induces deconjugation of excreted bilirubin. It appears that asymptomatic patients convert to symptomatic ones at a rate of 1 to 3% per years (Crawford '94: 884). The herbal remedy is works overnight. Ingredients of the new formulation of Stone Breaker™: formerly Madden/Hydrangia now includes extracts of: Stonebreaker herb (*Phyllanthus niruri*), Hydrangea root (*Hydrangea arborescens*), Celery seed (*Apium graveolens*), Burdock seed (*Arctium lappa*); and other Ingredients: certified organic grain alcohol & distilled water. The old formula of this over-the-counter formula available online, not prescribed by physicians, has been known to completely dissolve plain x-ray film detectable urinary stones in two days to avoid surgery and make a complete recovery. The new formula is far more edible and reasonable to the common naturopath but untried. At around $10 a bottle and no known side-effects it should definitely be taken before surgery or expensive medical treatment. Caution: Do not take during pregnancy and keep out of reach of children. Shake well before taking 40 drops in a full cup of water, three times per day. For children Clark's rule is to divide the child's weight (in pounds) by 150 to get the fraction of the adult dose to give to the child. Example: For a 50 pound child give 50/150 (or 1/3) of the adult dose. Therefore, if the adult dose is 40 drops taken 3 times per day, the child's dose will be 13.3 drops taken 3 times per day. Some extracts are not suitable for children. Consult your doctor for advice.

The nonspecific **infections of the genitourinary tract** are caused mainly by aerobic gram-negative rods (e.g., *Escherichia coli*, *Proteus mirabilis, Enterobacter spp., Gardnerella vaginalis [Haemophilus vaginalis], Klebisella spp., Proteus mirabilis, Proteus spp* [indole-positive], *Pseudomonas aeruginosa, Serratia spp.*) and gram-positive cocci (e.g. staphylococcus, *Staphylococcus aureus*, *S. epidermidis*, *S. saprophyticus*; enterococci; *Streptococcu*s Group D, *S. fecalis S. bovi*, Streptococcus, group B) and to a lesser extent by obligate anaerobic bacteria (e.g. *Bacteroides fragilis*, *peptrostreptococci*). In addition, nonspecific infections of the urethra frequently are caused by organisms that require special techniques of identification (e.g. *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Gardnerella vaginalis, Candida spp.*). Most uncomplicated urinary tract infections acquired outside the hospital environment are caused by coliform bacteria, chiefly *E. coli*. These pathogens tend to be susceptible to a variety of oral antimicrobial agents and respond quickly to short-term therapy. Hospital-acquired (nosocomial) infections often involve more resistant pathogens (e.g., *Pseudomonas aeruginosa*, *Serratia marcescens*) and may require parenteral antimicrobial agents. Infections caused by urease-producing (urea-splitting) organisms (e.g, *P. mirabilis*) are associated with markedly alkaline urine and a tendency for phosphates to precipitate form the urine to form magnesium ammonium phosphate (struvite) and calcium phosphate (apatite)

urinary stones. These infections can involve any of the genital or urinary organs and eventually can spread form one site to all of the others. Renal infections are of the greatest importance because of the parenchymal destruction. Antimicrobial sensitivity testing is often of paramount importance in clinical management (Meares '88: 196). Cranberry juice can prevent urinary tract infections because of proanthocyanidin, a prebiotic compound found in cranberries. It supports probiotics, and helps ward off UTIs, by preventing *E. coli* from attaching to the cells that line the urethra and the bladder. When *E. coli* can't cling to the walls of the urinary tract, they're swept away by the normal flow of urine. A 2004 review recommended one tablet of concentrated cranberry extract (300 to 400 mg) twice daily or 8 ounces of pure unsweetened cranberry juice three times daily. Care should be taken in recommending long-term use in people who have a history of kidney stones because cranberries also contain oxalate, a chemical that can create kidney stones when it combines with calcium (Huffnagle '07: 164, 165). Metronidazole (Flagyl ER) is completely absent from the long lists of antibiotics used in urology, although it is the only antibiotic that does not cause abdominal side-effects or deplete vitamin B^{12}. A course of metronidazole should be tried before undergoing elective surgery by a urologist whose literature neither prescribes nor warns of nephrotoxicity.

If the pathogen causing a urinary tract infection is not identified, infection with a gram-negative rod should be assumed. Empiric antibiotic therapy must be started immediately. Since most uncomplicated infections occurring outside the hospital environment are due to strains of *E. coli* sensitive to many antibiotics, metronidazole is usually effective. Hospital treatment need not await the results of culture and sensitivity tests. An aminoglycoside (amikacin, gentamicin, or tobramycin) is the drug of choice. Give amikacin, 5 mg/kg intravenously every 8 hours; or gentamycin, 1.5 mg/kg intravenously every 8 hours; or tobramycin, 1.5 mg/kg intravenously every 8 ours. If *P. aeruginosa* infection is suspected, give carbenicillin, 406 g intravenously every 4-6 hours ,or ticarcillin, 306 g intravenously every 6 hours, in addition to the aminoglycoside. If **sepsis** arising from a primary urinary tract infection involving enterococci is suspected therapy combining aminoglycoside with ampicillin, 2 g intravenously every 4-6 hours is indicated. For suspected polymicrobic infection involving gram-negative bacilli and anaerobes (especially *Bacteroides* species), optimal therapy consists of an aminoglycoside plus clindamycin, 450-600 mg intravenously every 6 hours. Drug dosage must be adjusted appropriately if renal failure is present and the drugs are not being adequately excreted in the urine. Once **septic shock** is suspected, give 1000 mL of crystalloid solution (e.g., normal saline solution, lactated Ringer's injection) intravenously over a 20 to 30 minute period unless congestive heart failure is present. Colloid solutions (albumin or low-molecular-weight dextran) should be administered as soon as possible, because their oncotic pressure tends to draw plasma back into the capillaries and this lessens tissue and cellular edema and helps to wash sludged red and white cells and platelets into the general circulation. Low-molecular weight dextran decreases blood viscosity and combat platelet adhesiveness. As long as central venous pressure (CVP) does not exceed 14 cm of water or the pulmonary capillary wedge pressure (PCWP) does not exceed 22 mm Hg, volume expansion with both crystalloid and colloid solution is continued at a rate of 15-20 mL/min. A sudden or continuously progressive increase in CVP of over 5 cm of water of CVP level greater than 14 cm of water, or an increase in PCWP of over 8 mm Hg or a PCWP level greater than 22 mm Hg, implies possible fluid overload and requires a cutback in infusion rates. The usual goal is to raise the blood pressure to a level about 20 mm Hg less than the normal systolic blood pressure observed before the onset of shock and maintain this level. The urinary output should be maintained at 40-50 mL/h. In most cases, antibiotic therapy plus correction of the circulating blood volume is all that is needed for complete recovery. Persistent oliguria may imply **acute renal tubular necrosis**, it should be treated by intravenous infusion of mannitol, 12.5 g over 5 minutes and repeated after 2 hours if a urine flow of 30 to 40 mL/h is not

achieved. Furosemide, 240 mg, is given intravenously at the time of the second infusion of mannitol. If the response to mannitol and furosemide is poor, furosemide, 480 mg, is given intravenously. If the response to this large second dose of furosemide is poor, no further attempts at diuresis are indicated and standard therapy for acute renal failure is initiated. Dialysis may become necessary (Meares '88: 221, 210, 211).

Tubercle bacilli may invade one or more or the organs of the genitourinary tract and cause a chronic granulomatous infection that shows the same characteristic as tuberculosis in other organs. Rifampin 600 mg, ethambutol 1.2 g and isoniazid (INH) 300 mg daily is the most efficacious . If resistance to first line treatment occurs one of two alternative regimes may be tried (1) cycloserine 250 mg twice daily, aminosalicylic acid (PAS) 15 g in divided doses and INH 300 mg daily, or (2) cycloserine 250 mg twice daily, ethambutol 1.2 g, and INH 300 mg daily. Most authorities advise appropriate medication for 2 years but a 6 month course may be adequate. If, after 3 months, cultures are still positive and gross involvement of the kidneys or epididymis is radiologically evident, nephrectomy or epididymectomy should be considered. Vesical instillation of 0.2% monoxychlorosene (Clorpactin) may stimulate the healing of tuberculosis of the bladder. If ureteral stricture develops, ureteral dilatations offer a better than 50% chance of cure. The prognosis varies with the extent of the disease but the overall control rate is 98% at 5 years (Tanagho '88: 246-252).

Candida albicans is a yeast-like fungus that is a normal inhabitant of the respiratory and gastrointestinal tract and vagina. The intensive use of antibiotics is apt to disturb the normal balance between normal and abnormal organisms, thus allowing fungi such as Candida to overwhelm an otherwise healthy organ. The bladder and, to a lesser extent, the kidneys have proved vulnerable. The patient may present with signs of pyelonephritis and fungus balls may be passed spontaneously. The diagnosis is made by observing mycelial or yeast forms of the fungus microscopically in a urine specimen. The diagnosis may be confirmed by culture. Vesical candidiasis usually responds to alkalinization of the urine with **sodium bicarbonate**. A urinary pH of 7.5 is desired. Should this fail **amphotericin B** should be instilled via catheter 3 times daily. Dissolve 100 mg of the drug in 500 mL of 5% dextrose solution the concentration should be 0.1 mg/mL. If there is renal involvement, irrigation of the renal pelvis with a similar concentration of amphotericin B are efficacious. The disadvantages of Amphotericin B (Fungizone) are that it is nephrotoxic and requires parenteral administration. In the presence of systemic manifestation or candidemia flucytosine (Ancobon) or ketoconazole are the drugs of choice. The dose of flucytosine is 100 mg/kg/day orally in divided doses, 400 mg 3 times daily for 1 week. The dose of ketoconazole is 200-400 mg/day for 2-4 weeks or longer. In the face of serious involvement, give 600 mg intravenously on the first day and then shift to the oral form of the drug (Tanagho '88: 253, 254).

More than 5 percent of Americans have had kidney stones. They prompt about 2.7 million consultations with healthcare providers and more than 600,000 emergency room visits. Men are more likely to develop them problems than women, and anyone who has had kidney stones in the past is vulnerable to a recurrence. A kidney stone that produces severe pain is readily diagnosed by an X-ray, CT scan or ultrasound. Archeologic studies show that **urinary tract stone disease** was an affliction of humans earlier than 4800 B.C. Ancient Greek and Roman physicians recorded the symptoms and treatment of urologic stone disease. In the 20th century, advances in technology and microscopic techniques have led to a better understanding of the structural characteristics of calculi, their chemical composition, and the various components of urine (Spirnak & Resnick '88: 275); however, the herbal stone dissolution remedies seem to have been forgotten in a rush to perform expensive surgeries. The herbal remedy Stone Breaker (Chanca

Piedra) is works overnight. Ingredients of the new formulation of Stone Breaker (Chanca piedra) formerly Madden/Hydrangia now includes extracts of: Stonebreaker herb (*Phyllanthus niruri*), Hydrangea root (*Hydrangea arborescens*), Celery seed (*Apium graveolens*), Burdock seed (*Arctium lappa*); and other Ingredients: certified organic grain alcohol & distilled water. The old formua of this over-the-counter formula available online, not prescribed by physicians, has been known to completely dissolve plain x-ray film detectable urinary stones in two days to avoid surgery and make a complete recovery. The new formula is far more edible and reasonable to the common naturopath but untried. At around $10 a bottle and no known side-effects it should definitely be taken before surgery or expensive medical treatment. Caution: Do not take during pregnancy and keep out of reach of children. Shake well before taking 40 drops in a full cup of water, three times per day. For children Clark's rule is to divide the child's weight (in pounds) by 150 to get the fraction of the adult dose to give to the child. Example: For a 50 pound child give 50/150 (or 1/3) of the adult dose. Therefore, if the adult dose is 40 drops taken 3 times per day, the child's dose will be 13.3 drops taken 3 times per day. Some extracts are not suitable for children.

Acute urinary retention is best managed by an indwelling Foley catheter left in place for 2-3 days. When the catheter is removed, the patient usually resumes a fairly normal voiding pattern, since vesical tone has been reestablished and **prostatic congestion** relieved (Johnson et al '88: 361-364). 80% of 200 patients using phenoxybenzamine, an α-adrenergenic blocker, experienced symptomatic relief. Uroflowmetry in 102 patients showed the flow to be more than doubled in nearly one-half of patients and increased by more than 50% in another one-fourth. Improvement was noticed within the first 2 days of therapy and reached its maximum after 7 days of treatment. The drug did not reduce the size of the prostate. Side-effects, reported by 30%, include hypostatic hypotension resulting in dizziness and tachycardia, retrograde ejaculation, fatigue and nasal congestion, only 10% felt it was so severe they discontinued treatment. **Castration** was observed to relieve urinary obstruction due to benign prostatic hyperplasia in the late 1800s. An 87% decrease in prostate size was reported in 111 patients so treated. In a series of 61 patients in 1896 reported that urinary retention disappeared in 27 and that 50 showed overall marked improvement following castration. Androgen deprivation affects the prostate. Androgen deprivation can be achieved by administration of estrogens but estrogens play a direct role in the development of benign prostatic hyperplasia. **Cyproterone acetate**, an antiandrogen, caused 11 of 13 patients in 1969 to experience subjective improvement including increased urinary flow rate and decreased volume of residual urine. An objective decrease in the epithelial cell size was apparent in 8 of 11 patients whose prostatic biopsies were available. **Flutamide**, a nonsteroidal veterinary antiandrogen, is a potent inhibitor of testosterone-induced prostatic growth, however a study in 1975 found that early subjective improvement in 30 patients was not maintained, and no significant change occurred in the size of the prostate or the volume of residual urine. A study of **Megestrol acetate** demonstrated a decrease in prostate size and improved urinary flow rates in 8 of 13 patients, however, the changes were insignificant. Cyproterone acetate seems to be the most highly recommended medicinal remedy for urinary retnetion (Johnson et al '88: 364, 365).

In the early 1960s came the development of **hemodialysis**, a method of removing waste products from the blood when the kidneys are unable to perform this function, to sustain the lives of patients with end-stage kidney disease. As kidney function deteriorates, doctors use the term renal insufficiency. When kidney function is extremely poor, and eventually absent, it’s called renal failure. At this point, the patient will die in the course of a couple of weeks if he or she does not undergo kidney dialysis, a complicated but routine procedure whereby the blood is withdrawn from a vein, sent through a series of external filters to remove toxins and water, and

returned to circulation. People can live for years undergoing dialysis, although their quality of life is usually significantly diminished. The other option for a patient with end-stage kidney disease is to undergo a kidney transplant operation (Wilson ’06: 38). As a result of this treatment advance, these patients were able to survive the underlying disease, but their damaged kidneys could no longer make erythropoietin, leaving them severely anemic and in desperate need of Epo therapy. In 1983, scientists discovered a method for mass producing a synthetic version of the hormone. Experiments were conducted to test the safety and effectiveness of the new drug, **Epo**, for treating anemia in patients with kidney failure. The results of these early clinical trials were dramatic. Patients who had been dependent on frequent blood transfusions were able to increase their red blood cell levels to near-normal within just a few weeks of starting therapy. Patients’ appetites returned, and they resumed their active lives. It was the convergence of two technologies – long-term dialysis and molecular biology – that set the stage for anemia management in this group of patients. Since then, millions of patients worldwide have benefited from Epo therapy (Adamsom '08). **Chronic periotoneal dialysis** is used electively, either intermittent thrice-weekly treatment (IPPD) or chronic ambulatory peritoneal dialysis (CAPD) is possible. With the latter, the patient performs 3-5 daily exchanges using 1-2 L of dialysate at each exchange. Bacterial contamination and peritonitis are becoming less common with improvements in technology. Chronic hemodialysis using **semipermeable dialysis membranes** is now widely performed. Access to the vascular system is by means of Scribner shunts, arteriovenous fistulas and grafts . The actual dialyzer may be of a parallel plate, coil or hollow fiber type. Bodty solutes and excessive body fluids can be easily cleared by using dialysate fluids of known chemical composition. Newer high efficiency membranes are serving to reduce dialysis treatenttime. Treatment is intermittent – usually 3-5 hours 3 times weekly. It may be givin in a kidneuy ceter, a satellite unit or the home. Home dialysis is optimal., but only 30% of dialysis patients meet the medical and training requirements for this type of therapy. Common problems with either type of chronic dialysis include infection, bone symptoms, technical accidents, persistent anemia, and psychologic disorders. Atherosclerosis often occurs with long-term treatment. Yealy costs range from an average of $15,000 for patients who receive dialysis at home to as much as $30,000-$50,,000 for patients treated at dialysis centers, but much of this is absorbed by Medicare. The mortality rates are 8-10% per year once maintenance dialysis therapy is instituted (Amend & Vincenti '88: 530-532).

A cornerstone of post-transplantation management is immunosuppression to prevent rejection of the transplant graft. The rejection response after liver transplantation most often occurs between postoperative days 4 and 10. Clinical manifestations of **acute rejection** include tachycardia, fever, right upper quadrant or flank pain, diminished bile flow through the T tube or a change in color of bile, and increasing jaundice. Laboratory findings include elevated serum bilirubin, transaminase and alkaline phosphatase levels and increased prothrombin time. Following the successful os of cyclosporine, a number of immunosuppressive drugs have appeared and provide several choices for improving outcome. **Immunosuppressives** may be broadly categorized into three groups: initial immunosuppression, maintenance immunosuppression, and management of acute cellular rejection. Prednisone is the primary posttransplantation immunosuppressive and is steadily tapered off in favor o maintenance drugs. The calcineurin inhibitors cyclosporine and tacrolimus are begun during induction and represent the mainstays of maintenance therapy. In many centers, tacrolimus has supplanted cyclosporine as the preferred immunosuppressive. Adjunctibe maintenance agents include either mycophenolate mofetil or the older drug aathiprine. Acute rejection is managed with infusion of either muromonab-CD3 (OKT#) or an interleukin-2 receptor blocker (e.g. basiliximab) (Sartin '05: 955).

Insulin is a naturally-occurring hormone secreted by the pancreas. Insulin is required by the cells of the body in order for them to remove and use glucose from the blood. From glucose the cells produce the energy that they need to carry out their functions. Researchers first gave an active extract of the pancreas containing insulin to a young diabetic patient in 1922, and the FDA first approved insulin in 1939. Currently, insulin used for treatment is derived from beef and pork pancreas as well as recombinant (human) technology. The first recombinant human insulin was approved by the FDA in 1982. Brands of Insulin (Humulin, Humulin 70/30, Humulin 70/30 Pen, Humulin 50/50, Humulin L, Humulin N, Humulin R, Humulin U Ultralente, Novolin, Novolin 70/30, Novolin 70/30 Innolet, Novolin 70/30 PenFill, Novolin N, Novolin R). Patients with diabetes mellitus have a reduced ability to take up and use glucose from the blood, and, as a result, the glucose level in the blood rises. In type 1 diabetes, the pancreas cannot produce enough insulin. Therefore, insulin therapy is needed. In type 2 diabetes, patients produce insulin, but cells throughout the body do not respond normally to the insulin. Nevertheless, insulin also may be used in type 2 diabetes to overcome the resistance of the cells to insulin. By increasing the uptake of glucose by cells and reducing the concentration of glucose in the blood, insulin prevents or reduces the long-term complications of diabetes, including damage to the blood vessels, eyes, kidneys, and nerves. Insulin is administered by injection under the skin (subcutaneously). The subcutaneous tissue of the abdomen is preferred because absorption of the insulin is more consistent from this location than subcutaneous tissues in other locations. Insulin is required in all patients with type 1 diabetes mellitus, and mandatory in the treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic states. The American Diabetes Association (ADA) and many clinicians recommend the use of physiologically based, *intensive* insulin regimens (i.e., 3 or more insulin injections daily with dosage adjusted according to the results of multiple daily blood glucose determinations [e.g., at least 4 times daily]. In general, adjust dosage of insulin based on blood and urine glucose determinations and carefully individualize to attain optimum therapeutic effect. Administer into the thighs, upper arms, buttocks, or abdomen using a 25- to 28-gauge needle, one-half to five-eighths inch in length. Insulin (regular) (i.e., purified pork insulin) generally is given sub-Q in a dosage of 2–4 units, 15–30 minutes before meals and at bedtime. No change in dosage usually is required when transferring to insulin human, Initiate replacement therapy at an insulin dosage of 0.5–1 units/kg daily given sub-Q in divided doses ((2/3) of the daily dosage in the morning [(1/3) as short-acting insulin, (2/3) as intermediate-acting insulin] and (1/3) in the evening [½ as short-acting insulin, ½ as intermediate-acting insulin]). In pediatric patients with newly diagnosed diabetes mellitus, may administer 0.1–0.25 units/kg of regular insulin every 6–8 hours during the first 24 hours to determine insulin requirements.

The first treatment for type 2 diabetes blood glucose (sugar) control is often meal planning, weight loss, and exercising. Sometimes these measures are not enough to bring blood glucose levels down near the normal range. The next step is taking a medicine that lowers blood glucose levels. All diabetes pills sold today in the United States are members of six classes of drugs that work in different ways to lower blood glucose (blood sugar) levels: Sulfonylureas, Meglitinides, Biguanides, Thiazolidinediones, Alpha-glucosidase inhibitors and DPP-4 inhibitors. **Sulfonylureas** stimulate the beta cells of the pancreas to release more insulin. Sulfonylurea drugs have been in use since the 1950s. Chlorpropamide (Diabinese) is the only first-generation sulfonylurea still in use today. The second generation sulfonylureas are used in smaller doses than the first-generation drugs. There are three second-generation drugs: glipizide (Glucotrol and Glucotrol XL), glyburide (Micronase, Glynase, and Diabeta), and glimepiride (Amaryl). These drugs are generally taken one to two times a day, before meals. All sulfonylurea drugs have similar effects on blood glucose levels, but they differ in side effects, how often they are taken, and interactions with other drugs. **Meglitinides** are drugs that also stimulate the beta cells to

release insulin. Repaglinide (Prandin) and nateglinide (Starlix) are meglitinides. They are taken before each of three meals. Because sulfonylureas and meglitinides stimulate the release of insulin, it is possible they cause hypoglycemia (low blood glucose levels). Alcohol and some diabetes pills may not mix. Occasionally, chlorpropamide and other sulfonylureas, can interact with alcohol to cause vomiting, flushing or sickness. Metformin (Glucophage) is a **biguanide**. Biguanides lower blood glucose levels primarily by decreasing the amount of glucose produced by the liver. Metformin also helps to lower blood glucose levels by making muscle tissue more sensitive to insulin so glucose can be absorbed. It is usually taken two times a day. A side effect of metformin may be diarrhea, but this is improved when the drug is taken with food. Rosiglitazone (Avandia) and pioglitazone (ACTOS) are in a group of drugs called **thiazolidinediones**. These drugs help insulin work better in the muscle and fat and also reduce glucose production in the liver. The first drug in this group, troglitazone (Rezulin), was removed from the market because it caused serious liver problems in a small number of people. So far rosiglitazone and pioglitazone have not shown the same problems, but users are still monitored closely for liver problems as a precaution. Both drugs appear to increase the risk for heart failure in some individuals, and there is debate about whether rosiglitazone may contribute to an increased risk for heart attacks. Both drugs are effective at reducing A1C and generally have few side effects. Acarbose (Precose) and meglitol (Glyset) are **alpha-glucosidase inhibitors**. These drugs help the body to lower blood glucose levels by blocking the breakdown of starches, such as bread, potatoes, and pasta in the intestine. They also slow the breakdown of some sugars, such as table sugar. Their action slows the rise in blood glucose levels after a meal. They should be taken with the first bite of a meal. These drugs may have side effects, including gas and diarrhea. A new class of medications called **DPP-4 inhibitors** help improve A1C without causing hypoglycemia. They work by by preventing the breakdown of a naturally occurring compound in the body, GLP-1. GLP-1 reduces blood glucose levels in the body, but is broken down very quickly so it does not work well when injected as a drug itself. By interfering in the process that breaks down GLP-1, DPP-4 inhibitors allow it to remain active in the body longer, lowering blood glucose levels only when they are elevated. DPP-4 inhibitors do not tend to cause weight gain and tend to have a neutral or positive effect on cholesterol levels. Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin (Nesina) are the DPP-4 inhibitors currently on the market in the US. Because the drugs listed above act in different ways to lower blood glucose levels, they may be used together. For example, a biguanide and a sulfonylurea may be used together. Many combinations can be used. Though taking more than one drug can be more costly and can increase the risk of side effects, combining oral medications can improve blood glucose control when taking only a single pill does not have the desired effects. Switching from one single pill to another is not as effective as adding another type of diabetes medicine.Generic versions of some sulfonylureas are available. These cost less than brand-name products and in general are reliable. There is now a generic Metformin (Glucophage). To save more money, ask for the largest tablet strength suitable for the dose needed. One 500-mg tablet, for example, often costs much less than two 250-mg tablets, and can be split. Diabetes pills aren't perfect, but they can help to lower glucose levels for many people with type 2 diabetes.All diabetes pills can interact with other medicines. Any sulfonylurea or meglitinide can cause blood glucose levels to drop too low (hypoglycemia). Metformin or the glitazones rarely cause hypoglycemia unless taken with insulin stimulators (sulfonylureas or repaglinide) or insulin injections. Acarbose or miglitol, taken as prescribed, does not cause hypoglycemia. However, hypoglycemia can occur when acarbose or meglitol is taken in combination with other diabetes medications. For pancreatic cancer diagnosed as insuloma Diazoxide inhibits release of insulin and has a peripheral hyperglycemic effect, a benzothiadizine diuretic should be given with diazoxide. Propranolol and glucocorticoids have also been used.

A deficiency in antidiuretic hormone (ADH) production by the posterior pituitary gland results in diabetes insipidus. People with **diabetes insipidus** are unable to concentrate urine normally and therefore excrete a large volume of urine. These individuals can have urinary flow rates as high as 25 L/day. Thirst increases as a result of the dehydration caused by the high urinary flow. People with neurogenic diabetes insipidus have high urine volume and a low urinary osmolality. If ADH is administered to people with this condition, they respond with a decrease in urinary volume and an increase in urinary osmolality. Those with nephrogenic diabetes insipidus have normal ADH production but lack a normal renal ADH response. If ADH is administered, the urinary flow rate does not decrease. Those with psychogenic diabetes insipidus are compulsive water drinkers. If water is withheld, the ADH secretion increases and urinary flow decreases while osmolality increases. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is associated with pulmonary tuberculosis and Grave's disease (the most prevalent form of hyperthyroidism). If water is restricted in an individual with this condition, serum sodium and osmolality will return to normal. Loss of mobility and urinary tract infection can cause nocturia and hyperuremia. Metronidazole is useful for treating urinary tract infections.

The fundamental principles of **naturopathic medicine** is defined primarily by its fundamental principles (1) the healing power of nature (2) do no harm (3) identify and treat the cause (4) treat the whole person (5) physician as teacher (6) prevention is the best care (7) establish health and wellness. Naturopathic medicine uses a variety of modalities including (1) nutrition (2) botanical medicine (3) homeopathy (4) counseling (5) lifestyle management (6) naturopathic physical medicine (7) vitamin and mineral therapy. A licensed Naturopathic physician (ND) attends a four-year graduate level naturopathic medical school. The education includes all of the same basic science courses as an M.D. along with holistic and nontoxic approaches to therapy with a strong emphasis on disease prevention and optimizing whole body wellness. In addition to a standard medical curriculum, the naturopathic physician is required to complete four years of training in clinical nutrition, homeopathic medicine, botanical medicine, naturopathic manipulation technique and counseling. Naturopathic physicians take professional board exams in order to be licensed by a state or jurisdiction as a primary care, general practice physician. There is no denying the logic and effectiveness of homeopathic remedies, such as **chamomile tea**, for digestive disorders. IBD Soothing GI Tea Peppermint and Chamomile. IBD Gas Relief Tea 1 part ground fennel seeds, 1 part ground fenugreek seeds, 1 part althaea (marshmallow) root, 1 part slippery elm bark (Black ’10: 111, 112, 143-144).

The best approach to preventing heart disease and cancer is the tried-and-true combination of exercise and eating a healthy diet (Mooney '07: 76). Meat centered diets are are almost always high in fat and low in fiber, resulting in a slow transit time through the colon and allowing toxic wastes to do their damage. True carnivores move raw meat through their digestive tract quickly, within about three hours. Humans, with their long digestive tracts, take between twelve and eighteen hours to process and digest flesh. Because the environment of the digestive tract is warm and moist, the meat rot and creates free radicals – unstable destructive oxygen atoms atoms that can cause cancer, premature aging, and other degenerative conditions. William Cestelli, MD, former director of the Framingham Heart Study, of the National Health, Lung and Blood Institute writes, “A low-fat, plant-based diet would not only lower the heart attack rate about eighty five percent, but would lower the cancer rate sixty percent.” (Swami '06: 4).

A **vegan diet** is necessary to treat atherosclerosis. The small portions of animal products tolerated by the American Medical Association, American Heart Association and other cardiologists help to prevent death, but allowing the consumption of any fat and cholesterol whatsoever, perpetuates the painful and life-threatening atherosclerosis. Anyone suffering

angina pectoris should keep a strictly vegan diet – brown rice and vegetables boiled in water is a nutritious staple that can be eaten twice a day perhaps with green salad with vinaigrette dressing, and a large fruit salad for breakfast. A vegan is someone who avoids all animal products; milk, eggs and all dairy products and by-products as well as all foods that contain these ingredients. The vegetable protein tolerance for heart disease is much higher than for cancer but complete vegetable proteins found in wheat gluten and vegetable combinations such as rice and beans and beans and corn can be cardiotoxic and should be avoided or minimized to less than 10% of meal mass. A vegetarian or lacto-ovo-vegetarian (including eggs) diet should be used as maintenance once a person has achieved an ideal weight.

Human teeth, like those of all herbivores, are designed for grinding and chewing. Humans lack the sharp canine teeth designed for tearing flesh that are characteristic of all carnivores. Meat-eating animals generally swallow their food without chewing it, so they require neither molars nor sideways-moving jaws. The human hand, is better suited to harvesting fruit and vegetables than to killing prey. Carnivorous animals can metabolize almost unlimited amounts of cholesterol and fat without adverse effect. In experiments with dogs, up to half a pound of butterfat was added to their daily diet over a period of two year, producing absolutely no change in their serum cholesterol level. Herbivorous creatures have a very limited ability to deal with any cholesterol or saturated fat. Fatty deposits (plaque) accumulate on the inner walls of the arteries, producing a condition known as atherosclerosis, or hardening of the arteries. Because the plaque deposits constrict the flow of blood to the hearts, the potential for heart attacks strokes, and blood clots is tremendously increased. As early as 1961, the Journal of the American Medical Association stated that 97 percent of heart disease in the United States could be prevent by a vegetarian diet. These findings are supported by an American Heart Association report that high-saturated fat diets cause heart disease. There is a 3-4 percent drop in the risk of heart disease for every one percent decrease in blood cholesterol. Blood cholesterol levels of vegetarians are 14 percent lower and the risk of death from heart disease or vegetarians compared to non-vegetarians one-half (Swami '06: 1-4).

Remedies for Hyperlipidemia

Drug	Indication
Statins	HMG-CoA reductase inhibitors (statins): Used to prevent cholesterol buildup in the coronary arteries. Can also prevent the inflammatory response that could cause atheromatous plaques to rupture in the heart and precipitate a heart attack. Side effects include muscle and liver injury.
Vitamin	
Niacin vitamin B3 (nicotinic acid), cholestyramine, gemfibrozil, clofirate:	Used to treat high cholesterol and high triglycerides.
Vitamin E	Antioxidant, regulation of oxidation reactions, supports cell membrane stabilization. Found in polyunsaturated plant oils (soybean, corn and canola oils), wheat germ, sunflower seeds, tofu, avocado and sweet potatoes.
Vitamin K	Synthesis of blood-clotting proteins, regulates blood calcium Found in Brussels sprouts, leafy green vegetables, spinach, broccoli and cabbage.
Mineral	Indication

Selenium	Antioxidant. Works with vitamin E to protect body from oxidation. Found in grains.
Culinary Herb	Indication
Garlic *Allium sativum*	Garlic, antibiotic, helps to maintain healthy blood cholesterol and prevent blood platelet aggregation, making it the herb of choice for many circulatory issues and lowers blood sugar levels in Type 2 diabetes
Ginger *Zingiber officinale*	Ginger lowers blood level triglycerides linked to diabetes and heart disease.
Rhododendrum caucasium	Antioxidant, blocks carcinogen absorption and 20% of fat absorption through intestines. Increases energy in heart muscles and uric acid excretion. Relaxes blood vessels, lowers blood pressure.
Rosemary *Rosmarinus offinalis*	Rosemary is a circulatory stimulant useful for the treatment of poor circulation and low blood pressure.
Sage *Salvia officinalis*	Sage is a superb aid in the digestion of rich, fatty meat. It also lowers cholesterol levels and is a bitter tonic for the liver. It rebuilds vitality and strength during long-term illness. Sage tea is a warming, bracing drink, nice mixed with mint or rosemary and lemon balm.
Hawthorne *Crataegus laevigata*	Hawthorn is considered the herb supreme for the heart. The berries, leaves and flowers are rich in bioflavonoids, antioxidants, and procanidins, which feed and tone the heart. Hawthorn works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy cholesterol levels. Hawthorn is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorn doesn't store in the body and isn't accumulative in action, it's important to take on a regular basis if using as a heart tonic. Hawthorn also helps to stabilize collagen and support the health and repair of ligaments, tendons and muscles. Hawthorn strengthens capillaries and heals bruises. The berries are tasty and often enjoyed in syrups, jams and jellies or dried infusions.
Lemon balm *Melissa officinalis*	Remedy for heart disease (and heartache), depression and anxiety, nervous disorders and a host of viral and bacterial infections. Paralesus called lemon balm the "elixir of life" and Dioscorides used it for "sweetening the spirit". In the 1600s herbalist John Evelyn wrote "balm is sovereign for the brain, strengthening the memory and powerfully chasing away melancholy". Because it's so delicious lemon balm is often prepared as tea, but it is also tasty as a culinary herb. Lemon balm is considered a thyroid inhibitor, those suffering from hypothyroidism or low thyroid activity should use it only under the guidance of a health care practitioner.
Valerian *Valeriana officinalis*	Valerian has a tonic effect on the heart and is especially recommended in cases of irregular heartbeat and anxiety that affects the heart. It is often combined infusion with hawthorne

	berry to treat high blood pressure and irregular heartbeat. For those people for whom valerian works, it works well. Some people find it irritating and stimulating, rather than relaxing.

Source: Gladstar '12; Brown '04: 82, 83

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Besides a vegan diet, an athletic level of cardiovascular exercise and sporadic prophylaxis with NSAIDs, antibiotics and antifungal drug to cure rheumatic complaints and achieve higher levels of athletic performance hopefully transcending concerns about health to develop beautiful large strong muscles, even on rainy days or when crippled by an idiopathic disorder. **Statin** cholesterol lowering drugs are an essential medicine for reducing the risk of death from heart attack or ischemic stroke but recovery is not given as a reason for discontinuing statin use. Statin drugs reduce the risk of death in patients with hyperlipidemia by around 50 percent and the stroke risk by 30 percent but the reasons given for quitting statins does not include a cure. Nitrates and Nitrites can be effective at restoring normal blood flow within 5 minutes and lead to a complete recovery from angina pectoris or congestive heart failure in some patients, it should be tried in an office visit to see if a prescription is wanted. The treatment of congestive heart failure would be much improved with the use of the supreme herb for the heart - **Hawthorne** leaves, berries and flowers as an herbal tea infusion, tincture or syrup are good for the heart and kidneys. Hawthorne works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy cholesterol levels. Hawthorne is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorn doesn't store in the body and isn't accumulative in action, it's important to take on a regular basis if using as a heart tonic (Gladstar '12).

The evidence that regular intake of **fresh vegetables and fruit** reduces cancer risk is very persuasive. A greater emphasis on diets enriched for these foods as well as fibre content, reduced in animal fat, and especially with diminished overall calorie content would make much

sense and bring other health benefits, particularly if combined with a generally less sedentary, more calorie burning lifestyle (Greaves '00: 259). In 1980 the National Cancer Institute Committee on Diet, Nutrition and Cancer suggested a diet which is likely to afford optimal protection from cancer is low in fat, low in calories, low in salt, high in fiber and high in fruits and green and yellow vegetables. In Western countries who derive as much as half of their total dietary calories from fats, experience a high mortality from cancer of the breast (in postmenopausal women), colon ovaries, prostate, pancreas and womb, compared to Japanese people, who typically derive much less of their calories from fat. On the other hand Japanese diets contain more salt than conventional Western diets, and this is reflected in a higher incidence of cancer of the stomach in the Japanese population. The influence of diet on cancer has been extensively studied in experimental animals. Rodents that have unlimited access to food develop cancer more frequently and also have shorter life spans in general, than animals with a diet that is restricted in calories, and these animals are relatively more resistant to the carcinogenic effect of known cancer-causing chemicals added to their diet. Despite the fact that fruits and vegetables contain some chemical carcinogens cancer patients should maintain a diet low in fat and calories and high in fresh fruits, grains and legumes, and vegetables, especially yellow vegetables (Friedberg '92: 104-105).

Protein-calorie malnutrition reflected in progressive loss of skeletal muscle, visceral protein and fat tissue is very common in certain forms of advanced cancers. Nutritional deficiencies in the cancer patient result from the effects of cancer on the host as well as from the effects of cancer therapy, including the vegan diet in people who have already metabolized their body fat. The etiology of cancer **cachexia** is complex. Reduced food intake is common in this population and has been reproduced in experimental animals bearing tumors. Some patients develop abnormalities of taste, others complain of early satiety, and may may be depressed. Obstructive lesions of the gastrointestinal tract such as esophageal and gastric tumors can induce pain, nausea and vomiting which understandably decrease nutritional intake. Rarely, gastrointestinal tumors such as diffuse lymphomas or pancreatic cancer will be associated with malabsorption. For the most part, however, cancer patients will lose weight despite apparently appropriate caloric intake. Metabolic abnormalities induced by the presence of the tumor may explain this phenomenon. The common clinical observation that tumor cells grow while host cells atrophy suggests that the cancer cell preferentially uses available energy sources. Much evidence supports the concept of accelerated glucose utilization by the cancer cell and increased levels of gluconogenesis in patients with cancer cachexia. Abnormal lipid metabolism in cancer is manifested by progressive depletion of body fat through persistent mobilization of free fatty acids as the preferential source of metabolic fuel even if exogenous glucose is provided. The Alterations in protein metabolism may be characterized by both decreased synthesis and increased catabolism of protein in cancer patients with weight loss (Bengoa '86: 379).

Oncologic texts are unfortunately devoid of normal nutritional information regarding vegan and vegetarian diets which is normally the mainstay of cancer treatment. This is probably to quickly drive the patients to seek expensive hospital treatments, particularly surgery, recovery from which seems to benefit greatly from a high protein preoperative diet. In one study 10 days of preoperative parenteral nutrition reduced the postoperative complication rate in patients with gastrointestinal carcinoma from 19% to 11% for wound dehiscence and mortality from 11% to 3% (Bengoa '86: 379, 381). Whereas the text does not label protein an oncologic poison, and many liquid diet formulas contain protein, the word protein in reference to the enteral and parenteral nutrition actually refers to amino acids, which are the building blocks of protein, but are much smaller and more easily absorbed. Generally speaking, protein is the tumor growth factor, and avoidance of complete protein denies neoplastic cells the protein they need to grow

and allows the normal human tissues to be well nourished, so that miraculous, or not so miraculous reduction in the acceleration of the cancer growth, can cure or give the patient less pain and more time to find effective medical treatment. When eating a low-calorie vegan or vegetarian diet it is important to consume much larger quantities and/or more frequently to avoid catastrophic weight loss and be well nourished, without having an overly full belly, larger than a fist, to tolerate physical exercise. Liquid diets may be necessary for cancer seriously affecting the digestive tract and this seems to be the entire nutritional concern of oncologists who are not nutritional specialists.

Diet, in the sense of Hippocrates, is a complete regime. Nutrition should be regarded as a remedy, prescribed as to kind and quantity or items to be forbidden. The Gerson Diet is based on the concepts (1) that cancer patients have low immune-reactivity and generalized tissue damage, especially of the liver, and (2) that when the cancer is destroyed, toxic degradation products appear in the bloodstream which lead to coma and death from liver failure. The therapy consists of high potassium, low sodium diet, with no fats or oils and minimal animal proteins or gluten (wheat protein). Juices of raw fruits and vegetables provide active oxidizing enzymes which facilitate rehabilitation of the liver. Iodine and niacin supplementation is used. The cancer diet is completely different from normal nutrition. It is limited to fresh juices of fruits, leaves and vegetables; large quantities of raw fruit and vegetables are given in their natural form, or finely grated, salads of fresh leaves, fruits and vegetables, vegetables stewed in their own juice, soups, compotes, stewed fruit, potatoes and oatmeal. Potatoes may be excluded. All must be prepared fresh and without addition of salt. After six to twelve weeks, animal proteins are added in the form of cottage cheese (saltless and creamless) and probiotic yoghurt. Inasmuch as the detoxification of the body is of the greatest importance, especially in the beginning, it is highly recommended to administer frequent **enemas**, about every four hours, day and night, against severe pain, nausea, general nervous tension and depression. Caffeine enemas cause dilation of bile ducts, which facilitates excretion of toxic cancer breakdown products by the liver and dialysis of toxic products from blood across the colonic wall. To make enemas most effective, the patient should lie on their right side, with both legs drawn close to the abdomen, and breathe deeply, in order to suck the greatest amount of the fluid into all parts of the colon. The fluid should be retained 10 to 15 minutes. For cancer patients, even in advanced stages, pain relief was promptly obtained by the use of coffee enemas, given every two hours in some cases (Gerson '90: 139, 191, 397).

This **diet** forms the basis of medical treatment. It is based on the principle that sodium must be excluded as far as possible and the tissues must be enriched with potassium to the highest possible degree. The diet is digested more easily and quickly than normal nutrition; it burdens the metabolism as little as possible and stimulates the elimination of poisonous substances as well as abnormal intermedial substances of the metabolism. The amount of calories is smaller and the body digests each meal fast; therefore, larger portions and more frequent meals must be served. Patients should eat and drink as much as possible. Tobacco, salt, sharp spices, tea (other than peppermint, chamomile and other effective herbal remedies), coffee, cocoa, chocolate, alcohol, refined sugar, refined flour, candies, ice cream, cream, cake, berries, nuts, mushrooms, soy beans and soy products, pickles, cucumbers, pineapples and avocados are forbidden. Juices should always be freshly prepared. All vegetables must be cooked slowly, over a low flame. Tomatoes, leeks and onions should be stewed in their own juices, as they contain an abundance of fluid by themselves. Red beets should be cooked like potatoes, in their peel, in water. All vegetables must be carefully washed and cleaned. Peeling or scraping is forbidden, because important mineral salts and vitamins are deposited directly under the skin. The pot (not aluminum) must close tightly, to prevent escape of steam. Cooked foods may be kept in the

refrigerator for 48 hours. It may be necessary for the patient to drink freshly prepared vegetable juice every hour. This consists of four glasses of the juice of apple and carrots in equal parts, and also four glasses of green leaf juice. They may lose 60 percent of their active oxidation power within half an hour, and must be consumed immediately after pressing. A good number of patients follow this prescription, are cured and live a normal life after five and more years (Gerson '90: 187-189, 217).

Herbal Remedies for Cancer

Vitamin	**Indication**
Vitamin E	Antioxidant, regulation of oxidation reactions, supports cell membrane stabilization. Found in polyunsaturated plant oils (soybean, corn and canola oils), wheat germ, sunflower seeds, tofu, avocado and sweet potatoes.
Mineral	**Indication**
Selenium	Antioxidant. Works with vitamin E to protect body from oxidation. Found in grains.
Herb	**Indication**
Asian Ginseng *Panax ginseng*	Increases nitric oxide in immune cells, blood vessels and erectile tissues. Increases Adrenocorticotrophic hormone (ACTH) and cortisol Increase protein synthesis. Antistress, antifatigue, muscle strength and recovery time, reaction time and alertness, intellectual performance, immune function and cancer prevention, sexual function, most beneficial for people over 40. Ineracts with MAOI (monoamine oxidase inhibitor, anticoagulants, steroids. Contraindicated for high blood pressure, heart disease, diabetes, bipolar disorder (manic depression) – may cause mania, discontinue 7 days prior to surgery, do not use for more than 3 months, may have long-term hormonal effects, do not use during pregnancy or when breastfeeding, do not use with steroids, not for children under age 12.
Bloodroot (*Sanguinaria canadensis*)	Red sap from bloodroot (*Sanguinaria Canadensis*) has been used for the treatment of cancerous disease by the North American Indians living along the shores of Lake Superior. In 1857 a British surgeon concocted a therapy based on a paste of bloodroot extract, zinc chloride, flour and water. The past was smeared on a cloth or cotton and placed on the tumor daily (if healthy tissue covered the tumor, it was eroded with nitric acid. When the tumor became encrusted, incisions were made about one-half inch apart and the paste was inserted into the cuts daily. Generally within 2 to 4 weeks the disease was destroyed, with the mass falling out in 10 to 14 additional days, leaving a flat healthy sore that usually healed rapidly. All cases illustrated remissions, if not cures. 8 of 10 surgical patients returned within 2 years for further treatment, only 3 of 10 returned after using his therapy.
Garlic *Allium sativum*	Garlic is not only tasty, it is the herb of choice for treating colds, flus, sore throats and poor or sluggish digestion. It stimulates the production of white blood cells, boosting immune function and is a potent internal and external antiseptic, antibacterial, and antimicrobial agent effective for treating many types of infection, including several forms of antibiotic-resistant strains of bacteria. It helps to maintain healthy blood cholesterol and helps prevent blood platelet aggregation, making it the herb of choice for many circulatory issues and lowers blood sugar levels in Type 2 diabetes. Garlic can irritate and burn sensitive skin, cause heartburn, stomach distress, provoke anger and should be avoided by nursing mothers as it can cause colick.

North American May apple (*Podophyllum peltatum*)	rRhizome or underground stem was used by the Penobscot Indians of Maine to treat cancer. Podophyllum resins was used by physicians in Mississippi and Missouri as early as 1897 and by urologists in Louisiana for the treatment of venereal warts (*condyloma acuminate*). Recent clinical reports signify that podophyllin has become the drug of choice in the treatment of human condyloma accuminata. Others report a destructive effect of podophyllin on different cancer cells in animals and in man, but is highly toxic
Turmeric *Curcuma longa*	Curcumin is a powerful agent against several types of cancers of the esophagus, breast, colon, prostate and skin and inhibits the growth of lymphoma cells.
Burdock *Arctium lappa*	The root is part of a very well-known Native American anticancer formula called Essiac.
Red Clover *Trifolium pretense*	Though the FDA states "there is not sufficient reason to suspect it of any medicinal value" studies conducted by the National Cancer Institute suggest that red clover should be considered, as a preventative agent and perhaps incorporated in a health-promoting tea for people at risk for cancer. Red clover has blood thinning properties and should not be used by those who are taking heart medication or who have any type of blood-thinning problem. Discontinue red clover for 2 weeks before and after surgery.
Roseroot, golden root *Rhodiola rosea*	Increase cellular energy production, protein synthesis, serotonin, norepinephrine and dopamine. Support DNA repair, antioxidant, anticarcinogenic, anticancer. Improves oxygen utilization.
Rhododendrum caucasium	Antioxidant, blocks carcinogen absorption and 20% of fat absorption through intestines. Increases energy in heart muscles and uric acid excretion. Relaxes blood vessels, lowers blood pressure. Physical performance, high blood pressure prevention, cancer prevention, weight loss, antigout. No contraindications known. Pregnancy, breastfeeding unknown.
Siberian Ginseng, eleuthero *Eleutherococcus senticosus*	Increase ACTH and cortisol, Norepinephrine, Serotonin and Protein Synthesis. Antistress, strength and endurance, intellectual productivity, immune cell response, resilience during cancer treatment Interacts with anticoagulants by interfering with some tests of digoxin levels. Contraindicated for high blood pressure, heart disease – use with caution, bipolar disorder (manic depression) – can cause mania, schizophrenia – can cause agitation, women with hormone-sensitive cancers or conditions, pregnancy breastfeeding unknown, not for children under age 12, lack of safety evidence beyond 6 weeks

Source: Elvin-Lewis '77

Herbal remedies have been developed for of a number of cancerous diseases. Red sap from bloodroot (*Sanguinaria canadensis*) has been used for the treatment of cancerous disease by the North American Indians living along the shores of Lake Superior. In 1857 a British surgeon concocted a therapy based on a paste of bloodroot extract, zinc chloride, flour and water. The past was smeared on a cloth or cotton and placed on the tumor daily (if healthy tissue covered the tumor, it was eroded with nitric acid. When the tumor became encrusted, incisions were made about one-half inch apart and the paste was inserted into the cuts daily. Generally within 2 to 4 weeks the disease was destroyed, with the mass falling out in 10 to 14 additional days, leaving a flat healthy sore that usually healed rapidly. All cases illustrated remissions, if not cures. 8 of

10 surgical patients returned within 2 years for further treatment, only 3 of 10 returned after using his therapy. North American May apple (*Podophyllum peltatum*) rhizome or underground stem was used by the Penobscot Indians of Maine to treat cancer. Podophyllum resins was used by physicians in Mississippi and Missouri as early as 1897 and by urologists in Louisiana for the treatment of venereal warts (*condyloma acuminate*). Recent clinical reports signify that podophyllin has become the drug of choice in the treatment of human condyloma accuminata. Others report a destructive effect of podophyllin on different cancer cells in animals and in man, but is highly toxic. Seeds of the common apricot (*Prunus armenicaca* or *Armeniaca vulgaris*) native to China, were used there against tumors as early as AD 502. They are as tasty as almonds. Laetrile therapy is based on the theory that once inside the body, the extract from apricot pit breaks down into several components including cyanide. Cyanide is released only when it comes into contact with an enzyme common to tumor cells, β-glucoronidase, at which time cyanide chokes off the tumor cells, leaving the healthy cells surrounding the growth untouched. 10 cases of inoperable cancer, with metastases, regressed, as well as dramatic relief from pain (Elvin-Lewis ’77: 123, 124, 125).

The total incidence of **oral cancers** is about 50,000 cases per year with 8,000 deaths. Surgeries to remove some of these cancers are traumatic and destroy the victim’s quality of life (Jerome ’00: 402). In the United States men between the ages of 40 and 65 have the highest rate of oral cancers. The most common sites are the lip, the floor of the mouth and the lateral tongue. Oral cancer makes up between 2 and 5 percent of all cancers. In general, a sore in or around the mouth that does not heal within 10 to 14 days, should by checked by a dentist. Pain and numbness develop later. Between 70 and 90 percent of oral cancers are squamous cell carcinomas. They are treated most often surgically by a head and neck cancer specialist. In many instances surgery is followed with radiation therapy and chemotherapy (Smith ’97: 153, 171, 161, 162). Radiation that is used to treat cancers of the head and neck can cause a number of acute and chronic dental problems – it can destroy the salivary glands so that the mouth is very dry, swallowing becomes difficult, and dental caries is rampant, mucositis, candidiasis, sensitivity of the teeth, loss of taste, and damage to the bone (Smith ’97: 201, 202, 171).

The maximum 5 year survival of **esophageal cancer** patients treated by surgery is generally 20%, and the vast majority of patients have less than a 5% to 10% probability of long-term survival with surgery only. Radiation therapy for patients with significant dysphagia can be palliative and can allow patients to eat. However, there is no good evidence, except for cervical esophageal cancer, that radiation alone has been curative. Chemotherapy of patients with advanced disseminated disease is clearly only palliative. Chemotherapy regimens utilizing combination of 5-fluorouracil (5-FU) (1000 mg/m^2 per day, IV continuous infusion on days 1 to 4; repeat on days 29 and 32) and cisplatin (75 mg/m^2, IV day 1 and day 29 only), or 5-FU and mitomycin and 3000 cGy of radiation, can be effectively used in the management of patients with esophageal cancer. In one study 17% were shown to have no tumor in the resected esophageal specimens. The median survival of patients achieving pathologic complete remission was 32 months with 67% and 45% at 2 and 3 years after surgery. Placement of intra-luminal esophageal intubation tubes allow the patient to feed and swallow but is associated with significant mortality (10% to 40%), the major life-threatening complication is esophageal rupture and subsequent mediastinitis (Macdonald '90: 225, 226).

The bowel tolerates radiation very poorly. 5-FU is the most commonly used chemotherapeutic agent. Combinations of irradiation and 5-FU may be useful in treating locally advanced s**mall bowel carcinoma**. FAM (5-FU, doxorubicin, mitomycin-C) might be more effective than a single agent (Macdonald '90: 231, 232). Systemic chemotherapy of **colorectal cancer** has been

disappointing. The 1 g/m2/day infusion schedule of 5-FU may be given generally for 7 to 10 days, is limited by stomatitis rather than myelosuppression and has a response rate of 31%. Combination chemotherapy has not been proven to be more effective than 5-FU. Studies of 5-FU plus methyl-CCNU and 5-FU, methyl-CCNU, streptozoin and vincristine demonstrated partial response rates as high as 40%, but this was not confirmed. Sequential methotrexate followed by 5-FU and 5-FU and leucovorin have produced response rates as high as 41%. There is no evidence in favor of chemotherapy adjuvant to surgery. A significant decrease in relapse rates has been noted with the use of combined-modality therapy (combined 5-FU and methyl-CCNU, and radiation therapy) compared to surgery alone (relapse rates of 55% versus 30%) (Macdonald '0: 237, 238).

Primary **carcinomas of the liver** are relatively uncommon in North America and Western Europe (2% of all cancers) but represent 20 to 40% of cancers in countries endemic for viral hepatitis. The following medicines are recommended to treat hepatic itching. Antihistamines hydroxyzine (Atarax) and diphenhydramine (Benadryl) are often the first drugs that are used. These may help the itching, usually by sedating the patient. Rifampin is an antibiotic which for some reason can also help itching. The patient should be monitored carefully since this drug can be hard on the liver. Ursodeoxycholic acid (Actigall or URSO) may also help itching by promoting bile flow. Questran is a material called a resin. This gritty substance binds bile salts in the stool, stimulating flow of bile from the liver. It should not be taken at the same time as certain other medicines such as URSO. Prednisone is a corticosteroid drug which is used to treat autoimmune hepatitis as well as to prevent rejection in liver transplant patients. Corticosteroids are normally made by the body in small amounts. Physicians may give these drugs in large amounts to suppress an overactive immune system. Prednisone causes bones to thin and may sometimes cause severe injury to bone. Prednisone can interfere with normal growth. Prednisone suppresses the immune system, making patients more susceptible to infection. Prednisone cannot be stopped suddenly since the adrenal glands, which normally make corticosteroids, may be suppressed. This can cause the patient to develop life-threatening adrenal insufficiency (the body goes into crisis due to lack of corticosteroids). Prednisone causes cosmetic changes such as weight gain, stretch marks and round, full cheeks. Facial acne may appear. Hypertension and cataracts are seen, mostly in adults, and mostly with prolonged treatment. Efforts are usually made to wean the dose down to the least amount that will keep the disease process under control. Azathioprine or Imuran (or a related drug called 6-MP or 6-mercaptopurine) may also be used to suppress the immune system, commonly in the context of autoimmune hepatitis. These drugs affect the DNA synthesis of rapidly dividing cells. Rarely, these drugs can cause hepatitis or pancreatitis. Low white counts are a more common problem, and blood work is monitored to assess this. An allergic reaction with fevers, rash, joint pains, gastrointestinal symptoms can develop 3 to 4 weeks after starting such a drug. Theoretically, since the drugs affect DNA repair, these drugs could be harmful to a developing infant, or even cause an increased risk of cancer. These are not common complications, although pregnancy should be undertaken with caution in patients on Imuran or 6-MP.

The majority of patients with **carcinoma of the pancreas** present with unresectable (incurable) malignancy. However, up to 20% of carefully screened patents can undergo a laparotomy with the expectation of a radical resection. Of those patients who undergo such a resection, perhaps 20% will be cured, resulting in an overall 4% or 5% cure rate. Of course, radical surgery (such as a Whipple procedure), is associated with an operative mortality of at least 5%, and morbidity. The median survival for all patients treated with radical surgery alone is approximately 11 months. Radiation therapy and 5-fluorouracil (5-FU) may be beneficial. Supervoltage radiation is given in fractions of 200 cGy/ day, five times per week, with a 2-week rest period, before the

second 2000 cGy is given for a total dose of 4000 cGy. A 1 month rest period after the completion of radiation is followed by weekly 5-FU (500 mg/m^2) therapy for a total treatment time of 2 years. Patients undergoing this combined modality approach had a median survival of approximately 21 months. The 2 year survival for this combination therapy group is 46%, with about 25% of the patients alive at 5 years with no evidence of disease. Toxicities include malaise, hematotoxicity, mucositis, and diarrhea. For unresectable patients a combination of radiation therapy and chemotherapy for local palliation is used. Conventional external irradiation results in a median survival of approximately 16 weeks. The combination of radiation and chemotherapy yields a median survival of 40 weeks. 5-FU is the most effective chemotherapeutic agent. Investigators have attempted to combine drugs to improved efficacy, such as 5-FU, mitomycin-C, streptozotocin and doxorubicin. Objective partial response rates range between 5% and 35%, with median survivals ranging from 9 to 26 weeks. Without any demonstrated improvements with combination therapy 5-FU alone is the most appropriate chemotherapy choice for pancreatic cancer (Friedman '90: 243, 244).

Immunotherapy is considered one of the standard treatment options for **kidney cancer** patients with advanced metastatic disease. Well-documented, but very rare, cases of spontaneous regressions in kidney cancer patients with metastatic disease suggest that the immune system can play an important role in the control and potential treatment of this disease. The building blocks of immunotherapy are **biologic response modifiers** (BRMs). They are substances that enhance the body's immune system and improve its ability to fight cancer. BRMs do their work by regulating the intensity and duration of immune responses. A BRM can be either a manmade drug or a natural substance produced by the body. Several BRMs can boost the body's natural immune defenses. The cytokines are an important family of BRMs that include Interleukin-2 (IL-2) and Interferons. Used either alone or in combination, they have represented the standard in the treatment of kidney cancer. **Interleukin-2** is a biologic response modifier (BRM) available for the treatment of advanced kidney cancer. It stimulates the growth of two types of white blood cells: T cells and "natural killer" (NK) cells. T cells are very important in your body's fight against cancer because they recognize cancer cells and set off an alarm to the body. The NK cells respond to this alarm and are transformed into lymphokine-activated killer (LAK) cells, which are capable of destroying cancer cells. Proleukin (interleukin-2) was approved by the FDA in 1992 for the treatment of metastatic renal cell carcinoma. A genetically engineered product, recombinant IL-2, is available for use in various therapeutic regimens. Several different routes of administration may be used: IV bolus, subcutaneous (SC), and continuous IV infusion (CIV).

Interferons are widely used to treat kidney cancer, alone or in combination with other drugs. Interferon therapy is typically self-administered by injection under the skin several times per week. Interferons work by "interfering" with the life processes within the cancer cell, preventing its growth and making the cell more susceptible to attack by other elements of the immune system. There are three major types of interferons — alfa, beta, and gamma — but interferon alfa has been most widely studied in the treatment of kidney cancer. Several interferon alfa products are available in the United States and have been used in the treatment of kidney cancer. INTRON* A, a product of Schering Corporation (Kenilworth, NJ), has been designated as interferon alfa-2b. Roferon*-A is manufactured by Roche Laboratories (Nutley, NJ) and has been designated as interferon alfa-2a. These drugs are very similar, and kidney cancer may be treated with either. Most insurance companies recognize the value of interferon alfa in treating kidney cancer and reimburse for this therapy. In several dozen clinical trials, an overall response rate of about 13% has been achieved with interferon alfa. However, in patients with high performance status (i.e., lack of symptoms related to their disease), previous nephrectomy, and metastases predominantly in the lung, the major response rate (complete plus partial responses)

with interferon alfa treatment is usually from 6 to 10%. It is also recognized that patients who receive interferon alpha, when compared with those who are treated with hormones or chemotherapy, have improved survival rates. Response to interferon alfa is characterized by slow regression of tumors; the average time from start of treatment to objective response is three to four months. The most common side effects of interferon therapy are flu-like in nature.

Though it is not considered a primary form of therapy, radiation can be used in the treatment of kidney cancer that has metastasized to the bone, brain or spine. Although chemotherapy is the standard treatment for most solid tumors, kidney cancer is generally resistant to chemotherapy. The reason for the resistance of kidney cancer cells to chemotherapy is not completely understood. However, it is now known that kidney cancer cells produce an overabundance of multidrug-resistance-associated protein, which acts to repel various chemotherapeutic agents away from the cancer cell. 5-Fluorouracil (5FU) appears to be the most effective conventional chemotherapeutic agent currently available for kidney cancer, but response rates are only in the range of 5% to 8%. In 2005 and 2006, the U.S. Food and Drug Administration (FDA) approved the first new medications to treat kidney cancer in more than a decade: sorafenib tosylate and sunitinib malate. Both of these new drugs disrupt the angiogenesis process. Known as tyrosine kinase inhibitors, they interfere with the proteins inside cancer cells, thus interfering with certain cell functions. These drugs are also known as "multi-kinase inhibitors" because they target both the tumor cell and the tumor blood vessel structures. They work by interfering with reproduction of cancer cells as they attempt to grow and divide uncontrollably. They also have the advantage of being administered orally. The goal of treatment with these newer medications is to slow the rate of growth of the cancer and, if possible, shrink the size of existing tumors. Some patients may experience a significant decrease in the amount of cancer in their body. Some patients may not experience shrinkage in the size of their tumors, but have long periods of "stable" disease. A physician will discuss how the cancer is responding to treatment, and will have additional options to consider for treatment when necessary. It should be noted that some patients will not receive any benefit from a medication. In some cases, a medication that was effective in treating a patient's cancer stops working and other treatment options must be considered. **Sutent** (sunitinib malate) claims to reduce tumor size and is not only seems to be the most highly recommended chemotherapy for kidney cancer, but is available in capsule form for oral consumption, but hepatoxicity and cardiotoxicity has been deadly, it is prescribed once a day for four weeks and two weeks off.

Nexavar (sorafenib tosylate) is a medication that targets the blood supply of a tumor, depriving it of the oxygen and nutrients it needs for growth. By blocking the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), Nexavar can interfere with the tumor cell's ability to increase its blood supply. By blocking the Raf-kinase pathway, Nexavar can also interfere with tumor cell growth and proliferation. Clinical studies show that it can significantly slow the progression of tumors. In the Phase III trial which led to the FDA approval of Nexavar, the median time for tumor progression was doubled for patients taking Nexavar, compared with patients taking a placebo. **Sutent** (sunitinib malate) also deprives tumor cells of the blood and nutrients needed to grow by interfering with VEGF and PDGF signaling pathways. Sutent was approved by the FDA in 2006 for kidney cancer patients because of its ability to reduce the size of tumors. Clinical studies showed a favorable response rate in patients with metastatic kidney cancer whose tumors had progressed following immunotherapy. **Torisel** (temsirolimus) is another recently approved kidney cancer drug. It was designed to inhibit the mTOR (mammalian target of rapamycin) kinase, which is important in cell growth and cell survival. By blocking the mTOR pathway, Torisel can interfere with the tumor's ability to multiply as well as reducing its ability to stimulate angiogenesis. **Afinitor** (everolimus), approved by the FDA in March 2009, is

an orally administered mTOR inhibitor. Afinitor works by blocking a specific protein known as the mammalian target of rapamycin (mTOR) and acts as a multifunctional inhibitor of cell growth and proliferation, angiogenesis, and cell metabolism. The drug is intended for those patients with advanced renal cell cancer who have already tried a kinase inhibitor, such as Sutent or Nexavar. **Votrient** (pazopanib), the sixth drug to be approved for kidney cancer since 2005, is an oral medication that interferes with angiogenesis, the growth of new blood vessels needed for solid tumors to grow. It is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma. **Inlyta** (axitinib), approved by the FDA in January 2012, is a prescription medicine used to treat advanced kidney cancer (advanced renal cell carcinoma or RCC) when one prior drug treatment for this disease has not worked. As with antibiotics chemotherapeutic drugs require **probiotic supplementation** to avoid vitamin B_{12} deficiency, chronic diarrhea, pernicious anemia and dental cavities.

Tumors of the bladder are the second most common genitourinary neoplasm. Only prostatic tumors occur more frequently. Cancer of the bladder accounts for approximately 2% of all malignant disease. Twice as often in men as in women. The average age of patients is 65 years and fewer than 1% of cases are reported in people under 40. The predominant symptom is hematuria, in 75-80% of patients. The preferred treatment is combination chemotherapy consisting of cisplatin, cyclophosphamide, and doxorubicin (CISCA) or methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC). These drug programs have result in long-term survivals with complete eradication of tumor (Johnson '88: 355, 357, 356, 360).

It is estimated that 80% of men 50-60 years of age or older have benign prostatic hyperplasia and approximately 10% of men over age 65 will eventually develop clinically apparent **prostate cancer**. The prostate is described as having 5 lobes. Benign prostatic hyperplasia and prostatic cancer are not sequential manifestations of the same pathologic process but, rather, are entirely different entities. The probability of a 40 year old man requiring surgery for benign prostatic hyperplasia by the age of 80 is 10.9%. For those patients with severe obstruction and evidence of bladder or upper urinary tract dilatation , surgical relief of obstruction is mandatory. Catheterization is often sufficient. Acute urinary retention is best managed by an indwelling Foley catheter left in place for 2-3 days. When the catheter is removed, the patient usually resumes a fairly normal voiding pattern, since vesical tone has been reestablished and prostatic congestion relieved.

80% of 200 prostate patients using **phenoxybenzamine**, an α-adrenergenci blocker, experienced symptomatic relief. Uroflowometry in 102 patients showed the flow to be more than doubled in nearly one-half of patients and increased by more than 50% in another one-fourth. Improvement was noticed within the first 2 days of therapy and reached its maximum after 7 days of treatment. The drug did not reduce the size of the prostate. Side-effects, reported by 30%, include hypostatic hypotension resulting in dizziness and tachycardia, retrograde ejaculation, fatigue and nasal congestion, only 10% felt it was so severe they discontinued treatment. Androgen deprivation affects the prostate. Androgen deprivation can be achieved by administration of estrogens but estrogens play a direct role in the development of benign prostatic hyperplasia. **Cyproterone acetate**, an anti-androgen, caused 11 of 13 patients in 1969 to experience subjective improvement including increased urinary flow rate and decreased volume of residual urine. An objective decrease in the epithelial cell size was apparent in 8 of 11 patients whose prostatic biopsies were available (Johnson et al '88: 361, 365).

3. Surgery

The reasons for **admissions to surgical wards** with acute abdominal pain were studied. In adults in Leeds in 1972 admissions were acute appendicitis (26.3%), cholecystitis (7.6%), small-bowel obstruction (3.6%), perforated peptic ulcer (3.1%), pancreatitis (2.9%), diverticular disease (2.0%), miscellaneous (4.0%) and non-specific acute abdominal pain (NSAP) (50.5%). In patients up to 13 years old, at the Royal Aberdeen Children's Hospital in 1974 found admissions NSAP (30.0%), acute appendicitis (28.0%), constipation (11.0%), upper respiratory tract infection (8.0%), urinary tract infection (6.9%), gastroenteritis (3.6%), bronchopneumonia (2.2%), small-bowel obstruction (inc. insususception) (2.2%), Mesenteric adenitis (2.2%), abdominal injuries (1.0%), infective hepatitis (1.0%), torsion of the testicle, acute pancreatitis, otitis media, acute glomerulonephritis and diabetic acidosis in less than 1% of cases. Not all patients who are referred to surgical wards have a surgical cause for their acute abdominal symptoms, so the emergency surgeon needs also to be a good physician. Among the children, only one-third actually required an operation, another one-third had a specific medical illness requiring diagnosis and treatment, whilst the remaining patients recovered spontaneously. Among the adults, nearly half of those admitted did not need surgery (Jones et al '85: 275, 276). For every malignant-small bowel neoplasm, the surgeon in Great Britain is likely to see about 50 colorectal and 30 gastric carcinomas Roughly one-third are carcinomas, one-third are lymphomas (there is an association with coeliac disease) and one-third are carcinoids (Jones et al '85: 299).

Gastric bypass surgery is a type of bariatric, or weight loss, surgery. During gastric bypass surgery, the surgeon makes changes to the stomach and small intestine to change the way they absorb and digest food. Gastric bypass aids weight loss by: Restricting the amount of food that your stomach holds Limiting the amount of calories and nutrients the body absorbs. Changing gut hormones, to feel fuller longer, contribute to appetite suppression and the reversal of obesity-caused metabolic syndrome. Roux-en-Y gastric bypass is considered the ‘gold standard’ of

weight loss surgery. It is the most commonly performed bariatric procedure worldwide. During Roux-en-Y gastric bypass surgery, the surgeon: Makes a small stomach pouch – about the size of an egg – by dividing the top of the stomach from the rest of the stomach. Then, the small intestine is divided, and the bottom end of the divided small intestine is brought up and connected to the newly created small stomach pouch. In the end, the top portion of the divided small intestine is connected to the small intestine further down so that the stomach acids and digestive enzymes from the bypassed stomach and first portion of your small intestine will eventually mix with the food. Gastric bypass surgery's advantages include: Very good short term weight loss (60 to 80 percent excess weight loss). Lasting, long term results. The data show that up to 20 years after surgery, most patients maintain more than 50 percent of their excess weight loss. Excellent resolution of obesity-related health problems.

Acute inflammation of the vermiform appendix, **acute appendicitis**, is a disease of the 20th century and of Western-style civilizations. At present, in Great Britain, the chance of a newly-born baby developing acute appendicitis during his or her life is about one in five, falling to one in ten by the age of 20. Some 70,000 new cases are seen each year, making acute appendicitis the commonest surgical emergency in both adults and children. Now that acute appendicitis is widely recognized it is generally treated promptly and the mortality rate of all cases in Britain is less than 1 in 200. However, to many patients still come to operation with peritonitis due to perforation, and 88% of deaths occur in this group. Two-thirds of patients arrive in hospital within 24 hours of the onset of appendicitis but, even so, 28% have already perforated. Among children under 5 years, three our of four have perforated by the time they come to operation. All patients complain of abdominal pain. In about 60% of patients this is at first an ache around the umbilicus, which may progress to severe colic if the appendix is obstructed. After a variable time the progression of inflammation causes local parietal peritonitis and pain shifts to the right iliac fossa. This is a steady pain, aggravated by coughing and movement. In some 40% of patients, pain starts and remains in the right lower quadrant, especially if the appendix is not obstructed. Patients are likely to have vomited several times and be dehydrated. At least 3-4 hours must be spent on rehydration commenced with Hartmann's solution and large intravenous infusions, especially in the elderly. While rehydration is processing it is important to treat bacteremia with gentamicin (5-6 mg/kg/da in three divided doses), ampicillin (500 mg 4-6 hourly, half dose in children) and metronidazole (500 mg thrice daily, 7.5 mg/kg thrice daily in children). Oral metronidazole 400 mg, thrice a day, or 200 mg, may help to avoid medical expenses but if it doesn't work at home or office within 24 hours **emergency appendectomy** is indicated. Safe removal of the gangrenous appendix requires a skillful operation through a generous incision. It is important to remove any fecolith shed for the necrotic appendix, which could lead to continued suppuration, and should conclude with thorough peritoneal debridement, in which all contamination is aspirated, fibrinous plaques removed, and all quarters of the peritoneum and intestines thoroughly lavaged with an antibiotic solution, e.g. tetracycline 0.1% in warm normal saline. Although modern anesthesia and antibiotics have robbed **general peritonitis** of most of its terrors, it is still a very serious abdominal condition. In patients with acute uncomplicated appendicitis the mortality rate is now down to 1 in 1500 but, when peritonitis is present, one patient in 50 succumbs (Jones et al '85:v 282-286).

Perforated peptic ulcer is an emergency. The first successful suture was performed (by candlelight) in the home of a man age 41 in 1892, in North Germany. By the time of the Second World War, perforated duodenal ulcer in men was one of the commonest surgical emergencies. After 1950 there was a steady fall for fifteen years, but the incidence seems to have stabilized. The patient present with sever upper abdominal pain which rapidly spread to involve the whole abdomen. When a peptic ulcer causes sufficient penetration of the gastric or duodenal wall to

breach it, there is a point at which the ulcer base gives way and the gastric content is suddenly released. The perforation is neat circular hole with smooth vertical sides. Peritoneal contamination can be very severe if a meal has recently been taken, and food can be recovered from all quadrants of the abdomen. If the stomach is empty, gastro-duodenal juices still cause severe peritoneal irritation but the signs tend to be rather less severe. There are three possible methods of treating perforation. The non-operative regime, in which the stomach is kept empty by effective nasogastric suction, nothing is taken by mouth, and fluids are supplied intravenously. If this regime is effective, the patient rapidly improves and the abdominal signs regress. It is not much used because an be valuable in patients who are already improving when admitted, or who have such sever cardiorespiratory disease as to be unacceptable for surgery. The classical treatment or a perforated peptic ulcer is simply to close the perforation by deep under-running sutures of catgut, often incorporating a patch of omentum. This is speedy and effective treatment, but some perforation are so large as to be technically uncloseable usually requiring partial gastrectomy. There is a good case, also, for emergency definitive surgery for the perforated chronic duodenal ulcer, because two-thirds of these patients, if treated by simple closure of the perforation, require later elective surgery. The popular operation for this group are truncal vagotomy and a pyloroplasty, but some duodenums are so scarred when they perforate that these patients require closure of the perforation and a gastrojejunostomy and vagotomy. Whatever operation is adopts, it is important to remember that there is widespread contamination of the peritoneal cavity. Sometimes food fragments have to picked out manually and every patient should have the peritoneal cavity thoroughly washed out with several liters of warm saline, containing 0.1% tetracycline, paying special attention to removal of debris for the subphrenic space, where a residual abscess is especially likely to occur. The mortality of perforated duodenal ulcer is now very low (2-4%, except in the elderly) but for gastric perforations the mortality rate is 10-15% (Jones et al '85: 301-302).

Blood loss can present in a number of ways which may suggest at an early stage whether bleeding is arising from the upper (principally oesophagus, stomach and duodenum) or lower (principally colon) gastrointestinal tract. A yearly admission rate of around 120 per 100,000 population may be expected and 25% of these patients will have bled sufficiently to drop their haemoglobin below 7.0 g/dl. Approximately 70% of patients will settle on conservative measures after the first bleed, and 30% will proceed to emergency or early surgery, because of continuous bleeding. Mortality from massive gastrointestinal haemorrhage varies from 5-50%, with most representative series quoting 8-15%. Appreciation of the need for an energetic team approach to the clinical problem has led to reports from one or two centres of strikingly redued mortality around 2%. **Hematemesis** means the vomiting of fresh blood, blod with clots or blood which has been subject to digestion by gastric juices, which produces a brown fluid with brown granules, so-called 'coffee-ground vomit'. **Melaena** means the passage of tarry black shiny stools, the discoloration being produced by the reduction hemoglobin, principally by the action of acid from the stomach. The presence of melaena implies bleeding from the upper gastrointestinal tract. If blood loss has been slow, the stool is formed, if, however, blood loss has been severe, bowel peristalsis is vigorously stimulated and the rapid transit of intestinal contents produces a bowel movement which varies in color from shiny black to dusky red and which has an instantly recognizable offensive odor.

Fresh rectal bleeding may take the form of bright red blood on the surface of the stool, admixed with the stool, present on the underclothes noted on toilet paper or staining the water in the lavatory pan. It usually implies bleeding from the lower alimentary tract due to hemorrhoids, rectal or colonic polyps or carcinoma, or diverticular disease or inflammatory bowel disease. When fresh rectal bleeding is associated with mucus and very little fecal material, the diagnosis

is usually inflammatory bowel disease. Occult blood loss is usually found in patients with hypochromic microcytic anaemia and who may have few gastrointestinal symptoms. **Occult blood loss** may result from lesions in the upper alimentary tract, e.g. carcinoma of the stomach, or lesions of the lower alimentary tract such as carcinoma of the caecum or ascending colon. Occult blood is detected by the guaiac test, which is claimed to be able to detect intestinal blood loss of the order of 10 ml per day. The specimen of stool is spread on guaiac-impregnated filter paper and if a blue color develops on addition of 2 drops of a solution of hydrogen peroxide the test is positive (Jones et al '85: 307, 308).

Severe blood loss is defined as the loss of 1500 ml of blood, or 25% of the circulating blood volume, within a period of several minutes to several hours. As central blood volume falls, baroreceptors, and volume-receptors are stimulated resulting in an increase in output of catecholamines for the adrenal medulla and from the sympathetic nerve endings. This produces splanchnic and peripheral vasoconstricution with maintenance of systemic blood pressure and preservation of blood supply to vital centres in the brain and myocardium, and initially to the renal circulation. The spasm induced in the wall of the bleeding artery may be sufficient to reduce or even stop gastrointestinal hemorrhage. If this occurs, the second wave of compensatory mechanisms which are hormonally mediated, come into play. These include the release of antidiuretic hormone and aldosterone, acting to restore blood volume by withdrawal of extravascular fluid and reduced urine flow. The resultant expansion of circulating blood volume leads to a reduction in hemoglobin concentration, with a fall in hematocrit and reduced oxygen carrying capacity. The patient then experiences quite marked thirst. The hemopoietic system reacts with an abrupt rise in white-cell count, and frequently with a rise in the circulating platelet count. With continuing or severe blood loss the patient enters a stage of hemorrhagic shock. The skin becomes cold and clammy and initially pale. The fall in mean and diastolic blood pressure is a late sign of hemorrhagic shock. The cerebral and coronary circulations are relatively well preserved, but the initial protection of the renal circulation is lost and urine output falls. As peripheral perfusion and oxygen supply fall, tissues convert from aerobic to anaerobic metabolism and a metabolic acidosis results. This stimulates a further rise in respiratory rate. Arteriolar vasoconstriction results in reduction of blood supply to the capillaries and more and more parts of the capillary bed become hypoxic. Finally, in a response to hemorrhagic shock, the oxy-hemoglobin dissociation curve shows a net shift to the left. Resuscitation at this stage is still possible and low mortality should be the rule. Unless resuscitation is adequate, there is a breakdown of cellular and subcellular membranes (in response to hypoxia and acidosis) with the release of multiple damaging toxins. The patient is now at serious risk of developing **refractory shock**, which carries a mortality of between 50-95% irrespective or further treatment (Jones et al '85: 310-312). Ideally, carefully cross-matched whole blood should be transfused to replace the estimated loss. This inevitably introduces a delay of the order of an hour. In dire necessity it may be essential to transfuse 'universal donor' Group O Rhesus negative blood. In the slightly less urgent situation the circulation may be temporarily maintained by infusions of mixtures of crystalloid and colloid (e.g. dextran or plasma protein substitute). Water and electrolyte replacement is achieved by infusing 5% dextrose and 0.9% saline or Hartmann's solution. When a large volume of blood has been transfused (4 units or more) there is a theoretical risk of circulating calcium becoming unavailable because of its reaction with citrate in the transfused blood. It is then recommended that 10 ml of 10% calcium gluconate be administered slowly into a separate vein (Jones et al '85: 316, 317).

The five year survival rate of surgically treated early gastric carcinoma is 90 to 95%, with only a small negative increment if lymph node metastases are present. In contrast, the 5 year survival rate for advanced gastric cancer remains below 10%. Gastric lymphomas represent 5% of all

gastric malignancies and are similar to intestinal lymphomas (Crawford '94: 783). The most reliable surgical method is to remove the ulcer completely by partial gastrectomy; a Billroth I gastrectomy is preferred because it allows complete removal of the ulcer and joins the stomach to the duodenal stump by end-to-end anastomosis. This promotes good mixing of the gastric contents with the bile and pancreatic secretions and the great majority of patients secure a satisfactory result. Reasons for an unsatisfactory result include recurrent ulcer, post-vagotomy diarrhea (3-4%), bilious vomiting, dumping, anaemia due to hypochlorhydria which reduces the amount of iron in the jejunum and as many of half of patients have iron deficiency anaemia, and/or vitamins B_{12} deficiency, osteomalacia can result from vitamin D deficiency and weight loss can be a serious complication because there is insufficient stomach to allow a normal meal to be eaten. Most carcinomas can be removed by excising two-thirds to three-quarters of the stomach, and anastomosing jejunum to the gastric remnant. In the course of such operation it is not uncommon to remove the body of the pancreas and the spleen along with the specimen, when a carcinoma has involved the pancreas. The great omentum is removed because it is often the site of transcoelomic spread of the carcinoma. Total gastrectomy is done when the carcinoma lies close to the oesophagogastric junction, the abdominal oesohpagus must included in the resection to secure clearance of invaded tissue. Reconstruction is usually effected by bringing up a loop of upper jejunum through the transverse mesocolon and joining the end of the oesophagus to the top of the loop. Oesophago-gastrectomy is done when the carcinoma invades the gastro-oesophageal junction then more oesophagus must be removed and the anastomosis can only be made by extening the abdominal incision into the left chest, which allows the diaphragm to be split down to the oesophageal hiatus and reveals the whole of the stomach as well as the lower oesophagus lying in the posterior mediastiunum so that a very radical operation can be performed by removing the upper half of the stomach, together with the spleen, and the whole of the left gastric artery and the coeliac lymph nodes. Reconstruction is often effected by closing the distal half of the stomach, bringing it up as a tube, and joining the open end of the oesophagus to an incision into the front of the gastric pouch. The diaphragm is carefully closed around the stomach and the chest wall and abdominal incision sutured with an underwater drain to evacuate the left pneumothorax. About 60% of carcinomas of the stomach can be resected by one or other of these rather major procedures. The mortality of the abdominal gastrectomies is about 5% and for the thoraco-abominal operations it is about 10%. Leiomyoma is an unusual gastric tumour arising from the muscular wall, that may be benign, or have a sarcomatous element and be locally infiltrative; wide local removal is usually the correct treatment. Lymphomas of the gastrointestinal tract are uncommon, about one-half arise in the stomach, but they represent only 1-2% of all gastric neoplasms; in the small bowel, many present as an emergency, either as a perforation with peritonitis, or with intestinal obstruction; there is an association with coeliac disease; radical surgical resection is the best treatment, adjuvant chemotherapy and radiation are often used (Jones et al '85: 90-99).

If colitis is active it is a serious mistake to give constipating drugs such as codeine phosphate or loperamide whereas there is a strong suspicion that they may precipitate toxic megacolon. However, after disease have been excised by right hemicolectomy, or colectomy and ileorectal anastomosis, these drugs are very helpful. After terminal ileal resection, cholestyramine may be useful. Sometimes lower abdominal pain is a feature of relapse and may be helped by antispasmodics such as mebeverine or propantheline (Jones et al '85: 234, 245, 240). One common sense procedure that many people with auto-immune disorders of the gut, particularly *antibiotic associated colitis* that is not treatable by antibiotics, although metronidazole (Flagyl ER) must be tried before attempting such an expensive procedure, might benefit from, is **fecal transplant**, otherwise known as bacteriotherapy. More than 15 fecal transplants have been performed, 13 of which cured their patients. It is a harmless procedure that one might be able to

perform at home with a healthy loved one, but neither modern or traditional medicine perform it. In 2008, Khoruts, a gastroenterologist at the University of Minnesota, took on a patient suffering from a vicious gut infection of *Clostridium difficile*. She was crippled by constant diarrhea, which had left her in a wheelchair wearing diapers. Khoruts treated her with an assortment of antibiotics, but nothing could stop the bacteria. His patient was wasting away, losing 60 pounds over the course of eight months. Khoruts decided his patient needed a transplant. But he didn't give her a piece of someone else's intestines, or a stomach, or any other organ. Instead, he gave her some of her husband's bacteria. Khoruts mixed a small sample of her husband's stool with saline solution and delivered it into her colon. Writing in the 'Journal of Clinical Gastroenterology', Khoruts and his colleagues reported that her diarrhea vanished in a day. Her *Clostridium difficile* infection disappeared as well and has not returned since. The procedure, known as bacteriotherapy or fecal transplantation, had been carried out a few times over the past few decades.

Fecal transplantation is a new treatment with 90% cure rates in the treatment of *Clostridium difficile*. One death from *E. coli* contaminated stool has been reported. The incidence of *C. difficile* infection (CDI) has risen sharply over the last two decades. The number of cases among hospitalized adults tripled between 1993 and 2005 and more than doubled between 2001 and 2005. Mortality rates have also increased, coincident with the emergence of the hypervirulent NAP1/BI/027 strain. Multiple relapses are increasingly common, too, with 20 to 30 percent of patients experiencing at least one recurrence two to four weeks after completing vancomycin therapy. Vancomycin therapy is however generally considered inadequate and ineffective substitute for metronidazole (Flagyl ER). Nonetheless, fecal microbiota transplantation (FMT or fecal transplantation) — has proved highly effective at eradicating *C. difficile* infection and restoring a healthy gut microbiota.The Mayo Clinic in Arizona FMT team first performed a colonoscopic fecal transplant in 2011 for a patient with severe refractory *C. difficile* pseudomembranous colitis, using donated stool from the patient's brother. Since then, Mayo Clinic in Arizona has performed 24 fecal microbiota transplants for CDI patients. In every case, the infection was completely eradicated — often within hours or days — although two patients with comorbidities experienced relapses. Fecal transplantation can be performed via nasogastric tube, nasojejunal tube, upper tract endoscopy, colonoscopy and retention enema, with colonoscopic infusion preferred. Mayo currently uses fecal transplantation only for patients with relapsing *C. difficile* infection. Exclusion criteria include concurrent gastrointestinal illnesses and the inability to undergo colonoscopy. Immunosuppressed and transplant patients — with the exception of recent bone marrow transplants — may qualify. Concerns about the safety of banked stool and patient preference have so far limited donors to family members, but a future project will involve collecting and banking donor stool for study and transplants. So far fecal transplantation has been negligent in the management of multi-drug resistant pathogens, focusing on vancomycin-resistant enterococci (VRE), although vancomycin is well known to be a defective substitute for metronidazole (Flagyl ER) and probiotics in the treatment of *C. difficile*.. The cure rates of fecal transplant are impressive and fecal transplant might be effective for IBS and Parkinson's and as an adjunct in the treatment of most serious abdominal diseases. It however cannot be stressed enough that Metronidazole is the definitive antibiotic treatment for infectious diarrhea.

The elective operation for ulcerative colitis is the **proctocolectomy**. All large-bowel mucosa is removed, so that the disease cannot recur, and the patient can therefore be offered complete relief at the cost of living with a permanent ileostomy. The whole colon is removed, from the ileocaecal valve. The rectum must be carefully removed so that the pelvic autonomic nerves are not disturbed and there should be no interference with bladder or sexual functions. An ileostomy

is fashioned in the right iliac fossa by bringing the cut end of the ileum through a carefully sited circular hole cut in the abdominal wall of the right iliac fossa. The ileum is turned bak to form a spout and the edge of the ileum sutured to the skin edge. An ileostomy bag is immediately applied which fits snugly around the ileostomy and received the ileal effluent. Ileostomy can be avoided in three ways: (1) total colectomy with ileo-rectal anastomosis for patients under 45 with no sepsis and little rectal ulceration in whom 50-60% of patients report highly satisfactory results. (2) Kock's ileostomy involves making an S-shaped pouch of ileum containing a valve which prevents the contents reaching the stoma at skin level. The pouch is emptied by intermittent catheterization and the patient wears only a small flat dressing over the stoma instead of a bag, but there are high complication rates and is not suited to patients with Crohn's disease. (3) perineal reservoir is a recent development where the whole colon and the upper half of the rectum are removed. Then the lower rectum is denuded of mucosa down to the dentate line. An S-shaped pouch of ileum is fashioned, to act as a reservoir, and the efferent limb is brought down and sutured to the upper end of the anal canal and many patients achieve normal defection. The main surgical principle in Crohn's disease is to relieve the complications whilst removing as little normal tissue as possible. There is no evidence that removing enlarged lymph nodes or lengths of normal-looking bowel on either side of diseased segments does anything to improve prognosis (Jones et al '85: 236-240).

The primary therapy of **colorectal cancer** is surgical resection. The overriding principle in surgical management is to resect an adequate segment of bowel containing the area of malignancy and the adjacent mesentery with its lymph nodes. For other than rectal carcinomas, the procedure are variations of rights, left, or transverse colectomies. For rectal cancer, an anterior resection may be performed if the tumor is located proximally enough to allow resection and low rectal anastomosis. If a rectal cancer is so far distal that anastomosis is impossible, then a variation of the Miles procedure, abdominal-perineal resection, must be performed, this procedure sacrifices the rectum, and patients have a permanent colostomy. Since more than 50% of patients with colon cancer develop recurrence, the treatment of advanced colorectal cancer is important. The most common sites of dissemination for colorectal cancer are the liver and the abdominal cavity, with local or disseminated intra-abdominal carcinomatosis. Survival is possible with as little as 25 cm of surviving bowel following resection, as the result of hypertrophy and elongation of the existing villi in adaptation (Jones et al '85: 113-116).

A **urethral catheter** will relieve the obstruction somewhat by eliminating the trigonal stretch. Normal intravesical pressure is about 30 cm of water at the beginning of micturition. Pressures 2-4 times as great may be reached by the trabeculated (hypertrophied) bladder in its attempt to force urine past the obstruction. This pressure tends to push mucosa between the superficial muscle bundles, causing the formation of small pockets, or **cellules**. If cellules force their way entirely through the musculature of the bladder wall, they become saccules, then actual **diverticula**, which may be embedded in the perivesical fat or covered by peritoneum. Diverticula have no muscle wall and are therefore unable to expel their contents into the bladder efficiently even after the primary obstruction has been removed. When **secondary infection** occurs, it is difficult to eradicate; surgical removal of the diverticula may be required. If a diverticulum pushes through the bladder wall on the anterior surface of the ureter, the ureterovesical junction will become incompetent. The pressure within the renal pelvis is normally close to zero. When this pressure increases because of obstruction or reflux, the pelvis and calices dilate. The degree of **hydronephrosis** that develops depends on the duration, degree, and site of the obstruction. The higher the obstruction, the greater the effect on the kidney. As urine is excreted into the renal pelvis, fluid and particularly soluble substances are reabsorbed.

In men the catheter is grasped near its tip with sterile gloves or forceps and is inserted into the external meatus while the penis is stretched with the other hand. The penis must be grasped laterally to avoid squeezing the urethra against the corpora. The catheter must be advanced gently, and if there is resistance, the site of resitance should be determined by palpation f the catheter tip. The male urethra normally offers resistance at the membranous urethra due either to involuntary constriction of the external sphincter because of discomfort or anxiety or due to resistance at the infrapubic angulation between the bulbous and the membranous urethra. Once the resistance of the external sphincter has been overcome, the catheter can usually be easily advanced into the bladder, even in the presence of an obstructing prostatic adenoma. Care must be taken not to injure the urethra by overly forceful manipulation or by passing the tip of the stylet through a side hole of the catheter. **In women**, short, straight catheters are best, especially for self-catheterization. Insertion of a vaginal speculum helps to engage a urethral catheter if the meatus is difficult to visualize. If transurethral catheter insertion is difficult the tip of the catheter can be guided by a finger inserted in the vagina (Thüroff '88: 154- 156).

Renal stones that must be surgically removed may be located in the pelvis, infundibula, calices, or combinations thereof. Indications for surgical removal of urinary stones confined to the upper collecting sytem include intractable urinary tract infection, progressive renal damage, urinary obstruction and persistent pain (despite medical treatment). **Renal cooling** reduces renal metabolism and prevents cellular damage during periods of ischemia associated with intraoperative occlusion of the renal artery. Studies indicate that the idney is optimally protected when it is maintained at approximately 15-20°C. Packing the kidney in ice slush prepared from physiologic salt solutions, applying external cooling coils, and other methods are acceptable ways of cooling the kidney. **Nephrectomy and partial nephrectomy** indiscriminately sacrifice salvageable renal tissue and should be performed only in patients with severe obstruction and parenchumal damage in whom th recovery of real function of that segment is expected to be minimal. Simple **pyelolithotomy** is used for removal of calculi confined to the renal pelvis. Extended pyelolithotomy is needed to remove entrapped calceal stones or large, branched renal caculi. **Pyelonephrolithotomy** is the removal of branched calculi located within the lower pole infundibulum. **Coagulum pyelolithotomy** consists of use of a mixture of pooled human fibrinogen and thrombin to form a clot within the renal collecting system that effectively traps multiple small stones in a large extrarenal renal pelvis and soft calculi, likely to crumble, and facilitates their removal in 10 minutes. **Intersegmental anatrophic nephrolithotomy** is indicated for the removal of multiple or branched calculi associated with infundibular stenosis and where pyelolithotomy is technically impossible, e.g. in the kidney with a small intrarenal renal pelvis, reconstruction of the collecting system should be done to facilitate drainage and reduce the incidence of recurrent stone formation. **Radial nephrotomy** is indicated for the removal of a solitary caliceal stone or a caliceal stone associated with a larger intrapelvic stone. **Ex vivo or "Bench" surgery and autotransplantation** may have a role in the treatment of patients with recurrent stone disease and ahistoyr of multiple surgical procedures, steonosis of the pelvis of proximal ureter, or calculi associated with congenital renal anomalies or of patients with intractable ureteral colic (Spirnak & Resnick '88: 291, 292).

Percutaneous stone removal can be done with (1) a nephroscope inserted through a nephrostomy tract to remove a stone from the renal pelvis or (2) an ultrasound probe to fragment a large (>1.5 cm or branched calculus. No incision is required, many procedures can be performed under local anesthesia, and recovery time is shortened. However, occasionaly nephrostomy drainage will be needed for several weeks and there is a possibility of secondary bleeding. Antimicrobial drugs should be used to treat urinary tract infections before stone manipulation. Extracorporeal shock-wave lithotripsy permits the removal of renal stones without

direct surgical intervention. The patients is given an epidural local or general anesthetic and lowered into a tank of distilled water at the bottom of which is placed the shock-wave electrode used to produce the shock waves that fragment the renal stone. The shock wave produce dby the electrod are focused and directed at the stone by a 2 dimensional radiographic scanning system and are keyed to follow the R wave of the patient's ECG. The average patient receives 1000-1500 shock-wave pulses. After about 200 pules, the stone begins to fragment. Small particles are passed in the urine the next several days. Staghorn calculi may be managed using a combination of percutaneous and ESWL techniques (Spirnak & Resnick '88: 292, 293).

About 10% of all injuries seen in the emergency room involve the genitourinary system to some extent. Microscopic or gross hematuria following trauma to the abdomen or flank indicated injury to the urinary tract. Ureteral injury from external violence is manifested by microscopic hematuria in 90% of cases. Prompt treatment of ureteral injuries is required. The best opportunitie for repair is in the operating room when the injury occurs. About 15% of all pelvic fractures are associated with concomitant bladder or urethral injuries. Iatrogenic injury may result from gynecologic and other extensive pelvic procedures as well as from hernia repairs and transurethral operations. A pelvic abscess may develop from extraperitoneal bladder rupture, if the urine becomes infected, the pelvic hematoma becomes infected too. Intraperitoneal bladder rupture with extravasation of urine into the abdominal cavity will cause delayed peritonitis. Partial incontinence may result from bladder injury when the laceration extends into the bladder neck. Disruptions of the tunica albuginea of the penic (penile fracture) can occur during sexual intercourse. The patient has penile pain and hematoma. This injury should be surgically corrected. Gangrene and urethral injury may be caused by obstructing rings placed around the base of the penis. These objected must be removed without causing further damage. Penile amputation is seen occasionally and in a few patients the penis can be surgically replaced successfully by mirosurgical techniques. Total avulsion of the penile skin occurs from machinery injuries. Immediate debridement and skin grafting are usually successful in salvage. Injuries to the penis suggest possible urethral injuries. Superficial lacerations of the scrotum may be debrided and closed primarily. Blunt trauma may cause local hematoma and ecchymosis, but these injuries resolve without difficulty. One must be certain that testicular rupture has not occurred. Total avulsion of the scrotal skin may be caused by machinery accidents or other major trauma. The testes and spermatic cords are usually intact. These structures must be protected by immediate surgical debridement and by placing the testes and spermatic cords in the subcutaneous tissues of the upper thighs. Later reconstruction of the scrotum can be done with a skin graft or thigh flap. Blunt trauma to the testes causes severe pain and often, nausea and vomiting. Lower abdominal tenderness may be present. A hematoma may surround the testes and make delineation of its margin difficult. Ultrasonagraphy can better define the organ. If rupture has occurred, the sonogram will delineate the injury, which should be surgically repaired (McAninch '88: 302, 306).

The most effective method of relieving obstruction due to benign prostatic hyperplasia is **surgical extirpation**. The objective of surgery is to remove the portion of the enlarged prostate that is causing the obstruction by a technique that is considered effective and safe. Mandatory indications include cases in which ther is total outflow obstruction due directly to enlargement o the prostate and cases in which ther is chronic outflow obstruction impairing renal function or producing distressing symptoms. Bladder tumors may necessitate transurethral resection of the prostate to provide easy access to the bladder for endoscopic inspection, resection of tumors, and obliteration of residual urine. Recurrent gross hematuria or chronic congestive cardiac failure exacerbated by prostatic obstruction may require surgical intervention. When chronic urinary retention produces severe symptoms such as overflow urinary incontinence, urgency, intense

frequency, or severe nocturia, surgery is mandatory. **Transurethral resection** of the prostate is employed in over 90-95% of patients. The mortality rate ranges from 0 to 1.3%, with 0.4% considered the average for experienced urologists. Those not recommended for transurethral resection are (1) patients with a life expectancy less than 6 months who might best be treated by catheter drainage instead, and (2) patients with a physical deformity that prevents proper positioning for endoscopic surgery. Patients with a serum creatinine level of 1.5 mg/kg have a 6-fold increase in postresection morbidity and mortality rates, but they can be treated safely if ther fluid and electrolyte status is continually monitored. During resection, a patients absorbs (on average) about 900 mL of irrigating fluid through the prostatic fossa and open veins. Patients with active urinary tract infections should receive appropriate antimicrobial drugs before they undergo surgery. Many urologists limit their use of transurethral resection to prostates that weight no more than 45 g, while other urologists are comfortable resecting 100 g of tissue or more. Greater morbidity and mortality among patients with glands 60 g or larger has been reported.

More than 90% of patients can anticipate a satisfactory result from surgery, with excellent urinary control and a satisfactory urinary stream. Total permanent urinary incontinence is a postoperative complication that occurs in fewer than 1% of patients.I ntermmittent hematuria may occur in the first 4-6 weeks post-operatively. Urethral stricture has been reported in 6% of patients and epididymitis in 2%. Erectile impotence is rare. Retrograde ejaculation has been reported in 40-50% of patients and is an important issue for preoperative discussion. **Open prostatectomy**, enucleation of adenomatous hyperplastic tissue can be performed by (1) an anterior transcapsular incision (retropubic); (2) a posterior transapsular incision (perineal); or (3) an incision above the pubis and through the bladder neck (suprapubic). In none of these procedures is the entire prostate removed. Indications for an open prostatectomy include, prostates in excess of 60 g, large bladder diverticular or calculi that can be corrected at the time of open surgery, the presence of a sever impassable urethral stricture, and orthopedic conditions that do not allow proper patient positioning for endoscopic surgery. Prolonged postoperative catheter drainage by a urethral catheter, a suprapubic tube, or both is generally necessary for 7-10 days or until healing is complete. Intraoperative bleeding is greater in open prostectomy than in endoscopic surgery and 15% of patients require blood replacement. Postoperative complications of delayed bleeding, urinary incontinence, erectile impotence, and urethral stricture are uncommon. Retrograde ejaculation occurs frequently. About 50% of cases remain clinically stable for years, and a few may even improve spontaneously. In most patients, progression of symptoms eventually requires removal of the obstructing adenoma (Johnson et al '88; 365, 366).

After immunosuppression techniques and genetic matching were developed, **renal homotransplantations** became an acceptable alternative to maintenance hemodialysis. Improved transplantation results are now noted due to the development of newer immunosuppressant drgus (cyclosporine and antilymphocyte preparations). Diet can be less restrictive. The disavantages include bone marrow suppression, susceptibility to infection, cushingoid body habitus, and the psychologic uncertaining of the homograft's future. Most of the disadvantages are related to the medicines (azathioprine and corticosterois) given to counteract the rejection. Later problems with transplantation include recurrent disease in the transplanted kidney (Amend et al '88: 532). Renal transplantation is an effective form of therapy for patients with end stage renal disease. The surgical technique of **renal transplantation** involves vascular anastomoses and establishment of urinary tract continuity. In adults the kidney is laced through an oblique lower abdominal incision and the common iliac and internal iliac (hypgastric) arteries are mobilized. The iliac veins are similarly mobilized ot hath an end-to-side

renal vein-to-iliac vein anastomosis can be performs. When multiple arteries are present in cadaver donors, the kidneys are transplanted with anastomosis of a Carrel patch of aorta to the common iliac artery. In small children, a mdline abdomal incision is used and the cecum and ascending colon are mobilized, exposing the aorta and vena cava. An end-to-side anastomosis of the renal vessels to the vena cava and aorts is then easily accomplished. Arterial anastomosis is performed by using a Carel patch of donor aorta, and wheneve possible a Carel patch of the vena is used for the venous anastomosis. Urinary tract continuity can be established by pyeloureterostomy, ureteroureterostomy, or ureteroneocystostomy. Ureteroneocystostomy has an incidence rate of primary ureteral leaks of less than 1%.

Foley catheter drainage is maintained for 1 week, because of the impaired wound healing associated with immunosuppressive therapy. Intravenous fluids are given immediately after the operation at a rate to maintain a good diuresis. Renal failure following transplantation can be difficult when urinary output suddenly decreases shortly after and transplantation or when rejection is superimposed upon acute tubular necrosis. Hyperacute rejection is mediated by humoral antibodies. It occurs in patients who have preexisting circulating cytotoxic antibodies that react with the donor kidney. Acute rejection generally presents during the first several months following transplantation. This type of rejection is usually characterized by fever, oliguria, weight gain, tenderness and enlargement of the graft. Treatment has traditionally been by increasing the dosage of corticosteroids, but the use of antithymocyute globulin or monoclonal antibodes has also proved very effective at reversing rejection. Chronic rejection is a late cause of renal deterioration over several years after inception of impaired renal function. The principal drugs used in conventional immunosuppression are prednisone and azathioprine or (Imuran) an antimetabolite, or cyclosporine, are used in combination. After a policy of low-dose immunosuppressve therapy was adopted in 1972, the cumulative patient mortality rate has been reduced to 2% at 1 year and 3% at 2 years for living related transplants and 4% and 6% for cadaver transplants. Living related transplantations should achieve greater than 90% graft survival at 2 years with conventional immunosuppression. The survival rate of cadaver grafts has been about 60% at 1 year and 55% at 2 years with conventional immunosuppression and with refined immunosuppression cadaver graft survival rates are approximately 80% at 1 year and 75% at 2 years (Salvatierra & Faduka '88: 535-537).

More than 2800 **renal transplants** have been performed at the University of California, San Francisco (UCSF) by 1988. The principal indication for renal transplantation is end stage renal failure. Patients with active infections or primary oxalosis are not accepted for transplantation. Approximately 90% of patients now receive transplants with their own kidneys left in situe. The indications for preliminary nephrectomy are anatomic abnormalities, severe hypertension, some cases of polycystic renal disease. Some transplant centers have performed splenectomy before transplantation, but there is still not clear evidence that it modifies the immunologic reaction. In addition, there is evidence the patients who have undergone splenectomy are predisposed to pneumococcal and other infections. The kidney to be transplanted can be obtained from either a living related donor or a cadaver donor. Living related donors are usually siblings or parents, but in some cases, more distant relative may be accepted. Histocompatibility is assess by determination of human leukocyte antigens (HLA) to establish the inheritance pattern in a family group. The best donor-recipient combinations share all HLA antigens The prognosis for long term graft survival is about 90%. Cadaver kidneys are not acceptable from newborns or those over age 55, preexisting renal disease or neoplastic disease, Blood transfusions prior to transplantation enhance graft survival. Preservation of the cadaver kidney prior to transplantation can be accomplished by hypothermic storage (up to 24 hours) or by pulsatile perfusion (up to 3 days). When perfusion preservation was started immediately after

nephrectomuy, the postoperative dialysis rates following transplantation has been 20% and an average of only 2 or 3 dialysis treatments was required for each patient. One year cadaver graft survival rates of greater than 80% are regularly achieved with conventional immunosuppression (Salvatierra & Feduska '88: 533, 534, 536).

Liver transplantation is the replacement of the native, end stage diseased liver by a normal organ (allograft). The preferred and technical most advanced approach is orthotopic transplantation, in which the native organ is removed and the donor organ is inserted int eh same anatomic location. Pioneers in the 1960s by Starzl at the University of Colorado and, later, at the University of Pittsburgh and by Calne in Cambridge, England, liver transplantation is now performed routinely by dozens of centers throughout North America and western Europe. Success and survival have improved from approximately 30 percent in the 1970s to >80 percent today. These improved prospects for prolonged survival, dating back to the early 1980s, resulted from refinements in operative techniques, improvements in organ procurement and preservation, advances in immunosuppressive therapy, and, perhaps most influentially, more enlightened patient selection and timing. Despite the perioperative morbidity and mortality, the technical and management challenges of the procedure, and its costs, liver transplantation ahs become the approach of choice for selected patients whose chronic or acute liver disease is progressive, life-threatening, and unresponsive to medial therapy. Based on the current level of success, the number of liver transplants has continued to grow each year; in 1995, as many as 6000 patients in the United States were on a waiting list for a donor liver (Dienstag '98: 1721).

Transplantation should be considered in patient with **end-stage liver disease** who are experiencing or have experienced a life-threatening complication of hepatic decompensation, whose quality of life has deteriorated to unacceptable levels, or whose liver disease will result predictably in irreversible damage to the central nervous system (CNS). The most common reaons for transplantation in children is biliary atresia, inherited or genetic disorders of metabolism associated with liver failure. Liver transplantation is indicated for end-stage cirrhosis of all causes in adults. In sclerosing cholangitis and Caroli's disease (multiple cystic dilations of the intrahepatic biliary tree, recurrent infection and sepsis associated with inflammatory amnd fibrotic obstruction of the biliary tree may be an indication for transplantation. Beause prior biliary surgery complicates, and is a relative contraindication for, liver transplantation, surgical diversion of the biliary has been all but abandoned for patient with sclerosing cholangitis. In patients who undergo transplantation for hepatic vein thrombosis (Budd-Chiari syndrome), postoperative, anticoagulation is essential; underlying myeloproliferative disorders may have to be treated but are not a contraindication to liver transplantation. If a donor organ can be located quickly, before cerebral edema set in, patients with fulminant hepatitis are candidates for liver transplantation. More controversial as candidates for liver transplantation are patient with alcoholic cirrhosis, chronic viral hepatitis and primary hepatoculleular malignancies. Absolute **contraindications for transplantation** include life-threatening systemic diseases, uncontrolled extrahepatic bacterial or fungal infections, preexisting advanced cardiovascular or pulmonary disease, multiple uncorrectable life-threatening congenital anomalies, metastatic malignancy, active drug or alcohol abuse, and human immunodeficiency virus (HIV) infection. Because carefully selected patients in their sixties and seventies have undergone transplantation successfully, advanced age per se is no longer considered an absolute contraindication; however, in older patients, a more thorough preoperative evaluation should be undertaken to exclude ischemic cardiac disease (Dienstag '98: 1721, 1722).

After the patient has been identified as a candidate and a donor organ has been procured, the actual **liver transplantation** surgical procedure can take 8 to 22 hours to complete. The procedure involves five anastomoses between recipient and donor organs, including the following vascular anastomosis sites: suprahepatic inferior vena cava, infrahepatic vena cava, portal vein, hepatic artery and biliary tract. The biliary anastomosis site varies, depending on the patient's extrahepatic biliary tract. Critical issues in the post-transplantation period include the following: hypertension, renal dysfunction, hyperlipidemia and cardiovascular disease, obesity, osteoporosis and increased risk for cancer. Psychological issues are especially prominent and caregivers and family should be alert for signs of depression and anxiety. Many of the antirejection medications exacerbate these symptoms. With careful follow-up, OLT recipients can live productive lives for many years after transplantation. Chronic rejection, often in the setting of progressive ductopenia, and recurrence of primary pre-transplantation liver disease tend to cause graft failure with time. Actuarial survival at 5 years is approximately 88% for persons with cholestatic liver disease, 78% for patients with non-cholestatic liver disease who are HCV negative, and 70% for persons with HCV (Sartin '05: 954, 955).

The **survival rate** for patients undergoing liver transplantation has improved steadily since 1983. One-year survival rates have increased from approximately 70 percent in the early 1980s, to 80 to 90 percent in the mid – 1990s. Currently, the 5-year survival rate approaches 60 percent. Survival after retransplantation for primary graft nonfunction is approximately 50 percent. Causes of failure of liver transplantation vary with time. Failures within the first 3 months result primarily from technical complications, postoperative infections and hemorrhage. Transplant failures after the first 3 months are more likely to result from infection, rejection, or recurrent disease (such as malignancy or viral hepatitis). The recurrence of autoimmune hepatitis or primary sclerosing cholangitis has not been reported. There have been reports of recurrent primary biliary cirrhosis after liver transplantation; however the histologic features of primary biliary cirrhosis and acute rejection are viturally indistinguishable and occur as frequently in patients with primary biliary cirrhosis as in patients undergoing transplantation for other reasons. Patients who undergo liver transplantation for chronic hepatitis B plus D have a better survival rate than patients undergoing transplantation for hepatitis B alone. Recurrence of hepatitis C virus (HCV) after liver transplantation can be documented in almost every patient and about 5 to 10 percent of patients have sufficiently severe recurrent hepatitis C to merit antiviral therapy with interferon. Patients who undergo liver transplantation for end-stage alcoholic cirrhosis are at risk of resorting to drinking again after transplantation, a potential source of recurrent alcoholic liver injury. Currently alcoholic liver disease is one of the most common indication for liver transplantation and most transplantation centers screen candidates carefully for predictors of continued abstinence. Recidivism is more likely in patients whose sobriety prior to transplantation was shorter than 6 months. **Full rehabilitation** is achieved in the majority of patients who survive the early postoperative months and escape chronic rejection or unmanageable infection. Psychosocial maladjustment interferes with medical compliance in a small number of patients, but most manage to adhere to immunosuppressive regimen, which must be continued indefinitely. In one study, 85 percent of patients who survived their transplants returned to gainful activities. In fact, some women have conceived and carried pregnancies to term after transplantation without demonstrable injury to their infants (Dienstag '98: 1724, 1725).

Part VI Agriculture

1. Federal Administration

The Historical Supplemental Nutrition Assistance Program (SNAP) budget table has been switched with a patently defective monthly and Food and Nutrition Service (FNS) is unavailable by regular email. Due to undeclared use of undistributed offsetting receipts by the United States Department of Agriculture (USDA) and Office of Management and Budget (OMB) to, for instance, subsidize agriculture with commodity insurance for trade war losses, with unspent food stamp agricultural subsidy estimates, there is not much cause for alarm regarding theft, this is a declaration of anorexia by the FNS incidental to failing to sustain SNAP benefit growth. Having Bachelored the exclusion of revenues in federal outlay estimates, the USDA Budget Office must take full responsibility accounting for FNS, especially the largest UDSA program SNAP, and cannot rest until the Historical SNAP table is updated right. FNS has made many verifiable mathematical errors since they started to cut SNAP benefits. Cutting SNAP benefits is also the reason that morale is low in the USDA. The Forest Service (FS) needs to be transferred to the Interior Department, who cannot currently afford to adopt the FS budget, in every case, and by Congress, to prevent agricultural fire risk, 65 times greater in National Forests than National Parks. To master their job the budget office is instructed to upgrade their balance sheet(s) at the end of their congressional budget justification, to account for undistributed offsetting receipts, federal outlays and program level, in one consolidated balance sheet, that is internally consistent with sub-agency descriptions in the same document, that requires further investigation, regarding the Department's largest program, from most recent Historical SNAP spending data.

USDA Consolidated Balance Sheet FY 17 – FY 20
(millions)

	2017 Review	2018 Estimate	2019 Budget	2020
Total Federal Outlays	129,786	137,848	133,299	141,299
Budget Request	145,939	143,606	139,429	157,161
Undistributed Offsetting Receipts	[16,153]	[5,758]	[6,130]	[15,862]
Total Budget Authority	214,622	218,848	210,264	228,558
Farm Production and Conservation FPAC				
Farm Service Agency, Federal Outlays	1,458	1,328	1,012	1,593
Transfer from Program	[310]	[308]	[267]	[339]
Farm Loan Programs	[8,003]	[7,996]	[7,618]	[8,328]
Commodity Credit Corporation Fund	[7,065]	[8,450]	[10,318]	[7,027]

Commodity Credit Corporation Outlays	[9,969]	[11,277]	[7,655]	[11,481]
Subtotal, Farm Service Agency	[26,805]	[29,359]	[26,870]	[28,768]
Risk Management Agency, Federal Outlays	5,254	8,962	8,818	6,003
Crop Insurance Premiums	[3,677]	[3,786]	[3,639]	[3,730]
Subtotal, Risk Management Agency	[8,847]	[12,764]	[12,390]	[9,642]
Natural Resources Conservation Service	4,520	4,306	4,336	4,934
Subtotal Federal Outlays FPAC	11,232	14,596	14,166	12,530
Subtotal Budget Authority, FPAC	[40,256]	[46,413]	[43,663]	[43,435]
Trade and Foreign Agricultural Affairs				
Foreign Agricultural Service				
Salaries and Expenses, Federal outlays	197	195	193	215
Market Development Programs	278	398	230	304
Foreign Food Assistance	1,802	1,789	0	1,969
Subtotal Federal Outlays, TFAA	2,277	2,382	423	2,488
Expense Transfer from CCC Export Credit	[6]	[6]	]6]	[7]
Export Credit	[1,582]	[5,500]	[5,500]	[2,000]

Guarantees				
Subtotal, Budget Authority TFAA	[4,032]	[7,957]	[6,098]	[4,679]
Rural Development				
Rural Utilities Service	[8,886]	[8,884]	[7,402]	[8,967]
Loans	[8,190]	[8,195]	[7,408]	[8,230]
Federal Outlays	696	689	-6	737
Rural Housing Service	[30,059]	[30,033]	[29,503]	[30,435]
Loans	[27,991]	[27,978]	[27,760]	[28,200]
Federal Outlays	2,068	2,055	1,743	2,235
Rural Business-Cooperative Service	[1,420]	[1,580]	0	[1,544]
Loans	[1,243]	[1,415]	0	[1,358]
Federal Outlays	177	165	0	186
Subtotal, Federal Outlays Rural Development	2,941	2,909	1,737	3,158
Subtotal, Budget Authority Rural Development	[40,376]	[40,497]	[36,905]	[40,946]
Food Nutrition and Consumer Services				
Food and Nutrition Service				
Supplemental Nutrition Assistance Program	70,507	70,500	70,500	72,827
Child Nutrition Programs	22,794	24,444	23,147	25,126
Woman, Infants and Children (WIC)	6,350	6,313	6,465	7,000
All Other	698	702	717	759
Total, FNCS	100,349	104,872	105,709	110,319

Food Safety				
Federal Outlays	1,032	1,021	1,031	1,116
Revenue Funded	[247]	[236]	[240]	[270]
Food Safety and Inspection Service	[1,279]	[1,257]	[1,271]	[1,386]
Natural Resources and Environment				
Forest Service	6,077	6,006	5,172	5,305
Marketing and Regulatory Programs				
Animal and Plant Health Inspection Service	1,305	1,289	1,035	1,402
Agricultural Marketing Service, Federal Outlays	1,079	1,096	996	1,176
Subtotal Federal Outlays MRP	2,384	2,385	2,031	2,578
AMS User Fee Funded	[222]	[226]	[255]	[243]
AMS Budget Authority	[1,301]	[1,322]	[1,251]	[1,419]
Subtotal, Budget Authority MRP	[2,606]	[2,611]	[2,286]	[2,821]
Research, Education and Economics, Subtotal	3,068	3,049	2,650	3,355
Agricultural Research Service	1,277	1,267	1,070	1,396
National Institute of Food and Agriculture	1,533	1,526	1,370	1,677
Economic Research Service	87	86	45	95
National Agricultural Statistics Service	171	170	165	187

Departmental Activities, Subtotal	426	428	380	450
Office of the Secretary	52	54	54	57
Office of Civil Rights	24	24	22	26
Office of Inspector General	98	98	87	106
All Other Staff Offices	253	253	218	262
Total Federal Outlays	129,786	134,935	128,419	141,299
Budget Request	145,939	143,606	139,429	157,161
Undistributed Offsetting Receipts	[16,153]	[8,671]	[11,010]	[15,862]
Total Budget Authority	214,622	215,935	205,384	223,951

Source: USDA Budget Summary FY 19 [non-add in re: outlays]; USDA FNS 2017

The whiting out of FNS SNAP historical tables is perplexing because 3.3% spending growth from the previous year is the welfare program settlement, but they don't produce previous year statistics anymore. Because the have broken the SNAP promise made in the Farm Bill of 2008 to not cut benefits, and marked immigrants for death by starvation, a crime of genocide, consumer confidence in the program is ill-advised and it was planned to increase benefits with 2.7% average annual inflation and population growth of only 0.6%, costing 3.3% more than previous year. Booms precedes bust, arrears from FY 16 are therefore ill-advised at the macroeconomic level for welfare programs and large agencies, enjoyed by smaller agencies, but 1% population growth would be considered normal. Since FY 17, the last year for which SNAP statistics were done, it is can be guesstimated that there are slightly fewer beneficiaries, and slightly lower spending, but the decline is not as much as FY 16- FY 17 when immigrants were initially targeted for death by starvation. Therefore the settlement is 3.3% SNAP spending growth from FY 17 program levels, to provide for a benefit that is perpetually 2.7% greater than the previous year, and 1% population growth FY 20 and 0.6% population growth every year thereafter. The White House OMB will appreciate that the Hebrew the word for “leek” is the same as “cut” and while weapons of war are to be turned into plough-shares by the $2.1 billion FY 20 Food for Peace program, the consolidated balance sheet will turn his agricultural budget cuts into leeks, and obese people will be tempted to make famine with “pork” barrel politics, no more, and “grow SNAP benefits”. SNAP spending is re-estimated at zero growth FY 18 – FY 19 and 3.3% growth from FY 17 in FY 20. The burden of proof is upon the USDA budget office to re-produce the following consolidated balance sheet so that it is internally consistent with sub-agency descriptions in the congressional budget justification. It is good that the USDA produce the first FY 21 budget, because their issues regarding internal consistency and the declaration of undistributed offsetting receipts are the same as OMBs.

The U.S. Department of Agriculture (USDA) provides leadership on issues related to food, agriculture, food safety, rural development, and natural resources. The USDA was founded by President Abraham Lincoln's signature of the Act to Establish a Department of Agriculture on May 15, 1862. The U.S. Department of Agriculture (USDA) is made up of 30 agencies and offices with nearly 100,000 employees who serve the American people at more than 4,500 locations across the country and abroad. The U.S. Department of Commerce, Bureau of the Census conducted the census of agriculture for 156 years (1840-1996). The 1997 Appropriations Act contained a provision that transferred the responsibility for the census of agriculture to National Agricultural Statistics Service (NASS). Since 2017 the USDA was reorganized several times, without authorization of Congress, to negotiate with torturous Presidential budget cut and negative subsidy demands. Farm and Foreign Agricultural Services was divided into Farm Production and Conservation (FPAC) governed by a worthless Business Center and Trade and Foreign Agricultural Affairs with responsibility for the Codex Alimentarius. P.L. 480 International Food Assistance transfer to USAID must be sustained at 3% annual growth from FY 17 to redress an increase in global hunger since 2016. Estimates of outlays for the Commodity Credit Corporation, Risk Management and Rural Business Cooperative Services have moderated after revenues ceased to be accounted for by more carefully differentiating program level and outlays pursuant to right interpretation of the Federal Credit Reform Act of 1990 under 2USC§661c. Because of the comfortable (silo) profit margin of undistributed offsetting receipts, by the agriculture department, the budget request should increase 2.5% annually from FY 17. OMB should not attempt to cut agricultural spending, OMB should account for Agriculture Department undistributed offsetting receipts to reduce the deficit and pay for the beginning of next year's agriculture budget. The USDA Budget Office balance must produce a consolidated balanced sheet to add exact sub-agency budget requests. This is the same problem that OMB is having with adding a list of exact Cabinet agency congressional budget request entries. The USDA budget office must double check SNAP spending against the FNS historic record. SNAP consumer spending and producer morale could grow 3.3% annually for the same agricultural subsidy price as accounting errors and commodity insurance.

The USDA governs and subsidizes the agricultural sector with loans, insurance, food stamps and international assistance to sustain consumer economic growth with a minimum of consumer price inflation, in a free market. Outlays for government are expected to grow 2.5% government, 3% services and 3.3% SNAP to afford 2.7% average annual consumer price inflation and 0.6% population growth. Because of the comfortable margin of undisclosed undistributed offsetting receipts the official budget request is estimated to grow 2.5% while most USDA sub-agencies grow 3%. USDA would sustain 1% net new employees and 1.5% raise FY 19 and FY 20. The Forest Service who needs to be transferred to the Interior Department to prevent agricultural fire risk. The Interior cannot however afford the Forest Service without the continuing support of USDA until it is integrated into the Interior Department congressional budget request by Act of Congress. SNAP benefits need 3.3% annual growth in total spending, to help a growing population of consumers afford 2.7% average annual rate of consumer price index inflation more than the bare bones diet of the previous year, rather than less to re-interpret the totalitarian famine ordered by the Thrifty Food Plan to pay for the bare bones diet of the previous year. The USDA anticipates it will exhaust savings from hyperinflation in their previous total budget requests by FY20, but their overestimates of sub-agency outlays in the USDA total outlay table continues to be a $10 billion a year rescission business. The bulk of the continuing agriculture department budget errors involves overestimates of SNAP spending in the FNS sub-agency budget that must checked against the historic SNAP table to begin to sustain 3.3% annual total consumer agricultural subsidy growth. The entire USDA Budget table however must be internally consistent with all subagency budgets. The USDA Budget Office needs to produce a

consolidated balance sheet to accurately express the USDA budget authority, budget request, federal outlays and undistributed offsetting receipts.

The programs and funding of Food, Nutrition, and Consumer Services (FNCS) provide access to safe, nutritious, and wholesome meals, while promoting a healthy diet. Within FNCS, the Food and Nutrition Service (FNS) administers USDA's domestic nutrition assistance programs. Working in partnership with State agencies and other cooperating organizations, FNS helps ensure children and low-income Americans have sufficient food to support nutritious diets. Over the course of a year, one in four Americans will be served by one of USDA's 15 nutrition assistance programs. The Budget includes funding to support estimated participation levels under current law, including $73.2 billion for the Supplemental Nutrition Assistance Program (SNAP), $23.1 billion for Child Nutrition Programs, and $5.8 billion for the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). In 2019, participation levels are estimated: 40.8 million per month for SNAP, 30.7 million per day for the Child Nutrition Program (CNP), and 6.9 million per month for WIC. The U.S. Department of Agriculture (USDA) Food and Nutrition Services (FNS) Supplemental Nutritional Assistance Program (SNAP) serves as the first line of defense against hunger. It enables low-income families to buy nutritious food with Electronic Benefits Transfer (EBT) cards. Food stamp recipients spend their benefits to buy eligible food in authorized retail food stores. The USDA is not accountable for the larger FNS programs SNAP and WIC but the microprograms appear well-estimated. The FNS must ensure the USDA uses accurate SNAP and WIC statistics when calculating the FNS budget and USDA totals. It is advised provide for 2.7% average annual inflation and 0.6% population growth, 3.3% annual growth for SNAP, CNP and WIC program spending, 3% for other nutrition services. Due to the moral hazards of accounting errors and commodity insurance, it does not cost more to subsidize consumers with agricultural subsidies.

Food and Nutrition Service (FNS) Outlays FY 17 – FY 20
(millions)

	FY 2017	FY 17 Review	FY 2018	FY 2019	FY 2020
Discretionary					
Special Supplemental Nutrition Program (WIC)	6,350	6,350	6,313	6,465	7,000
Commodity Assistance Program					
Commodity Supplemental Food Program	236	236	238	244	258
The Emergency Food Assistance Program, Soup	59	59	59	61	65

Kitchens, Food Banks					
Farmers' Market Nutrition Program	19	19	19	19	19
Pacific Island Assistance and Disaster Assistance	1	1	1	1	1
Nutrition Services Incentive Program	3	3	3	3	3
Total Commodity Assistance Program	318	318	320	328	346
Nutrition Programs Administration	171	171	170	174	187
Total, Discretionary Programs	6,839	6,839	6,803	6,967	7,533
Mandatory					
WIC Universal Product Database	1	1	1	1	1
Supplemental Nutrition Assistance Program (SNAP)	78,481	70,507	70,500	70,500	72,827
Child Nutrition Programs (CNP)	22,794	22,794	24,244	23,147	25,126
Permanent Appropriations	187	187	190	193	204
Farm Bill: Seniors	21	21	21	21	21

Farmers' Market Nutrition Program					
Total Mandatory Programs	101,484	93,510	98,069	98,742	98,178
Total, Discretionary Programs	6,839	6,839	6,803	6,967	7,533
Total Current Law	108,323	100,349	104,872	105,709	105,711

Source: USDA FY 19 pg. 42; FNS 1969-2017

After re-estimating the Food and Nutrition Service (FNS) on pg. 42 of USDA FY 19, using much lower estimates from FNS 1969-2017, 3.3% growth in SNAP spending FY 19 – FY 20 can be calculated for less FY 17 – FY 18 and nearly exactly the same FY 19 – FY 20 as requested in the total FNS request on pg. 80 of USDA FY 19. SNAP benefit amount determined by the Thrifty Food Plan could begin to grow at exactly the 2.7% (2018) annual average rate of consumer price index inflation more than the year before, rather than less, and the beneficiary population could grow 0.6% annually, for 3.3% annual growth in federal outlays. The Budget includes a bold new approach to nutrition assistance that combines the use of traditional SNAP Electronic Benefit Transfer (EBT) cards with a USDA Foods Box that contains 100 percent American grown products. Specifically, the USDA Foods Box proposal has self-incriminated regarding potential to reduce waste, fraud, and abuse by limiting opportunities for benefits to be misused or trafficked. The USDA has deprived SNAP beneficiaries of the tenure promised by Food, Conservation and Energy Act of 2008 H.R. 2419. Taking into consideration the extremely high 22%-33% rates of child poverty, it is necessary to rule that CNP, SNAP and WIC benefits grow at an annual rate of 2.7% to compete with 2.7% average annual consumer price inflation, to feed 0.6% more people annually, with 3.3% annual spending growth.

The Food Stamp Act of 1977 codified at 7USC§2011 set forth a program of food stamps to guarantee low income people and families an adequate nutritious diet to eliminate hunger and malnutrition. Participation in the food stamp program is limited to those households whose incomes and other financial resources, held singly or in joint ownership, are determined to be a substantial limiting factor in permitting them to obtain a more nutritious diet, upper limit of household income is 130% of the poverty line. SSI beneficiaries are automatically eligible under 7USC§2014. Under SNAP rules, the maximum benefit levels for each fiscal year — which are the benefit amounts that go to households with no disposable income after deductions for certain necessities — are set at 100 percent of the cost of the Thrifty Food Plan, USDA's estimate of the minimum amount that a family needs to afford a bare-bones, nutritionally adequate diet, for the preceding June. Thrifty Food Plan needs to be reformulated to provide for 2.7% average consumer price inflation more than the bare bones diet of the previous year, to avoid being charged with totalitarian famine.

Supplemental Nutrition Assistance Program (SNAP) Statistics 1969-2020

Fiscal Year	Average Participation	Average Benefit	Total Benefits		Total Costs
	--Thousands--	--Dollars--	----------Millions of Dollars----------		
1969	2,878	6.63	228.80	21.70	250.50
1970	4,340	10.55	549.70	27.20	576.90
1971	9,368	13.55	1,522.70	53.20	1,575.90
1972	11,109	13.48	1,797.30	69.40	1,866.70
1973	12,166	14.60	2,131.40	76.00	2,207.40
1974	12,862	17.61	2,718.30	119.20	2,837.50
1975	17,064	21.40	4,385.50	233.20	4,618.70
1976	18,549	23.93	5,326.50	359.00	5,685.50
1977	17,077	24.71	5,067.00	394.00	5,461.00
1978	16,001	26.77	5,139.20	380.50	5,519.70
1979	17,653	30.59	6,480.20	459.60	6,939.80
1980	21,082	34.47	8,720.90	485.60	9,206.50
1981	22,430	39.49	10,629.90	595.40	11,225.20
1982	21,717	39.17	10,208.30	628.40	10,836.70
1983	21,625	42.98	11,152.30	694.80	11,847.10
1984	20,854	42.74	10,696.10	882.60	11,578.80
1985	19,899	44.99	10,743.60	959.60	11,703.20
1986	19,429	45.49	10,605.20	1,033.20	11,638.40
1987	19,113	45.78	10,500.30	1,103.90	11,604.20
1988	18,645	49.83	11,149.10	1,167.70	12,316.80
1989	18,806	51.71	11,669.78	1,231.81	12,901.59
1990	20,049	58.78	14,142.79	1,304.47	15,447.26
1991	22,625	63.78	17,315.77	1,431.50	18,747.27
1992	25,407	68.57	20,905.68	1,556.66	22,462.34
1993	26,987	67.95	22,006.03	1,646.94	23,652.97
1994	27,474	69.00	22,748.58	1,744.87	24,493.45
1995	26,619	71.27	22,764.07	1,856.30	24,620.37
1996	25,543	73.21	22,440.11	1,890.88	24,330.99
1997	22,858	71.27	19,548.86	1,958.68	21,507.55
1998	19,791	71.12	16,890.49	2,097.84	18,988.32
1999	18,183	72.27	15,769.40	2,051.52	17,820.92
2000	17,194	72.62	14,983.32	2,070.70	17,054.02
2001	17,318	74.81	15,547.39	2,242.00	17,789.39
2002	19,096	79.67	18,256.20	2,380.82	20,637.02
2003	21,250	83.94	21,404.28	2,412.01	23,816.28
2004	23,811	86.16	24,618.89	2,480.14	27,099.03
2005	25,628	92.89	28,567.88	2,504.24	31,072.11
2006	26,549	94.75	30,187.35	2,715.72	32,903.06
2007	26,316	96.18	30,373.27	2,800.25	33,173.52
2008	28,223	102.19	34,608.40	3,031.25	37,639.64
2009	33,490	125.31	50,359.92	3,260.09	53,620.01
2010	40,302	133.79	64,702.16	3,581.78	68,283.94

2011	44,709	133.85	71,810.92	3,875.62	75,686.54
2012	46,609	133.41	74,619.34	3,791.27	78,410.61
2013	47,636	133.07	76,066.32	3,866.98	79,933.30
2014	46,536	125.35	69,999.81	4,130.17	74,129.98
2015	45,800	126.83	69,705.77	4,233.42	73,939.19
2016	44,300	125.52	66,672.64	4,339.27	71,011.91
2017	43,857	125.52	66,059.17	4,447.75	70,506.92
2020	44,120	128.90	68,244.82	4,581.18	72,826.00

Source: USDA Food and Nutrition Service 2017, projection 2020 HA

Using accurate statistics from 2017 SNAP benefits remained the same as the previous year at $125.52, total food stamp spending declined from $71 billion (2016) to $70 billion (2017), while administrative spending increased from $4.3 billion (2016) to $4.5 billion (2017). Because food stamps has been subjected to so many cuts, growth the estimates for 2018, 2019 and 2020 are more than the market can bear. Trump Administration anti-immigrant policy regarding SNAP constitutes genocide. The immigration applications of people who apply for food stamps have been denied so that they are both deprived of food and deported so that it is as if they had been exterminated and no longer exist and this constitutes a grave breech of Sec. 2, Arts. 23, 55 and 147 of the Fourth Geneva Convention Relative to Civilians in Times of War (1949) and genocide under 18USC§1091. The genocide convention is applicable if a particular class of people has been marked for extermination by the authorities- even if by starvation rather than outright execution. Punitive rationing occurred in the Chinese famine of 1958-62 village families who descended from landlords were not fed at all or were fed a lower ration than the poorer class of peasants. Research on the Ukrainian famine in the early 1930's proved that Stalin's objective was to liquidate the kulak class of farmers (Natsios '01: 49-54). Trump Administration growth at the expense of benefit reductions, in both its forms, racial discrimination against ethnic Hispanics, other immigrants and work requirements, are prohibited as incitement to ethnic violence by means anti-immigrant worker propaganda under Art. 20 of the International Covenant on Civil and Political Rights. Food Stamps are unpopular because the USDA has broken the promise not to cut SNAP benefits made by the Farm Bill of 2008 so many times, few people qualify under the asset test and fewer want to be cut again. Anti-immigrant policies and work requirement must be overruled to sustain SNAP growth under the Farm Bill of 2008 and stop burdening the budget with the USDAs several failed attempts to account for a depressed SNAP balance. SNAP grows 3.3% - 2.7% benefit inflation and 0.6% population. Because the SNAP agricultural subsidy is expensive, the FNS has one of two settlement options, a program level that is 3.3% greater than the previous year, estimated to be the same as 2017 or a program level that is 3.3% annually more than 2017, and is expected to buy the cheaper option – 3.3% greater than previous years (+/- = 2017) – to administrate $72.8 billion for 44,120,000 $128.90 benefits in 2020.

Food stamp statistics date to 1969 when $250.5 million fed 2.8 million people. The Food Stamp Act of 1977 wrongly reduced benefits from $5.7 billion for 18.6 million beneficiaries in 1976 to $5.5 billion for 17 million beneficiaries in 1977. Beneficiaries rose to 21 million in 1981 but fluctuated downward until Public Law 100-435, the Hunger Prevention Act of 1988 was signed into law September 19, 1988. Following this initiative, Public Law 101-624, the Mickey Leland Memorial Domestic Hunger Relief Act of November 28, 1990 established EBT as an issuance alternative and permitted the Department to continue to conduct EBT demonstration projects. Following the Personal Responsibility and Work Opportunities Reconciliation Act of 1996 (PRWORA) that removed the entitlement of recipients to AFDC and replaced that with a new

block grant to states called Temporary Assistance to Needy Families (TANF) food stamp benefits languished.

The Farm Bill of 2008 changed the name of the Food Stamp Program to Supplemental Nutrition Assistance Program (SNAP). Promising not to cut benefits the average benefit amount increased rapidly from $96.18 in 2007 to $102.19 in 2008, to $125.31 in 2009 to $133.79 in 2010. Participation increased 53% from 26.3 million in 2007 to 40.3 million in 2010 reaching a high of 47.6 million in 2013. SNAP promised not to cut benefits and between 2008 and 2013 had the longest uninterrupted spurt of food stamp benefit growth the nation has ever enjoyed. The USDA then intentionally, abruptly, and with significant terrorism, cut aggregate SNAP benefits on Halloween 2013 and Thanksgiving 2016, but couldn't do the math right, although they tried twice on October 7 and November 10, 2016. Average benefits payments went down from $133.07 in 2013, to $125.01 in 2014, up to $126.83 in 2015 and down again to $125.52 in 2016 this counts as two counts of intentional deprivation of relief benefits under 18USC§246. A strange section pertaining to publicly operated community health centers (from 1985?) needs to be repealed under 7USC§212a.

After the Farm Bill of 2002 food stamp participation increased from about 17.2 million in fiscal year 2000 to 26 million people in July 2006. The rate of payment accuracy in the FSP improved 34 percent between FY2000 and FY2004 and the 94.12% overall payment accuracy rate was the highest achieved since the inception of the program. USDA awarded $48 million to 24 States for their exemplary administration of the program in fiscal year (FY) 2005. By August 2008, participation had reached an all-time (non-disaster) high of 29 million people per month. The 2008 farm bill (H.R. 2419, the Food, Conservation, and Energy Act of 2008) was enacted May 22, 2008 through an override of the President's veto. The new law increased the commitment to Federal food assistance programs by more than $10 billion over the next 10 years. In efforts to fight stigma, the law changed the name of the Federal program to the Supplemental Nutrition Assistance Program or SNAP as of Oct. 1, 2008, and changed the name of the Food Stamp Act of 1977 to the Food and Nutrition Act of 2008. Additional Recovery Act funds were terminated as of October 31, 2013 in accordance with an illegitimate Republican interpretation of section 442 of the Healthy, Hunger-Free Kids Act of 2010 (Public Law 111-296). The cuts were deep and totalitarian, as has happened so many times before under the Food Stamp Act of 1977. SNAP beneficiaries did not get the tenure promised by Food, Conservation and Energy Act of 2008 H.R. 2419 and the longest uninterrupted growth in good stamp from the Farm Bill of 2002 was brought to end. Food Stamp had their best run with the renaming of the program to Supplemental Nutrition Assistance Program (SNAP) between 2009 to Halloween 2013. Since then, with more cuts on Thanksgiving 2016, benefits have gotten smaller and beneficiaries are poorer. For poor Americans receive a full ration of SNAP benefit spending increases 3.3% annual SNAP growth = 0.6% growth in beneficiaries + 2.7% consumer price index (CPI) inflation. The irony is that the cost of SNAP growth is well-within the FNS spending over-estimates and it would not cost more to keep the promise to not cut SNAP benefits. The accounting errors in the consumer food subsidy are paid out in the form of commodity insurance for large export companies damaged by the trade war with China in conflict with the Swiss Formula for Unilateral Tariff Reductions (2007) upgrade from algebra to calculus, 0.99 developing, 0.97 industrialized.

Under SNAP rules, the maximum benefit levels for each fiscal year — which are the benefit amounts that go to households with no disposable income after deductions for certain necessities — are set at 100 percent of the cost of the Thrifty Food Plan, USDA's estimate of the minimum amount that a family needs to afford a bare-bones, nutritionally adequate diet, for the

(unconstitutionally vague) preceding June. 3.3% spending growth is estimated because FNS must make a conscious effort to increase benefit amount with 2.7% average consumer price inflation, population growth is expected to be low, only 0.6%, because the USDA has broken the promise not to cut "SNAP" benefits made in the Farm Bill of 2008. To prevent anorexic policy from breaking bones, the Thrifty Food Plan needs to set a new standard of beauty, 2.7% average consumer price inflation, more than the basic ration of the previous year. Furthermore, the sedentary calorie requirement can be misleading to active pregnant and lactating women, males age 14-30, physical laborers, alcoholics and athletes, especially female athletes who can suffer osteoporosis, like everyone, and anovulation – reversible premature menopause or delayed puberty - if undernourished, require up to double the normal calorie estimate, and can often eat more without ill-effect, and are due extra-rations, as a matter of law. The Thrifty Food Plan must therefore minimally recognize that pregnant and lactating women require extra-rations, 30-50% more, for a year-and-a-half.

Food stamps cost more, and spending grows faster, than services 3%, or government 2.5%. Every tax-dollar spent on agricultural subsidies is estimated to contribute 16 dollars to the local economy. Food stamps are the most effective and sustainable consumer driven agricultural subsidy. Otherwise producers will sue for commodity insurance and other agricultural subsidies, that do not feed the poor for no extra cost. The beauty of growing federal SNAP benefit spending 3.3% annually is that by eliminating the moral hazards of breaking the SNAP promise not to cut benefits and targeting immigrants for death by starvation, in-between the commodity insurance due to Chinese agricultural tariffs and accounting errors, it costs taxpayers nearly exactly the same amount to pay for SNAP growth and use the federal agricultural subsidy to feed Americans, as it does to have low morale and engage in undeclared undistributed offsetting receipts with OMB. Government cheese costs extra, but is needed to enforce the expiration date on dairy products at the food bank.

The Food and Drug Administration (FDA) has finally produced a hyper-inflationary FY 19 budget. To be patently defective, the FDA website Center email contacts have been deleted overnight and one is now expected to communicate with a geographically named Public Affairs Specialist in conflict with Art. 28 of the 4th Geneva Convention Relative to the Protection of Civilians in Times of War (1949). The Commissioner and Congress must be informed that to combat Departmental and medical sector hyperinflation, FDA budget authority spending growth should be reduced by law from 14.4% FY 18-FY 19 to 2.5% FY 19 – FY 20. The FDA is an a unique position among federal 'revenuers' to possibly find Congress's patented defective zero budget authority growth acceptable, thanks to the liberal sharing of easy Alcohol, Tobacco and Marijuana (ATM) user fees within the FDA. The FDA must learn compete with, and regulate, generalized medical hyperinflation, within the limits of 7.5% growth in user-fees FY 18-FY 19 to sustain normal 2.5% government and 3% services annual spending growth. The strategy is to sustain user-fee revenue growth, including alcohol, tobacco and marijuana (ATM) inspection fees, while requiring the complete abolition of Center for Tobacco Products (CTP) spending under the Family Smoking Prevention and Tobacco Control Act, in the strongest terms of the Nuremberg Code (1949) and Eighth Amendment to the US Constitution. $662 million FY 19 CTP spending of $712 million user-fees in the All-Purpose Table and page 211 must be terminated FY 20 to put an end to their ill-informed adulteration of tobacco and vaping products terrorizing Sec. 301 and 302 of the Food, Drug and Cosmetic Act (FD&CA) under 21USC§331 and §332. Furthermore, the FDA must better distinguish their congressional budget request from federal outlays and corporate executive officer income growth. The FDA must admit that 14.4% budget authority hyperinflation is neoplastic and that they have cachexia regarding food spending, and 2.5% growth in budget authority and 7.5% growth in user-fees, would help to

combat medical hyperinflation in the Department. As successful small-time 'revenuer' the FDA has a collective duty to be non-violent and distribute user fees within the agency on the basis of need. Zero budget authority growth in a future bright with ATM user fees, remains to voted on after 2.5% budget authority growth is tried FY 20.

Food and Drug Administration, Budget Authority FY 17 - FY 20
(millions)

Budget Authority	FY 17	FY 18	FY 19	FY 20
Foods B.A.	1,029	1,022	1,030	1,056
Foods P.L.	1,041	1,033	1,041	1,067
Human Drugs B.A.	492	488	686	703
Human Drugs P.L.	1,329	1,611	1,853	1,870
Biologics B.A.	215	214	252	258
Biologics P.L.	340	358	403	415
Animal Drugs and Feed B.A.	163	162	180	185
Animal Drugs and Feed P.L.	196	187	225	222
Devices and Radiological Health B.A.	330	327	455	482
Devices and Radiological Health P.L.	448	505	636	665
National Center for Toxicological Research B.A. only	63	63	65	67
Family Smoking Prevention and Tobacco Control Act P.L. only	596	593	662	0
FDA Headquarters B.A.	182	181	199	204
FDA Headquarters P.L.	283	316	347	399
FDA White Oak Consolidation B.A.	43	43	49	50

FDA White Oak Consolidation P.L.	47	46	57	56
Other Rent Related B.A.	72	72	87	89
Other Rent Related P.L.	117	123	139	142
GSA Rental Payments B.A.	170	169	168	172
GSA Rental Payments P.L.	232	239	240	246
21st Century Cures B.A. only	20	20	70	30
MCMI B.A. only	10	10	0	0
Buildings and Facilities B.A. only	12	12	12	12
Total B.A.	2,801	2,783	3,253	3,308
Total User Fees	1,954	2,355	2,545	2,749
Total Program Level	4,755	5,138	5,798	6,057

Source: Gottlieb, Scott. FY 19 Department of Health and Human Service Justification of Estimates for Appropriation Committees.

Use of the term 'budget request' is misleading the Treasury regarding 'budget authority' and 'program level'. The FDA 'budget request' for 'budget authority' to make 'federal outlays' is actually unacceptably high 14.4% growth FY 18 – FY 19. It is true, FDA user-fees are growing fast, 7.5% FY 18-FY 19 and, unlike Customs or the Internal Revenue Service (IRS), FDA program funding revenues are in unique position to gradually reduce and theoretically ultimately eliminate all need for federal outlays for their programs in time. In no circumstance should FDA 'revenuers' be allowed more than 2.5% annual growth in 'federal outlays', synonymous with 'budget authority', nor, without their informed consent, less. To redress the dietary cachexia and hyper-inflationary neoplasm reparation demands are 2.5% annual growth in budget authority since FY 17 meaning more food and less medical hyperinflation and bankruptcy. The FY 17 Actual fails to respect Foods user-fees, and cannot be believed, and the $1 million reduction in fee revenues, estimated FY 18 – FY 19 is also difficult to swallow. The FY 17 Actual seems to be a feeble attempt to pay for drugs with the fuzz and spare change, and should be disregarded, whereas the Actual did not declare food revenues. The 75% increase in Animal Drugs and Feed revenues estimated FY 18- FY 19 is unsustainable and therefore subjected to a repeat of reduced revenues FY 17- FY 18 by 20% from the high FY 19 level. The FDA Headquarters revenues are expected to decline an estimated 1% FY19 – FY 20. The FDA White Oak Consolidation revenues may decline 20%. The FDA argues they have reorganized, and to be competitive, it is banking institutions who need to stop marking 'international transactions' as suspicious and arbitrary blocking accounts, to stop interfering with the $10 billion annual Indian pharmaceutical import industry among others. The hyperinflation in budget authority requests however indicates

the FDA is less cost-effective than before, and the FDA must atone for their unethical business practices. It is however easier to write off FY 17-FY 19 hyperinflation and gentrification as CTP terrorism damage, and settle for 2.5% growth from the previous year, than immediately restructure their small federal organization, independent of Food and Nutrition Service (FNS) anorexia, to feed humans alfalfa as calcium source, prescribe metronidazole to treat all abdominal infections without causing antibiotic associated colitis, with probiotics as the adjunct not professional subsidies for marketing inferior new patent and IV league medicines, doxycycline for *Staph*, chlorine in hospital cleansers, and Stonebreaker (Chanca piedra) to cure urinary and gallstones overnight. To temporarily and partially sustain their unhealthy, carcinogenic, hyper-inflationary expectations, or merely be a law abiding agency with reasonable inflationary demands, the FDA must quit CTP user-fee spending.

The Food and Drug Administration (FDA) grew from a single chemist in the U.S. Department of Agriculture in 1862 to a staff of approximately 9,100 employees and a budget of $1.294 billion in 2001, comprising chemists, pharmacologists, physicians, microbiologists, veterinarians, pharmacists, lawyers, and many others. Beginning as the Division of Chemistry and then (after July 1901) the Bureau of Chemistry, the modern era of the FDA dates to 1906 with the passage of the Federal Food and Drugs Act; this added regulatory functions to the agency's scientific mission. The Bureau of Chemistry's name changed to the Food, Drug, and Insecticide Administration in July 1927, when the non-regulatory research functions of the bureau were transferred elsewhere in the department. In July 1930 the name was shortened to the present version. FDA remained under the Department of Agriculture until June 1940, when the agency was moved to the new Federal Security Agency. In April 1953 the agency again was transferred, to the Department of Health, Education, and Welfare (HEW). Fifteen years later FDA became part of the Public Health Service within HEW, and in May 1980 the education function was removed from HEW to create the Department of Health and Human Services (DHHS), FDA's current home. The agency grew from a single chemist in the U.S. Department of Agriculture in 1862 to a staff of approximately 9,100 employees and a budget of $5.1 billion in 2017, comprising chemists, pharmacologists, physicians, microbiologists, veterinarians, pharmacists, lawyers, and many others.

The FDA needs to stop addictively spending tobacco user-fees on the Center for Tobacco Products (CTP) and continue to regulate Alcohol, Tobacco and Marijuana (ATM) agriculture with user-fees that can be distributed within the FDA, on the basis of need to regulate medical hyperinflation, rather than greed. User-fees are all that is needed to ensure trained FDA field staff and genetic testing technology are federally available to inspect recreational drug quality, in cooperation with the National Institute on Drug Abuse (NIDA). The Center for Tobacco Products has extended FDA drug regulation to tobacco products made available to people over the age of 18 by specially licensed vendors since the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) became law on June 22, 2009 charged with developing a more informative drug label. Although required to do so by July 22, 2010 the Federal Cigarette Labeling and Advertising Act has settled on: Warning: This product contains nicotine. Nicotine is addictive.. The Food and Drug Administration (FDA) spent (obligated) less than half of the $1.1 billion in tobacco user fees it collected from manufacturers and others from fiscal year 2009 through the end of fiscal year 2012; however, FDA's spending increased substantially in fiscal year 2013. Through December 31, 2013, FDA spent nearly 81 percent of the approximately $1.75 billion in fees collected by that time. According to officials in FDA's Center for Tobacco Products (CTP), the center established by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) to implement the act's provisions, the time it took to award contracts contributed to the center spending less than it had planned to spend. In fiscal year 2013, FDA

was able to carry out a number of activities that were originally planned for fiscal years 2011 and 2012, such as efforts to educate youth on the dangers of smoking. About 79 percent ($1.12 billion) of user fees spent as of December 31, 2013, was spent by three CTP offices: Office of Health Communication and Education, Office of Science, and Office of Compliance and Enforcement.

CTP spending must be terminated because their teenage biological experimentation with tobacco and vaping products adulterates, falsely represents and there is no certified organic tobacco to be purchased anymore. Any FDA officer could do their job. As of January 7, 2013, CTP had finished initial, but not final, review steps for most of about 3,800 submissions it had received for new tobacco products (those not on the market on February 15, 2007). Ninety-nine percent of the submissions received were made under the substantial equivalence (SE) pathway, through which CTP determines whether the product has the same characteristics as a predicate tobacco product (a product commercially marketed in the United States on February 15, 2007, or previously found to be substantially equivalent) or has different characteristics that do not raise different questions of public health. For most SE submissions received by January 7, 2013, CTP took more than a year and a half from the date a submission was received to the date CTP's initial review steps were completed; initial review steps precede a scientific review step during which CTP determines whether the product is substantially equivalent to a predicate product. CTP made its first decisions on SE submissions in late June 2013—about 3 years after FDA's receipt of the first SE submission—and as of December 31, 2013, had made final decisions for 30 of the 4,490 SE submissions the agency had received. CTP officials stated that CTP requests for additional information from manufacturers for submissions and having to hire and train new staff impacted the time it took to review submissions. GAO also found that CTP has not had performance measures that include time frames for making final decisions on SE submissions by which to assess its progress. Time frames would allow CTP to evaluate its efficiency and effectiveness and help it make appropriate adjustments. As of December 31, 2017: 2,652 regular reports have been received, 2,411 or 91% of regular reports have been resolved, 241 regular reports are pending. 240 have begun scientific review and 198, or 83%, have been issued a deficiency letter after a cycle of scientific review was completed.

Since the program's inception in October 2010 through December 31, 2017, FDA has commissioned more than 2,500 officers and conducted more than 874,000 compliance check inspections at tobacco retail establishments. On May 10, 2016, FDA finalized a rule – Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act (FD&C Act) – which extended FDA's tobacco authorities to all tobacco products, including electronic nicotine delivery systems (such as e-cigarettes and vape pens), cigars, hookah (waterpipe) tobacco, pipe tobacco and nicotine gels, among others. In FY 2016, CTP contracted with the Institute of Medicine – now called the Health and Medicine Division of the National Academy of Sciences – to conduct an evaluation of health effects from e-cigarettes and identify gap areas for future federally funded research in this area. FDA collaborates with NIH to fund the 14 Tobacco Centers of Regulatory Science (TCORS). The objective of the Centers is to conduct multidisciplinary research that will inform FDA's regulatory actions related to the manufacture, distribution, and marketing of tobacco products. FDA will collaborate with NIH to fund new TCORS and a Center for Coordination of Analytics, Science, Enhancement and Logistics (CASEL) in FY 2018. FDA funds the Population Assessment of Tobacco and Health (PATH) Study via NIH's National Institute on Drug Abuse (NIDA).

After the great success of growing the monoclonal antibody for the ebolavirus cure Zmap in tobacco plants, there is some concern that there may be genetic damage to tobacco crops after the

2015 tobacco harvest was contaminated with green tomatoes. It is not known whether the ebola virus research was financed by CTP. On May 12, 2015, FDA launched the first phase of its tomacco farming "Fresh Empire" campaign of entrapment that must be discontinued – a youth-focused effort to reduce the number of smokers in our country. The campaign is designed to prevent and reduce tobacco use among at-risk multicultural youth aged 12 to 17 including African American, Hispanic, and Asian American/Pacific Islander youth. By harvest season the product of many fields of tobacco or tobacco drying in sheds had been contaminated with unmistakable throat damaging contamination of green tomatoes. The discomforting degeneration of throat tissue can last weeks to months, and surely leads to throat cancer. Throat Coat echinaceae and lemonbalm tea is safe and effective treatment. After diagnosing the green tomatoes, tobacco quality has improved. Green tomatoes are an even greater threat to tobacco than tobacco mosaic virus is to tomatoes; the two plants, tobacco and tomato, should be grown far apart. Throat cancer is one of modern oncological treatments' 95% cure rates, along with Gleevec (Iminitab) for lymphoma and leukemia. *Aspergillus niger* mold, found in peanuts, a laboratory supply catalogue, and CTP adulterated tobacco, can cause a life threatening lung infection, that can be transmitted by contaminated tobacco, and is cured with $1 hydrocortisone crème to the chest and/or throat to avoid a swift death from the two year prognosis for lung cancer. Smoked crushed small pellets of rat poison cause stomach sphincter relaxation; drunk rat poison causes a slimy rectum, consumption of rat poison contaminated products must cease to prevent death by stomach or colon cancer.

As of December 31, 2015, FDA had contracts to conduct compliance check inspections at tobacco retail establishments with 55 States, territories, and tribal jurisdictions. Compliance check inspections pertain to tobacco marketing, sales, and distribution of tobacco products at retail locations. Since the October 2010 inception of FDA's Tobacco Retail Compliance Check Inspection Program through December 2015, FDA has: completed over 549,300 inspections issued over 38,800 warning letters, levied more than 6,400 civil monetary penalties, filed 8 No-Tobacco-Sale Order (NTSO) complaints commissioned more than 2,300 officers and employees from the States, territories, and their political subdivisions and provides a training program for those that perform inspections. Tobacco use is alleged to remain to be the leading cause of preventable disease and death in the United States, causing more than 480,000 deaths every single year. Tobacco use also causes substantial financial costs, with direct health care and lost productivity costs totaling nearly $300 billion a year. In 2017, FDA announced a new comprehensive plan for tobacco and nicotine regulation that will serve as a multi-year roadmap to better protect kids and significantly reduce tobacco-related disease and death. The approach places nicotine, and the issue of addiction, at the center of the agency's tobacco regulation efforts. The goal is to ensure that FDA has the proper scientific and regulatory foundation to efficiently and effectively implement the Family Smoking Prevention and Tobacco Control Act. FDA plans to continue to "strike an appropriate balance between regulation and encouraging development of innovative tobacco products that may be less dangerous than cigarettes". Affordable organic pipe tobacco is currently not available. The FDA must discontinue the tobacco industry's long history of putting chemical additives in cigarettes. CTP spending is dangerous, especially the biological experimentation with the addictive tobacco genome without informed consent, must be terminated under the Nuremberg Code to prevent continuing adulteration, misbranding and false representation of tobacco and vaping products by Sec. 301 and 302 of FD&CA under 21USC§331 and §332. The ATM is worth so much to FDA user-fees, it must be priceless. Furthermore, the ATM acronym is the property of the Alcohol and Tobacco Tax and Trade Bureau (ATTB) and neither the FDA nor Center for Food Safety and Applied Nutrition (including Cosmetics, Alcohol, Tobacco and Marijuana) should pay for it.

2. International Agricultural Assistance

The US international agricultural assistance program has been effectively terminated since FY 2018 by (continuing resolution) CR 18. Congress failed to defend international assistance programs, against budget cuts, with the defective zero growth policy that protects other federal programs, and international agricultural assistance was especially targeted for total discrimination, by President Donald J. Trump. Funding spiked from $1.9 billion FY 16 to $2.1 billion FY 17 before reaching zero in FY 18 – FY 19. $2.1 billion FY 20 is needed to refinance both International Agricultural Assistance programs, on the condition that it grows 3% to $2.2 billion FY 21 and increases 3% annually thereafter. Congress may be perplexed by the xenophobic role reversal of the Mayor to sue the US Congress for discriminating against the Buy American Act under 24USC§225h in regards to the international treaty obligation to sustain US financing for international agricultural assistance programs under 7USC§1691. Termination of US international agricultural assistance constitutes a grave breech of Arts. 23, 55 and 147 of the Fourth Geneva Convention Relative to the Protection of Civilians in Times of War (1949). he number of undernourished people is reported to have increased to 821 million in 2017 from 800 million in 2016– around one out of every nine people in the world, by the Food and Agriculture Organization (FAO) in 2018. *The Report of the Secretary General on SDG Progress 2019* estimated 821 million people – approximately 1 in 9 people in the world – were undernourished in 2017, up from 784 million in 2015. This represents a worrying rise in world hunger for a third consecutive year after a prolonged decline. Government spending on agriculture compared to agriculture's contribution to the total economy has declined by 37 per cent; the ratio fell from 0.42 in 2001 to 0.26 worldwide in 2017. In addition, aid to agriculture in developing countries fell from nearly 25 per cent of all donors' sector-allocable aid in the mid-1980s to only 5 per cent in 2017, representing a decrease of $12.6 billion (Guterres '19: 7, 8). WHO once estimated every dollar invested agricultural subsidies means $16 to the local economy. Termination of US international agricultural assistance 2018-2019 has obviously compromised achievement of Sustainable Development Goals 2.1 By 2030, end hunger and ensure access by all people, in particular the poor and people in vulnerable situations, including infants, to safe, nutritious and sufficient food all year round. The genocide convention is applicable if a particular class of people has been marked for extermination by the authorities - even if by starvation rather than outright execution (Natsios '01: 50). North Korea and US immigrants can be described as being targeted for death by starvation because of the termination of US international agricultural assistance and anti-immigrant food stamp rules, respectively.

International Agricultural Assistance Spending FY 16 – FY 20
(millions)

	FY 16	FY 17	FY 18	FY 19	FY 20
P.L. 480, Title II	1,716	1,900	0	0	1,927
McGovern-Dole International Food for Education and Child Nutrition	202	202	0	0	227
Total	1,918	2,102	0	0	2,154

Source: State Department, Foreign Operations and Related Organizations FY 17 and FY 19

The termination of US agricultural assistance could lead to widespread famine and must be prioritized as the absolutely most affected program by the Trump budget cuts, second are international assistance programs undefended by CR 18, third are civilian Cabinet agencies suffering from abuse of congressional zero spending growth policy. 2 - 3 million people died in the North Korean famine of 1996 when the Soviet food assistance program was terminated, before news had even crossed the DMZ to their families in southern Korea that they were starving (Natsios '01). Because too much food can be a wasteful problem for the 672 million people who are obese worldwide, like Presidents Trump and Un sometimes, the international assistance program and other food programs that were cut are not tempted with arrears in the first instance, they are offered 3% annual program level growth from $1.9 billion FY 16 to $2.1 billion FY 20. Costing less and making more over the long-term, a 3% agricultural inflation allowance is a better deal than arrears from FY 16 or high FY 17 levels. To feed a growing population, spending for food service programs needs to grow faster than spending for paper-pushing governments, that grow 2.5% annually, due to 2.7% average annual consumer price inflation in foodstuff, in the United States, but food perishes. Total State Department budget program levels must be recalculated from FY 16 total levels of $56.0 billion, at annual 2.5% government and 3% International Agricultural Assistance P.L. 480 spending growth, to $60.1 billion FY 20. This FY 20 estimate includes $1 billion arrears for United Nations Educational, Scientific and Cultural Organizations (UNESCO) and United Nations Relief and Works Administration for Palestine Refugees in the Near East (UNRWA).

It is the policy of the United States to use its abundant agricultural productivity enhance the food security of the developing world through the use of agricultural commodities and local currencies to – 1. Combat world hunger and malnutrition and their causes; 2. Promote broad-based, equitable, and sustainable development, including agricultural development; 3. Expand international trade; 4. Develop and expand export markets for United States agricultural commodities; 5. Foster and encourage the development of private enterprise and democratic participation in developing countries under 7USC§1691. Countries are eligible for emergency food assistance if a country has a famine and is recognized as a least developed country with an agricultural deficit evidenced by, 1. That the daily per capita calorie consumption of the country is less than 2300 calories. 2. Food security requirements are that the country cannot meet its food security requirements through domestic production or imports due to a shortage of foreign exchange earnings. 3. Child mortality rate of children under 5 years of age in the country is in excess of 100 per 1000 births under 7USC§1727a.

The number of undernourished people is estimated to have increased to 821 million in 2017 from 800 million in 2016– around one out of every nine people in the world. The State of Food Security and Nutrition in the World: Building Climate Resilience for Food Security and Nutrition 2018 monitors progress towards the targets of ending both hunger (SDG Target 2.1) and all forms of malnutrition (SDG Target 2.2). New evidence continues to signal a rise in world hunger and a reversal of trends after a prolonged decline.While some progress continues to be made in reducing child stunting, levels still remain unacceptably high. Nearly 151 million children under five – or over 22% – are affected by stunting in 2017. Wasting continues to affect over 50 million children under five in the world and these children are at increased risk of morbidity and mortality. Furthermore, over 38 million children under five are overweight. Adult obesity is worsening and more than one in eight adults in the world – or more than 672 million – is obese. The absolute number of people in the world affected by undernourishment, or chronic food deprivation, is now estimated to have increased from around 804 million in 2016 to nearly 821 million in 2017. The situation is worsening in South America and most regions of Africa;

likewise, the decreasing trend in undernourishment that characterized Asia until recently seems to be slowing down significantly.

A total of 5 nations suffered totalitarian famines in the 20th century – Soviet Ukraine (1930-1933), the People's Republic of China (1958-62), Ethiopa (1984-85), Cambodia (1974-79) and North Korea (1994-98). The dekulakization and forced collectivization in the Soviet Union killed 14.5 million people nationwide with particular focus on the Soviet Ukraine between 1929 and 1933 Stalin is particularly noted for attempting to cover up evidence of this debacle. Mao Zedong launched the Great Leap Forward in 1958 after having begun forced collectivization of agriculture in 1956 Great Leap Forward borrowed from Stalin's agriculture minister. The ensuing Chinese famine from 1958 to 1962 resulted in an estimated 30 million deaths. Another hidden famine killed several hundred thousand people in Ethiopa between 1972 and 1973 precipitating a coup by military officers in 1974 that unseated Emperor Haile Selassie. The subsequent famine of 1984-85 which killed one million people, was reportedly a consequence of drought induced crop failure. Robert Kaplan reported in his book on the famine however that attempts to resettle hundreds of thousands of people from the Amharic and Tigrayan highlands to resettlement camps in the fertile lowlands where they were served miniscule portions of food for 11 hours of work; hundreds of thousands of people died. Starvation was one of the means used by the Khmer Rouge in Cambodia 1974-1979 to water the killing the fields and it is estimated that perhaps a third of the casualties of resulted from deliberately planned starvation that included preventing people from scavenging for wild foods. The North Korean famine of 1994 to 1998 after the severance of Eastern Bloc aid after the dissolution of the Soviet Union resulted as the result of the massive corruption, secrecy and greed that led to the collapse of the public distribution system (PDS) during the social transition to a market distribution system led to an estimated 2 to 3 million deaths (Natsios '01: 49-54).

The World Food Program was established in 1963, WFP is the United Nations frontline agency in the fight against global hunger. In 2003, WFP fed 104 million people in 81 countries, including most of the world's refugees and internally displaced people. Since it was set-up in 1963, the Rome-based organization has invested US$27.8 billion and more than 43 million metric tonnes of food to combat hunger, promote economic and social development and provide relief assistance in emergencies throughout the world. In USAID the Office of Food for Peace administrates food relief to famished regions of the world under 7USC§1691. The World Food Program (WFP) and Food and Agricultural Organization (FAO) alleviated famine in Yemen and are deeply concerned that North Korea had a bad harvest, in the total absence of any US international agricultural assistance whatsoever. Congress may be perplexed by the role reversal of the Mayor to sue the US President for discriminating against Buy American provisions under 24USC§225h in regards to sustaining federal financial support for international agricultural assistance under 7USC§1691. If the United States is unable to continue to coordinate the delivery of agricultural assistance commodities, and restart P.L. 480 and the McGovern-Dole International Food for Education and Child Nutrition, the equivalent of the international agricultural assistance budget may be contributed directly to the WFP, but this is unsolicited. The Democratic People's Republic of Korea (DPRK) FAO/WFP Joint Rapid Food Security Assessment was issued May 2019. Prolonged dry spells, abnormally high temperatures and foods, coupled with limited supplies of agricultural inputs, had a severe impact on yields of the 2018 main crops harvested last September/October. Production prospects for the 2018/19 early season crops – to be harvested in June – are unfavorable due to widespread low rainfall and lack of snow cover, which left crops exposed to freezing temperatures during winter. Post-harvest losses from harvesting to storage are expected to be higher than usual as shortages of fuel and electricity hampered the timely transport and processing of crops as well as the ventilation of

stocks. The 2018 aggregate food crop production is estimated to be below-average at 4.9 million mt, 12 percent below the previous year's near-average level and the lowest level since the 2008/09 season. Cereal import requirements in the 2018/19 marketing year (November/October) are estimated at 1.59 million mt. With commercial imports officially planned at 200,000 mt and food assistance (already received or pledged) set at about 21,200 mt, the uncovered deficit for the full marketing year is estimated at an elevated level of about 1.36 million mt.

Food consumption levels are low and dietary diversity is very poor. Diets mainly consist of rice, maize or potatoes complimented by kimchi (cabbage) or vegetables and greens, when available. Protein intake is very low. Poor food consumption is widespread in the surveyed population in both November (37 percent) and April (46 percent) assessments and only a few households have an acceptable diet. Food-related coping strategies are widely adopted, including reducing consumption by adults for children to eat and reducing meal sizes. Urban households who typically rely on relatives in rural areas to access food and diversify their consumption are no longer able to do so to the same extent, as also rural households increasingly face food shortages. Since January 2019, rations of the Public Distribution System (PDS) have been reduced to 300 grams per person per day (g/pp/day), which compares to 380 grams during the same period in 2018. Rations may decline further during the July to September period, when PDS rations are typically lower compared to other months of the year. Overall, it is estimated that 10.1 million people (40 percent of the population) are food insecure and in urgent need of food assistance. The situation could further deteriorate during the lean season from May to September, if no proper and urgent humanitarian actions are taken.

DPRK does not officially release economic data and widely varying estimations of macroeconomic numbers exist. Estimations of the Bank of the Republic of Korea suggest that in 2016 the local economy grew at its fastest pace in 17 years, when for the first time, GDP per capita surpassed the US $1,000 mark. More recent analyses by the Economist Intelligence Unit (EIU) suggest that the country experienced an economic downturn in 2017 and 2018, amid reduced trade activities as a consequence of sanctions targeting top-earning export sectors, such as coal, minerals and textiles. The primary economic activities in the DPRK are mining, some heavy industry, agriculture and fisheries. The agricultural sector is estimated to contribute to roughly one quarter of the country's GDP, with significant fluctuations over the years due to frequent climatic shocks impacting agricultural production. The geography of the country is largely mountainous, with only 15 percent of the land (or 1.9 million ha) suitable for agriculture. Of this, about 30 percent is irrigated, mostly paddy fields and winter/spring crops. The most productive agricultural land is located in the western plains of the country, and narrow strips along the east coast. Rice, maize and potatoes constitute the major food crops, with the first two commodities contributing 45 and 34 percent of overall grain production respectively. However, the proportion of each crop produced and consumed in local diets varies greatly in different parts of the country. Soybean, barley and wheat are also widely cultivated as well as minor grains such as millet, sorghum, oats and rye. The organization of the rural economy is mostly characterized by the operation of cooperative farms, with a smaller number of state farms. According to the CBS, the farming population involves 2,513 cooperative farms with 2.54 million farmers and 707 state farms, employing 802,000 farmers. State farms tend to be specialized in large -scale production of livestock, fruits, vegetables and other cash crops. By contrast, cooperative farms are responsible for producing most of the grains and staple foods. They also produce vegetables, fruits and livestock, which are sold into the government marketing system and distributed to cooperative farm members.

Cultivated lands with slopes below 15 degrees are managed by cooperative farms, while lands above 15 degrees of slope are officially administered by the Ministry of Land and Environmental Protection (MoLEP). Sloping lands are also used by households, both from cooperative farms and from urban areas, to grow maize, soybean, vegetables and other crops for their own consumption. This practice dates back to the late 1990's when, due to the general shortages of food, land use regulations were relaxed and households expanded cultivation onto sloping lands. In 2014, however, the government initiated a reforestation program that is resulting in a gradual decline in production from sloping lands. The main agricultural season starts in April, with the arrival of the spring rains, and the harvest normally takes place between September and October. One important element for achieving food security involves expanding the area under double cropping as broadly as possible through practices such as using greenhouses to produce seedlings for transplanting to open fields, using tunnel houses and plastic mulch to preserve soil moisture, and the introduction of short-season and cold-tolerant varieties that can extend the growing season. The availability of vegetables in the winter months is very limited. Traditionally in October/November both urban and rural households use cabbage to make kimchi as their main source of vegetables until the following March/April. Assuming average productivity of 15 mt/hectare from an area of 30,000 hectare on cooperatives and state farms, vegetable production could be estimated at about 0.45 million mt. This compares to a requirement of 2.7 million mt based on a recommended minimum consumption of 300 g/pp/day, suggesting a gap of vegetables as high as 2 million mt. the overall number of livestock between 2015 and 2017, with the exception of pigs, which increased by about 8 percent from 2.41 million head in 2015 to 2.6 million head by 2017. The country has no traditional rangelands, but some forest lands has been converted to grazing lands totaling up to about 200,000 ha.

The sanctions imposed on the country by the United Nations Security Council (UNSC) in December 2017 were the strictest yet. The text of the resolution states that sanctions "are not intended to have adverse humanitarian consequences for the civilian population of the DPRK". Nevertheless, the unintended negative impact sanctions can have on agricultural production, through both direct and indirect impacts, cannot be ignored. The most obvious are restrictions on the importation of certain items that are necessary for agricultural production, in particular fuel, machinery and spare parts for equipment. In 1991, the country's oil consumption amounted to 3.8 million mt/year, subsequently falling to 750,000 mt by 2017. According to data received from CBS, the national allocation of fuel for agriculture in 2018 was 44,502 mt, including 40,502 mt of diesel and 4,000 mt of petrol. Given an average annual amount of 1.4 million hectares cultivated between 2012 and 2018, this amounts to 31 kg of diesel fuel per hectare. Shortages of fuel, electricity and pumping equipment limit the ability to irrigate, reducing yields and making crops susceptible to extreme weather shocks, such as drought and heatwaves. Lack of energy can result in grain with high moisture content going into storage, making it susceptible to spoilage or the occurrence of mould, fungus and mycotoxins. Storage of crops in facilities lacking proper ventilation, temperature and humidity control can further add to post-harvest losses. Potatoes are particularly sensitive to humidity and temperature, and post-harvest losses of potatoes in storage areas are reportedly as high as 20 percent. In the potato growing region such as Ryanggang Province, families may receive two mt of potatoes or more at distribution and be responsible for storing them until the food distribution in the following year. Storage at a household level in rudimentary facilities undoubtedly results in a high degree of household waste.

The 2018 harvested area of soybeans has decreased for the second consecutive year and it is estimated at 107,000 hectares, about 40 percent below the area harvested in 2016. Overall, the area planted with the soybeans has been steadily increasing between 2013 and 2016, reflecting

government efforts to enhance nutrition security and diet diversity. The average yield of rice paddy in 2018 is set at 4.4 mt/hectare, about 12 percent lower than the 2017 level of 5 mt/hectare. All provinces registered severe paddy yield reductions, while crops in Ryangang and North Hamgyong provinces were less affected by the dry weather conditions and offcial estimates show an increase in yields compared with 2017. Rice production in 2018 is o cially estimated at 2.1 million mt (in paddy terms), 12 percent below previous year below -average level. The average maize yield in 2018 is estimated at 3.7 mt/hectare, showing a decline of 14 percent compared with the previous year level. Yields of soybean are set at 1.3 mt/hectare, about 15 percent below the previous year's above-average level. The only exception were yields of crops which are more resistant to dry weather, such as sorghum, millet, and buckwheat and potatoes. The average yields other cereals, including sorghum, millet, and buckwheat, is officially estimated to have increased by 13 percent compared with the previous year's level and were also well above average. The yields of the main season potatoes is o cially estimated at 5.6 mt/hectare, 14 percent above the 2017 level of 4.9 mt/hectare. The aggregate 2018/19 cereal production is estimated at about 4.9 million mt (in cereal equivalent and paddy terms), 12 percent below the 2017 near-average output.

In broad terms, in DPRK households access food through multiple and diverse avenues. According to the government, most of the population gets its greatest share of food staples from PDS rations (if the household is headed by workers, governmental officials or pensioners) while the rest receive staples directly through post-harvest allocations (if the household is headed by a cooperative or state farmer). In 2017, 17.5 million people (71.5 percent of population) were reported to be PDS-dependent6, while 7 million people were either working in cooperative farms (6.1 million) or state farms (800,000) and therefore not PDS -dependent. Across the country, farmers work in 3,220 farms (2,513 cooperative farms and 707 state farms) distributed in almost every county. In addition to staple food, food is also accessed at household level through kitchen gardens, state shops, farmers markets and through relatives. Cash plays an important role in accessing food purchased at farmers' markets as well as in collecting food from state shops and at PDS distribution centers where in both cases commodities need to be paid for, though at highly subsidized prices, as reported to the FAO/WFP team in different counties. Eating meals in institutions is also a common food access strategy. For example, children from six months of age, commonly attend nurseries where they receive three meals per day. The Food Procurement and Distribution Authority sets the average monthly ration for the coming month, one month ahead of time. Distributions take place twice per month, normally between 1st - 5th and 15th - 20th day of each month following a distribution schedule for registered households managed at the Public Distribution Centers (PDCs). The PDS rations, distributed through the PDCs, are acquired at fixed subsidized prices (44 KPW/kg for rice, 24 Korean KPW/kg for maize), relatively low if compared to fluctuating prices for other staple food items (such as soybeans and potatoes) in the farmers markets or state shops. The PDS rations vary in quantity and composition throughout the year and between years. The official national target ration for planning was 573 g/ pp/day for several years, but for 2019 it has been lowered by 5 percent to 550 g/pp/day. At time of writing, the reported effective PDS ration is 300 g/pp/day (January-April 2019), which represents a sharp reduction compared to the 2018 ration size (that started with 380 g/pp/day in January and ended with 360 g/pp/day in December), and the lowest registered for the initial months of any calendar year. On average, households (including both PDS-dependent and cooperative farmers) surveyed in April 2019 received 1,393 kcal/pp/day in the form of PDS rations or post- harvest allocations (with 394 g/pp/day on average8) whereas those surveyed in November 2018 got higher rations on average (1,529 kcal/pp/day from 447 g/pp/day9). This decline in average food rations received by PDS- dependent and cooperative farmers alike reflects the impact of the declining harvest and the growing food gap that has been

announced at the national level. Based on rations reportedly received by the interviewed households, in April 2019, PDS-dependent households could access 1,080 kcal/pp/day (average PDS ration of 306 g/pp/day), while cooperative farmer households could access 2,285 kcal/pp/day (in form of post-harvest allocations of 647 g/pp/day of staples). When analyzed from the caloric point of view, PDS- dependent households in the April 2019 dataset are provided with 1,369 kcal/pp/day, which falls short of the recommended daily calorie intake of 2,100 kcal/pp/day by 35 percent and of the minimum basal requirements of 1,800 kcal/pp/day by 24 percent (Figure 9). In absolute terms, the PDS ration size is not enough to provide enough caloric intake. For cooperative farmers, the situation seems to appear less challenging as they receive 2,285 kcal/pp/day on average and need at least 2,500 kcal – 5,000 kcal to perform hard manual agricultural labor.

Different types of state shops exist in DPRK and serve as one of the food sources selling daily food items such as salt, oil, bean paste, eggs, other processed foods, as well as vegetables and fruits in specific seasons. Food items at state shops are sold at a fixed, subsidized price, which does not change through the year or by season. People visit the shop, show their coupons and pay in cash. Coupons work as entitlements to buy certain kinds of food items (the amounts per household are indicated on the coupon and those amounts vary by households depending on the household member occupation, hard or light labour, and number of dependents). Coupons are a means to distribute the relatively small supply of certain items as compared to the total population in the area being serviced. In addition to state shops, markets play an important role in food systems as a place to source foods, receive cash or barter items. The relevance and importance of this mechanism has been growing relentlessly since the severe food shortages in the 1990s but remains poorly understood. One form of market is the farmers markets, where people from farming families gather on the 11th, 21st and 31/1st of each month and sell or exchange food products (vegetables and animals), largely coming from their kitchen gardens. A farmers' market can be as sizable as 600-700 sellers, reflecting the widespread need among people to satisfy their food consumption needs through market exchanges, plus the need for cash to purchase other items. In April, all the surveyed households reported buying food, with 72 percent visiting farmers' markets regularly to purchase food, which is consistent with the November datasets. Prices of sea sh have almost tripled, and basic (and more affordable) sources of proteins such as eggs have double in price from 150 KPW/piece to 300 KPW/piece. It is worth mentioning that eggs in state shops (when available, which is often not the case) only cost 10-12 KPW. Around 90 percent of cooperative farmer households have a kitchen garden, while only 40 percent of PDS-dependent households do.

Among surveyed households in April 2019, only 7 percent had an acceptable diet with a more frequent intake of high-protein foods and fruits (see Table 19). The other 93 percent (poor and borderline food consumption) of the households reported a daily diet that is insufficient in diversity and nutrients. When compared to the November 2018 dataset, the food security situation is clearly worsening. According to the 2017 Multi Indicator Cluster Survey (MICS) carried out by CBS with technical and financial support from UNICEF, higher stunting rates are registered in older children. According to the survey, the prevalence of stunting in DPRK can be as high as 32 percent in some provinces. It also showed that young children in rural areas are more likely to be stunted than those living in urban areas. Several nurseries reported percentages of undernourishment between 15-25 percent. Based on the analysis and converging findings of the November 2018 and April 2019 household assessments, the Mission estimated that 10.1 million people are food insecure and in urgent need of assistance, including 7.5 million PDS dependents and 2.6 million farmers. The food gap stands at 1.36 million mt for the whole marketing year 2018/2019. It would be discrimination for the US President to require the North

Korean dictator Kim Jong Un to eliminate nuclear weapons and missile testing as a condition for the receipt of US agricultural and food assistance under 24USC§225h. It would however be uncharacteristic for the US to pass on such an opportunity to reason with Un. The ballistic missile tests have backfired and are even now still causing artificial warming of the Pacific. North Korea will be stricken with drought until the ocean completely cools. Un is advised to use this evidence of self-inflicted global warming to justify ceasing to deposit spent ballistic missiles from (nuclear?) tests, in the Pacific Ocean, and support efforts to neutralize any thermal pollution therefrom, pursuant to the Framework Convention on Climate Change (1992) under Art. 27 of the Declaration on Social Progress and Development (1969).

The US President is similarly charged with responding to evidence of the consequences of his unlawful actions, and must cease his unlawful economic interventions, whereas his current account budget and international trade balances are defective or unpublished, respectively, and must pay reparations so it would be as if the unlawful budget cuts had never occurred. There is no denying unlawful tariff increases have caused the US international trade deficit to increase and are struggling to declare customs revenue growth against the prevailing policy of tariff reduction (from 2016 where hyper-inflationary). Anti-immigrant policy has caused several years of zero income tax revenue growth that cannot be entirely concealed by the tax cut for the rich. Budget cuts have depressed civilian government who are due redress in the form of an inflation allowance of 2.5% for government and 3% for services since FY 16, before the illegal cuts. 3.3% growth is needed for food full food stamp benefit payments, 2.7% inflation and 0.6% cowed population increase, and 4% for disability, for a 3% COLA and 1% population growth, is from the previous year, whereas costs and benefits are significantly higher for public welfare than other professional government programs and brutal eligibility requirements and prior recertification torture treatment despite the SNAP promise that there would be no more cuts, furthermore inhibit enrollment, damage to these programs is done, it is evidence of robbery against the President and Congress, who are conspicuously unable to produce an accurately balanced federal budget or Food and Nutrition Service budget, respectively. The genocide convention is applicable if a particular class of people has been marked for extermination by the authorities- even if by starvation rather than outright execution. Punitive rationing occurred in the Chinese famine of 1958-62 village families who descended from landlords wither were not fed at all or were fed a lower ration than the poorer class of peasants. Research on the Ukrainian famine in the early 1930's proved that Stalin's objective was to liquidate the kulak class of farmers. Similarly, US government intelligence sources reported that as the public distribution system broke down, the North Korean authorities focused food supplies on three groups: members and immediate families of the military, of the party, and of workers in strategic industries such as mining (Natsios '01: 49-54, 211).

Trumps unlawful anti-immigrant starvation genocide and work for food stamps requirement incited workplace shootings are much more descriptive of totalitarian famine as an act of genocide. Contemporary theory directs that when confronted with famine to suspect the presence of a totalitarian regime that must be closely regulated for the domestic administration of relief to have any chance of succeeding in meeting the nation's agricultural needs because the totalitarian state makes the wealthy and politically connected overweight without so much as a grain of rice being given to the poor. There is deep concern that the DSM-V does not recognize overeating as a mental disorder, like anorexia and bulimia, due to non-self incrimination. Totalitarian famines caused by Trump, Un, and Astrue indicate that the obese obsess about eating the poor people's food. The legal standard of mental illness is that a person can be institutionalized if they are a harm to themselves, others, and/or extremely destructive to the environment under *Washington v. Harper* (1990). It is extremely harmful for Congress to

discriminate against the Buy American Act under 24USC§225h in regards to the international treaty obligation to sustain US financing for international agricultural assistance programs under 7USC§1691. Terminating US international agricultural assistance impoverishes US producers, dollar for dollar, and gravely compromises achievement of Sustainable Development Goal 2.1 By 2030, end hunger and ensure access by all people, in particular the poor and people in vulnerable situations, including infants, to safe, nutritious and sufficient food all year round. The genocide convention is applicable if a particular class of people has been marked for extermination by the authorities - even if by starvation rather than outright execution (Natsios '01: 50)

Because the charge against President Trump is **incitement to violence**, the remedy is prohibition of propaganda under Art. 20 of the International Covenant on Civil and Political Rights (1978), to charge the United States with genocide in regards to the totalitarian famine in international agricultural assistance, it is necessary to charge Speaker of the House Pelosi, who did not defend agricultural assistance against totalitarian famine, or international assistance with their self-incriminating zero spending growth policy, with **torture**, intrinsic to her obsession with the Permanent Select Intelligence Committee, as a crime of genocide under 18USC§1091. It is the Speaker of the House and the ex-CIA Secretary of State who must be impeached before the 2020 Presidential elections. It is not enough for President Obama to say, "the United States does not torture" in 2009 when the torture statute got fuzzy to subsidize Pelosi as Speaker and Clinton as Secretary of State. The "balanced" budget has been proven to be a myth regarding the unsustainable Clinton robbery surplus. Revenues must grow faster than spending that must grow to compete with inflation 2.5% government, 3% services (since FY 16), 3.3% food stamp and 4% disability from previous year. The Swiss Formula for Unilateral Tariff Reduction needs to be upgraded from algebra to calculus – 0.99 for developing and 0.97 for industrialized nations (from 2016 where hyper-inflationary). The genocide convention obligates Congress to amend federal torture statute, since 2009, to comply with Arts. 2, 4 and 14 of the Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (1987) by repealing the phrase "outside the United States" from 18USC§2340A(a) and amending Exclusive Remedies at §2340B so: The legal system shall ensure that the victim of an act of torture obtains redress and has an enforceable right to fair and adequate compensation, including the means for as full rehabilitation as possible. In the event of the death of the victim as a result of an act of torture, their dependents shall be entitled to compensation under Art. 14 of the Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (1987).

Cuts to international agricultural assistance constitute discrimination against the Buy American Act under 24USC§225h in regards to the international treaty obligation to sustain US financing for international agricultural assistance programs under 7USC§1691. Terminating US international agricultural assistance impoverishes US producers, dollar for dollar, and gravely compromises achievement of Sustainable Development Goal 2.1 By 2030, end hunger and ensure access by all people, in particular the poor and people in vulnerable situations, including infants, to safe, nutritious and sufficient food all year round. This totalitarian famine of US international agricultural assistance constitutes a grave breech of Arts. 23, 55 and 147 of the Fourth Geneva Convention Relative to the Protection of Civilians in Times of War (1949). By reason of attitude not in accordance with the Geneva Conventions the government is under obligation to make good to consequence of injury. Thus every wrong creates a right for the court to rectify pursuant to the *Case Concerning the Factory of Chorzow* Permanent Court of Justice A. No. 9 (1927). Damages incurred to claimants regards their property, rights and interest and person. It was held that the essential principle contained in the actual trial of an illegal act is **non-repetition**, and that reparation must, as far as possible, wipe out all the consequences of the

illegal act and re-establish the situation which would, in all probability, have existed if that act had not been committed *Interpretations of Paragraph 4 of the Annex following Article 179 of the Treaty of Neuilly of 29 November 1919* (Greek Republic v. Kingdom Bulgaria) by the Permanent Court of Justice in No. 3 (12/9/1924) cited by *Advisory Opinion regarding the Legal Consequences of Constructing a Wall in the Occupied Palestinian Territory* No. 131 on 9 July 2004.

All persons born or naturalized in the United States, and subject to the jurisdiction thereof, are citizens of the United States and of the State wherein they reside. No State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States; nor shall any State deprive any person of life, liberty, or property, without due process of law; nor deny to any person within its jurisdiction the equal protection of the laws under Section 1 of the 14th Amendment to the US Constitution. When a person has by a final decision been convicted of a criminal offence and when subsequently his conviction has been reversed or he has been pardoned on the ground that a new or newly discovered fact shows conclusively that there has been a miscarriage of justice, the person who has suffered punishment as a result of such conviction shall be compensated according to law, unless it is proved that the non-disclosure of the unknown fact in time is wholly or partly attributable to him under Art. 14(6) of the International Covenant on Civil and Political Rights of 23 March 1976. The State shall ensure in its legal system that the victim of an act of torture obtains redress and has an enforceable right to fair and adequate compensation, including the means for as full rehabilitation as possible. In the event of the death of the victim as a result of an act of torture, his dependents shall be entitled to compensation under Art. 14 of the Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment of 26 June 1987**.**

3. Food Bank

A **food-bank** is a non-profit, charitable organization that distributes food to those who have difficulty purchasing enough to avoid hunger. Some food banks operate on the "front line" model, giving out food directly to the hungry. Others operate on the "warehouse" model, supplying food to intermediaries like food pantries, soup kitchens and other front-line organizations. St. Mary's Food Bank was the world's first food bank, established in the US in 1967. Since then, many thousands have been set up all over the world. In Europe, which until recently had little need for food banks due to extensive welfare systems, their numbers grew rapidly after the global increase in the price of food which began in late 2006, and especially after the financial crisis of 2007–08 began to worsen economic conditions for those on low incomes. Food banks salvage food that would otherwise go to waste. In the US, cities will often have a single food bank which acts as a centralized warehouse and will serve several hundred front line agencies. For many US food banks, most of their donated food comes from food left over from the normal processes of for-profit companies. It can come from any part of the food chain, e.g. from growers who have produced too much or whose food is not sufficiently visually appealing; from manufacturers who overproduced; or from retailers who over-ordered. Often the product is approaching or past its "sell by" date. In such cases, the food bank liaises with the food industry and with regulators to make sure the food is safe and legal to distribute and eat. Other sources of food include the general public, sometimes in the form of "food drives", and government programs that buy and distribute excess farm products mostly to help support higher commodity prices. Food banks can also buy food either at market prices or from wholesalers and retailers at discounted prices, often at cost.

Sometimes farmers will allow food banks to send gleaners to salvage leftover crops for free once their primary harvest is complete. A few food banks have even taken over their own farms, though such initiatives have not always been successful (Riches '12). Many food banks don't accept fresh produce, preferring canned or packaged food due to health and safety concerns, though some have tried to change this as part of a growing worldwide awareness of the importance of nutrition. As an example, in 2012, London Food Bank (Canada) started accepting perishable food, reporting that as well as the obvious health benefits, there were noticeable emotional benefits to recipients when they were given fresh food (Gillespie '12). It is not difficult to cut out the rotten part, clean, serve, freeze, can and/or dehydrate, before the expiration date, slightly de-nourished food. In the United States, where there is reported to have been a meat and milk surplus since the 1960s, the sacred cow of food banks is that they need to stop serving expired dairy products and restart production of **government cheese**. Moldy grain products can also be a pervasive problem in coastal areas, for grocers as well as food banks. To prevent dependency to dangerous food bank supply, school children are fed subsidized lunches and severely disabled and elderly people are fed separately by other professional nutrition programs, supplied in part by the food bank e.g. **Meals on wheels**.

When the world's first food bank St. Mary's Food Bank in Phoenix, Arizona, was founded in 1967, according to sociology professor Janet Poppendieck, hunger within the US was widely considered to be a solved problem until the mid-1960s. By the mid-sixties, several states had ended the free distribution of federal food surpluses, instead providing an early form of food stamps which had the benefit of allowing recipients to choose food of their liking, rather than having to accept whatever happened to be in surplus at the time. However, there was a minimum charge and some people could not afford the stamps, leading to severe hunger. One response from American society to the rediscovery of hunger was to step up the support provided by soup kitchens and similar civil society food relief agencies – some of these dated back to the Great Depression and earlier, to native tribes feasting on venison and bison everyday was a diet diversifying and culturally enriching alternative to un-cookable 'jerky'. In 1965, while volunteering for a community dining room, van Hengel learned that grocery stores often had to throw away food that had damaged packaging or was near expiration. He started collecting that food for the dining room but soon had too much for that one program. He thought of creating a central location from which any agency can receive donations. Described as a classic case of "if you build it they will come", the first food bank was created with the help of St. Mary's Basilica, which became the namesake of the organization. Food banks spread across the United States, and to Canada. By 1976, van Hengel had established the organization known today as Feeding America. As of the early 21st century, their network of over 200 food banks provides support for 90,000 projects. Other large networks exist such as AmpleHarvest.org, created by CNN Hero and World Food Prize nominee Gary Oppenheimer which lists more than 8,200 food pantries (1 out of every 5 in America) across all 50 states that can utilize overproduction of fresh produce (Poppedieck '99). The municipal non-profit model is sustained by state human services statute that also administrates the federal food stamp program.

In the 1980s, U.S. food banks began to grow rapidly. A second response to the "rediscovery" of hunger in the mid-sixties had been extensive lobbying of politicians to improve welfare. Until the 1980s, this approach had greater impact, but was always treacherous, ie. The creation of the Food Stamp Program in 1977 resulted in a significant cut to funding, and Johnson (D-TX)'s 'war on poverty (and Vietnam)'. In response to the hyperinflation of the 1970s, U.S. federal expenditure on hunger relief grew by about 500%, with food stamps distributed free of charge to those in greatest need. Welfare was widely considered preferable to grass roots efforts, as the latter could be unreliable, did not give recipients consumer-style choice in the same way as did

food stamps, and risked recipients feeling humiliated by having to turn to charity. In the early 1980s, president Reagan's administration scaled back welfare provision, leading to a rapid rise in activity from grass roots hunger relief agencies. According to a comprehensive government survey completed in 2002, over 90% of food banks were established in the US after 1981. For the first few years after the change, there was vigorous opposition from left, who argued that state welfare was much more suitable for meeting recipients needs. But in the decades that followed, food banks have become an accepted part of America's response to hunger (Poppendieck '99). Demand for the services of US food bank increased further in the late 1990s, after the "end of welfare as we know it" with President Clinton's Personal Responsibility and Work Opportunity Act.(Watson '02). In Canada, foodbanks underwent a period of rapid growth after the cutbacks in welfare that took place in the mid-1990s. As early as the 1980s, food banks had also begun to spread from the United States to the rest of the world. The first European food bank was founded in France during 1984. In the 1990s and early 2000s, food banks were established in South America, Africa, and Asia, in several cases with van Hengel acting as a consultant. In 2007, the Global FoodBanking Network was formed (Riches '86).

Following the financial crisis of 2007–08, and the lasting inflation in the price of food that began in late 2006, there has been a further increase in the number of individuals requesting help from American and Canadian food banks. By 2012, according to Food Banks Canada, over 850,000 Canadians needed help from a food bank each month (Cooper '15) For the United States, Gleaners Indiana Food bank reported in 2012 that there were then 50 million Americans struggling with food insecurity (about 1 in 6 of the population), with the number of individuals seeking help from food banks having increased by 46% since 2005. According to a 2012 UCLA Center for Health Policy Research study, there has been a 40% increase in demand for Californian food banks since 2008, with married couples who both work sometimes requiring the aid of food banks. The director of the Second Harvest Food Bank in Orlando, has said that college-educated professional couples have begun to turn to food pantries. By mid-2012, US food banks had expressed concerns on the expected difficulty in feeding the hungry. Rapidly rising demand has been coinciding with higher food prices and with a decrease in donations, partly as the food industry is becoming more efficient and so has less mislabelled and other slightly defective food to give away. Also there has been less surplus federal food on offer (Skillem '12). Additionally, there have been recent decreases in federal funding, and Congress debated possible further cuts, including potentially billions of dollars from the Supplemental Nutrition Assistance Program (food stamp program) (Bello '12). In September 2012, Feeding America launched Hunger Action Month, with events planned all over the nation. Food banks and other agencies involved hoped to raise awareness that about one in six Americans are struggling with hunger, and to get more Americans involved in helping out (Welch '19).

The first European food bank was founded in France during 1984. The first Italian food bank was established in 1989. Similar to the UK's experience, foodbanks have become much more common across continental Europe since the crisis that began in 2008, and especially since austerity began to take effect from late 2010 (Field et al'14). In Spain, food banks can operate on the warehouse model, supplying a network of surrounding soup kitchens and other food relief agencies. The Spanish federation of food banks helped to feed about 800,000 people during 2008–2011, according to the Carrefour Foundation. By October 2014, Spain had 55 food banks in total, with the numbers who depend on them having increased to 1.5 million (Buck '14). In Belgium, food banks helped about 121,000 people during 2012. That was an increase of about 4,500 compared with 2011, the biggest increase since the start of the 2008 crisis. Belgian food banks account for about 65% of all food aid given out within the country. The number of food banks has increased rapidly even in Germany, a country that has weathered the crisis relatively

well, and has not needed to implement severe austerity. In 2012, professor Sabine Pfeiffer of Munich University of Applied Sciences said there has been an "explosion" of food bank usage (Selke '12). While many European food banks have long been run by civil society with no government assistance, an EU funded project, the Most deprived persons program (MDP), had specialized in supplying food to marginalized people who are not covered by the benefit system, who were in some cases reluctant to approach the more formal food banks. The program involved the EU buying surplus agricultural products, which were then distributed to the poor largely by Catholic churches. The MDP was wound down in late 2013, and was replaced by Fund for European aid for the most deprived (FEAD), which is set to run until at least 2020. The FEAD program has a wider scope than the MDP, helping deprived people not just with food aid, but with social inclusion projects and housing. The actual methods employed by FEAD tend to vary from country to country, but in several EU states, such as Poland, its activities include helping to fund local food bank networks.

Professor Jon May, of Queen Mary University of London and the Independent Food Aid Network, said statistics showed rapid rise in numbers of food banks during the last five years. “There are now food banks in almost every community, from the East End of London to the Cotswolds. The spread of food banks maps growing problems of poverty across the UK, but also the growing drive among many thousands of people across the country to try and do something about those problems”. Though Foodbanks were rarely seen in the UK in the second half of the twentieth century, their use has started to grow, especially in the 2000s, and have since dramatically expanded. The increase in the dependency on food banks has been blamed on the 2008 recession and the Conservative government's austerity policies. These policies have included cuts to the welfare state and caps on the total amount of welfare support that a family can claim. As of January 2014, there were close to 1,000 UK food banks. The largest group co-ordinating UK foodbanks was The Trussell Trust, a Christian charity based in Salisbury. About 43% of the UK's foodbanks were run by Trussell, about 20% by smaller church networks such as Besom and Basic, about 31% were independent, and about 4% were run by secular food bank networks such as Fare Share and Food Cycle. Before the 2008 credit crunch, food banks were "almost unheard of" in the UK. In 2004, Trussell only ran two food banks, but by 2007–2008, there were 22 food banks in the Trussell Trust Foodbank Network and by early-2011, The Trussell Trust supported 100. As of May 2012, they had 201. By August, 252. Unlike oup kitchens, most, but not all UK food banks are unable to help people who come in off the street without a referral - instead they operate with a referral system. Vouchers are handed out to those in need by various sorts of frontline care professionals, such as social workers, health visitors, Citizens Advice Bureau, Jobcentres and housing officials. The voucher can typically be exchanged at the food bank for a package of food sufficient to last three days. The year to April 2013 saw close to 350,000 referrals to Trussell Trust foodbanks, more than double the amount from the previous year. A number of food banks have been set up outside of the Trussell system, some faith based others secular, in part as they don't like having to turn away people without referrals (Field et al '14).

There are over 900 food banks in Germany, up from just 1 in 1993 (Selke '17). In 2014, 1.5 million people a week used food banks in Germany. In total, around 3.5 million people rely on food banks in France. One provider, the Banque Alimentaire has over 100 branches in France, serving 200 million meals a year to 1.85 million people (Hacker et al '15). Several Asian places have begun to use food banks; these include Nepal, South Korea, Japan and Taiwan. Delhi Food Bank is an organization that feeds, empowers and transforms lives in the New Delhi–NCR Region. They hold that their shared capabilities can make the basic aspiration of universal access to food a reality. They attempt to pursue this vision through high quality and standards for

processes leveraged by technology to get the right aid to the right people at the right time. The first food bank in Hong Kong is Feeding Hong Kong. It was founded in 2009. Food Angel is also a food bank in Hong Kong. The Egyptian Food Bank was established in Cairo in 2006, and less than ten years later, food banks run on similar principles spread to other Arab countries in North Africa and the Middle East (Al Tamimi '12). In Sub-Saharan Africa, there are charity-run food banks that operate on a semi-commercial system that differs from both the more common "warehouse" and "frontline" models. In some rural LDCs such as Malawi, food is often relatively cheap and plentiful for the first few months after the harvest, but then becomes more and more expensive. Food banks in those areas can buy large amounts of food shortly after the harvest, and then as food prices start to rise, they sell it back to local people throughout the year at well below market prices. Such food banks will sometimes also act as centres to provide small holders and subsistence farmers with various forms of support. Formed in 2009, FoodBank South Africa (FoodBank SA) is South Africa's national foodbanking network and a member of The Global FoodBanking Network. FoodBank SA's vision is "A South Africa without hunger and malnutrition". There are over 30 countries with active food bank groups under the umbrella of The Global FoodBanking Network. Countries in the international network include Australia, Israel, Turkey, Russia, India, Taiwan, Colombia, Brazil, Argentina, Chile, Guatemala, South Africa, Hong Kong, Singapore, South Korea and the UK. There are also several countries with foodbanks but which have not yet joined the network, either as they don't yet meet the required criteria or as they have not applied.

The rise of food banks has been broadly welcomed. Not only do they provide a solution to the problem of hunger that doesn't require resources from the state, but they can be viewed as evidence of increasing community spirit and of active, caring citizenship. In the UK for example, Patrick Butler, society editor for The Guardian, has written that the rise of foodbanks has been most enthusiastically welcomed by the right, but also by many on the left of the political spectrum, who were often "nervously excited" about them (Butler '12). However, there has been considerable concern expressed by some researchers and politicians. Drawing on the United States's experience after the rapid rise of food banks in the 1980s, American sociology professor Janet Poppendieck warned that the rise of food banks can contribute to a long-term erosion of human rights and support for entitlements. Once food banks become well established, it can be politically impossible to return responsibility for meeting the needs of hungry people to the state. Poppendieck says that the logistics of running food banks can be so demanding that they prevent kind-hearted people from having time to participate in public policy advocacy; yet she also says if they can be encouraged to lobby politicians for long-term changes that would help those on low income, they often have considerable credibility with legislators. As of 2012, senior US food banks workers have expressed a preference to remain politically neutral, which political activists have suggested may relate to their sources of funding. Rachel Loopstra from University of Toronto has said foodbanks are often inefficient, unreliable and unable to supply nutritional food. She said a survey in Toronto found that only 1 in 5 families suffering from food insecurity would turn to food banks, in part as there is a stigma associated with having to do so (Butler '12). Elizabeth Dowler, Professor of Food & Social Policy at Warwick University, said that most British people prefer the state to take responsibility for helping the hungry. Hannah Lambie-Mumford, from Sheffield University, echoed the view that some users of food banks find having to ask for food humiliating, and also that food banks volunteers should be encouraged to advocate for long-term solutions to the underlying causes of poverty and hunger (Dowler et al '12). Olivier De Schutter, a senior United Nations official charged with ensuring governments honour their obligation to safeguard their citizen's right to food, has expressed alarm at the rise of food banks. He has reminded the governments of the advanced economies in Europe and Canada

that they have a "duty to protect" their citizens from hunger, and suggested that leaving such an obligation to food banks may be an abuse of human rights (Cooper '13).

4. Permaculture

The unsaid law of the land, parking agricultural and urban development is '**zero net land degradation**, despite increasing population, by eliminating waste.' The bottom line is that by increasing sustainable agricultural efficiency, it should not require more agricultural land to feed more people. Countries around the world currently produce an agricultural surplus, as high as 140%, in, often famine stricken, African nations with export commodities. Metropolitan Western Europe produces roughly 100% of its agricultural needs. By 2050 the Food and Agriculture Organization estimates the population demand for food will increase 60% from 2005. To keep net agricultural land degradation at zero, the strategy is to increase productivity by eliminating waste. Fruit, vegetables and grains are more efficient sources of nutrition than livestock. Grade A farmland is flat. Campers and urban developers also require flat land. Disputed low elevation valleys are to grow a mix of fruit and nut trees to camp under, in a native berry ecosystem, on private and public park-land, without the, clearcutting and tilling that leaves the ground too buggy for sleeping. Homes, gardens, fields of grain, apiaries, free range chickens and open range cattle are located between orchards. Cities grow vertically, invest in clean energy efficient technology and provide free camping for pedestrians, with sidewalks to trails to surrounding wildernesses, to live in harmony with nature. The organic certification program estimates that it takes three lean years for soil to recover from chemical farming. To create edible parklike settings out of organic farms, with a canopy, understory, and fields, permaculture design principles must be given tenure. Sustainable Development Goal 2 End hunger, achieve food security and improved nutrition and promote sustainable agriculture, challenges Goal 2.4 By 2030 ensure sustainable food production systems and implement resilient agricultural practices that increase productivity and production, that help maintain ecosystems, that strengthen capacity for adaptation to climate change, extreme weather, drought, flooding and other disasters and that progressively improve land and soil quality. Zero tariffs or sanctions on food paragraph 98 Alleged violations of the 1955 Treaty of Amity, Economic Relations, and Consular Rights (*Islamic Republic of Iran v. United States of America*) (2018).

Agriculture arose roughly ten thousand years ago and its expansion was the dominant force of ecological change over most of the Holocene, the relatively warm and stable geological epoch from the end of the last ice age that began around twelve thousand years ago. Agricultural surpluses enabled 10% of the population to live in cities around 6,000 B.C. who learned war. Food forests were slashed and burned and the population became increasingly reliant upon agricultural commodities that regrow in one year. The Industrial Revolution enabled 50% of the population to live in cities and today 80% of Americans live in the city and since 2008 the majority of people around the world live in cities (Steward '09). Today, in the United States, an acre of National Forest is 65 times more likely to burn than an acre of National Park. Every year, 10 times more forest is burned than logged. It is essential that the Forest Service is replanted in the Interior Department. The wasteful process of meat production, that requires far larger acreages of land than vegetable agriculture, has been a source of economic conflict in human society for thousands of years. An acre of grain produces five times more protein than an acre of pasture set aside for meat production. An acre of beans or peas products ten times more, and an acre of spinach twenty-eight times more protein. In 1974 the US Central Intelligence Agency (CIA) published a report warning that in the near future there may not be enough food for the world's population unless the affluent nations make a quick and drastic cut in their consumption of grain-fed animals. US livestock eats enough grain and soybeans each year to

feed more than five times the entire US population. According to one study, if Americans reduced their meat consumption by only 10 percent, 12 million tons of grain would be freed up annually for human consumption – enough to feed the 60 million children (40,000 a day) and adults who starve to death (Swami '06: 20 -21). Provided cattle are quarantined until non-native grass seeds have left their digestive tract, damage caused by open range cattle to water and ground is temporary, and they consume no grain for the duration they are allowed to forage on large public and private lands with multiple use sustainable yield policy that includes open range cattle. Livestock coexisted with agriculture and cities for thousands of years, before war burned the food forests of shepherds, fenced off from gardens and fields, and the unhealthy fattening of cattle with grain was targeted for derision by hungry agriculture dependent people. To improve efficiency of agricultural land usage livestock must be worked into crop rotation systems with ample open range in the mountains during the summer growing season. Feed the people the grain and livestock the straw. Human consumers would dramatically decrease pesticide and land usage.

There were more chickens processed in 2006 the United States than there are people in the world – 7.6 billion chickens versus 6 billion humans. Free range chickens are better layers and healthier than factory farmed birds. There were 300 million turkeys when there were 280 million humans. Plus there are 100 million hogs and 60 million beef cattle. The USDA reports, over 90 percent of all the grain produced in America is used to feed livestock. USDA Economic Research Service estimates we get only one pound of beef for every sixteen pounds of grain. According to the soil and water specialists at the University of California's Agricultural Extension, it takes 5,214 gallons of water to produce one pound of beef, 815 gallons of water to produce a pound of chicken, 1,630 gallons to produce a pound of pork, but only 23 gallons to produce a pound of wheat. Californians may save more water by not eating a pound of beef than by not showering for six months. In terms of calorie units per acre, a diet of grains, vegetables, and beans will support twenty times more people than a diet of meat.

As it stands now, about half the harvested acreage in America and in a number of European, African and Asian countries is used to feed animals. If the earth's arable land were used primarily for the production of vegetarian foods, the planet could easily support a human population of twenty billion and more. Even now, we are producing enough food for everyone on the planet. Unfortunately, it is being allocated inefficiently. Most hunger deaths are due to chronic malnutrition caused by inequitable distribution and inefficient use of existing food resources. At the same time, wasteful agricultural practices, such as the intensive livestock operations known as factory farming, are rapidly polluting and depleting the natural resources upon which all life depends. Trying to produce more food by these methods would lead only to more water pollution, more soil degradation and, ultimately, more hunger. A report submitted to the United Nations World Food Conference concurs: “The overconsumption of meat by the rich means hunger for the poor. This wasteful agriculture must be changed – by the suppression of feedlots where beef are fattened on grains, and even a massive reduction in beef cattle” (Swami '06: 13 -15). Feed people the grain and livestock the straw. Essentially, US meat and milk surpluses since the 1960s do not warrant fattening livestock with grain or recombinant Bovine Growth Hormone (rBGH).

A living cow yields society more food than a dead one in the form of a continuing supply of milk, cheese, butter, yogurt and other high-protein foods. In trying to solve the third-world hunger crisis, people have looked at countries like India and wondered why the people allow themselves to compete with cows for precious grain. Why don't they eat the cows? Most Hindus consider **cows sacred** and do not slaughter them. A detailed study of cows in West

Bengal, by Stewart Odend'hal of the University of Missouri found that far from depriving humans of food, cows ate only inedible remains of harvested crops (rice hulls, tops of sugarcane, etc.) and grass. Studies have shown that the food problem in India has more to do with occasional severe drought, political upheaval, or industrialization, than with cows. In the 80s in America, there was a deliberate attempt to limit dairy production and the government was forced to stockpile butter, cheese, and nonfat dried milk. The supply grew by about 45 million pounds each week. The 10 million cows in America at that time provided so much milk that the government periodically released million of pounds of dairy products for free distribution to the poor and hungry. Sadly, in the mid-'80s the US government bought and slaughtered millions of dairy cows to end the need to support milk process by stockpiling dairy products (Swami '06: 15 – 16). The warehouse that stored government cheese is rumored to have been contaminated by rats. **Government cheese**, medium and sharp cheddar, needs to be recreated to dispose of expired dairy products at the Food Bank, in a timely fashion, before expiration, rather than six days after when it is fed to livestock.

Silos are intended for storage for four or five months and are dependent for their success on by the same kinds of anaerobic bacteria that produce acid and alcohol. Nutritious, long-lasting silage (both corn and hay) is made by (1) a finely-chopped crop, (2) A tight packing to eliminate trapped oxygen (usually accomplished by driving a tractor back and forth over the silage), and (3) an airtight seal of plastic or other impermeable layer (Schwenke ’91: 42). Many *E.coli* outbreaks are linked to unsanitary slaughtering and harvesting practices, which are rampant in industrial agriculture. Some studies have shown that the unnatural diet of corn and soy and **silage** made therefrom, fed to cattle in concentrated animal feeding operations (CAFOs) increase the *E. coli* in their digestive tracts (Rodale ’10: 51). Cows mainly fed hay generate less than 1 percent the E coli produced by grain-fed animals (Robbins ’01: 370). Silage and grains are not a healthy substitute for natural grasses and hay. Many sustainable livestock operations address potential negative health and environmental impacts through their production methods. They produce less waste and forego dangerous chemicals and other additives. Grass pastured meat and dairy products have been shown to be high in omega-3 and other fatty acids that have cancer-fighting properties (Satter ’00). Feeding as little as five pounds of grain per day cuts the CLA (conjugated linoleic acid, which holds great promise in fighting cancer, obesity and diabetes) content of the milk in half! Grass finished beeves had 250% more CLA in their intra-muscular fat than grain-finished beeves (Jackson ’03: 165, 166). The most successful farms include animals, which are pastured on one area, then rotated to another, long before the pasture is overgrazed and turns to mud. These pastures are tilled once every 3 years to incorporate the animal manure, a key fertilizer, into the soil, to feed a diverse array of crops for the next few years. Rotating the crops and herds among the fields from year to year breaks the cycle of disease (Rodale ’10: 158). To increase agricultural production to feed 50% more people in 2050, by reducing waste, with zero net land degradation, acreage must be used more efficiently. The ancient solution is that farmers must sell the grain to the people and feed the hay to the livestock. Grain makes animals too fat. Grass fed livestock are healthier. Silage producing land also needs to be improved from most highly contaminated with pesticides to levels that are fit for human and animal consumption to organic. Alfalfa is a great source of calcium. Sell the wheat berries to humans and use the hay for livestock in the winter after they summer on the open range grass-lands. The land will recover. Grow no-till fruit and nut orchards along the native treeline, with berry filled understory to diversify the golden field of grain. Open range cattle are healthier. Provided that their digestive tracts are cleaned out of invasive grass seeds, open range cattle only cause transient degradation of water and land quality. No poaching. 96% of large game animals consumed by humans are domesticated, while only 4% are wild. It is better that humans eat of the species that are successful because of human animal husbandry, than get all twisted out of

shape trying to justify their license to hunt wild animals and conflict with cattle ranchers regarding multi-use sustainable yield of public land use as a environmental imperative. Open range cattle, crop rotations of grazing animals, and free range chicken farming are sustainable.

Concentrated animal feeding operations (CAFOs) degrade the environment. The USDA spent a total of $350 million on surplus beef and other meat products for schools – more than double what it spent on fruits and vegetables (most of which were canned or frozen). When diseased animals are destroyed, the government pays the owners an indemnity. Governments around the world pay farmers for their mad cows. In 2001 alone the UK paid out over 91 million pounds sterling or "mad cows". The US Agricultural Research Service calls the heavily contaminated runoff and sewage from America's thousands of slaughterhouses and feedlots a major source of pollution of the nation's rivers and streams. Mountains of manure have become a disposal problem. Much of its ends up in our waterways. Mass production of meat has become a staggering source of pollution. In recent years livestock waste has ben implicated in massive fish kills and outbreaks of such diseases as **pfiesteria** which causes memory loss, confusion and acute skin burning in people exposed to contaminated water. In the United States livestock produced 130 times as much waste as people in 1999. Another significant contributor to greenhouse gas (GHG) emissions is the use of large amounts of **nitrogen fertilizers**. Ammonium nitrate, the most common form of nitrogen fertilizer, is actually derived from natural gas, a fossil fuel. One quarter of nitrogen fertilizer used in the United States is used on corn grown as livestock feed (Swami '06: 17 -19). Smaller herds, more properly composted manure.

Some of the **health effects** from CAFOs air emissions include asthma, headaches, respiratory problems, eye irritation, nausea, weakness, and chest tightness. These health effects are felt by farm workers and nearby residents, including children. In addition, studies conducted by the University of Iowa show that the asthma rate of children of CAFO operators is higher than that of children from other farms. When skilled migrant workers were deported from slaughterhouses in 2019 there was a fatal outbreak of Salmonella in both the United States and Mexico. There is evidence that CAFOs affect the ambient air quality of a community. There are three laws that potentially govern CAFO air emissions—the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, also known as the Superfund Act), the Emergency Planning & Community Right to Know Act (EPCRA), and the Clean Air Act (CAA). CAFOs also emit greenhouse gases, and therefore contribute to climate change. Globally, livestock operations are responsible for approximately 18% of greenhouse gas production and over 7% of U.S. greenhouse gas emissions. While carbon dioxide is often considered the primary greenhouse gas of concern, manure emits methane and nitrous oxide which are 23 and 300 times more potent as greenhouse gases than carbon dioxide. The EPA attributes manure management as the fourth leading source of nitrous oxide emissions and the fifth leading source of methane emissions. One of the most common complaints associated with CAFOs are the odors produced. The odors than CAFOs emit are a complex mixture of ammonia, hydrogen sulfide, and carbon dioxide, as well as volatile and semi-volatile organic compounds. Depending on the weather conditions odors can be smelled from as much as 5 or 6 miles away, although 3 miles is a more common distance. Houseflies, stable flies, and mosquitoes are the most common insects associated with CAFOs (Hribrar et al '10: 6, 7, 8).

To date no insurance company has been willing to insure the **biotech industry**. In our society insurance is the litmus test for safety. If the insurance industry isn't willing to bet its money on the safety of a product or technology, the risks are too high for them to take the gamble. There is today no insurance whatsoever against the kinds of catastrophic losses and tragedies that could ensure form introducing transgenic organisms into the environment and into the human food

chain. In 1999 the EU announced its governments had drawn up a five-point Emergency Response Plan to cope if GM plants result in widespread illness or the death of wildlife. In France a band of 120 farmers broke into a storage facility of the biotech company Novartis and destroyed 30 tons of GM corn. In the US, Germany and the Netherlands GM crops have been destroyed by angry citizens. In 1999 the seven largest grocery chains in six European countries, Tesco, Safeway, Sainsbury's Iceland, Marks & Spencer, the Co-op and Waitrose, made a public commitment to go GMO free. In December 1999 a statement was posted to the cafeteria of the Monsanto Corporations United Kingdom headquarters in High Wycombe, England – In response to concerns raised by our customers…we have decided to remove, as far as is practicable, genetically modified soy and maize from all food products served in our restaurant. We will continue to work with our suppliers to replace GM (genetically modified) soy and maize with non-GM ingredients… We have taken the above steps to ensure that you, the consumer, can feel confident in the food we serve. African Civil Society groups, from more than 45 African countries, participating in the World Summit on Sustainable Development in 2002, joined hands with the Zambian and Zimbabwean governments and their people in rejecting GM contaminated food for our starving brothers and sisters.

Biotechnology is regulated **Convention on Biological Diversity** (CBD). Whether or not the United States is party to the CBD US exports may be rejected because they have been contaminated by transgenic organisms crops. Essentially the monopolistic tendencies of the North American biotechnology industry has encountered persistent legal opposition from the CBD of 1992 and its protocols of 2000 and the protocol of 2010 aims to share the benefits of biotechnology equitably. Art. 8(g) of the Convention on Biological Diversity (CBD) of 1992 aims to regulate the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health: Art. 19 of the CBD tires of waiting for the benefits of biotechnology to be shared and calls for a protocol to provide for the safe transfer, handling and use of any living modified organisms resulting from biotechnology that may have adverse affect on the sustainable use of biological diversity. Art. 24(2) of the Cartagena Protocol on Biosafety to the CBD of 2000 encourages non-Parties contribute appropriate information to the Biosafety Clearing-House on living modified organisms released in, or moved into or out of, areas within their national jurisdictions. Art. 25 allows Parties to penalize the illegal transboundary movement of living modified organisms; the cost of repatriation or destruction is paid by the country of origin. The Nagoyo Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising form the Their Utilization to the CBD of 2010. The objective of this Protocol is the fair and equitable sharing of the benefits arising from the utilization of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding, thereby contributing to the conservation of biological diversity and the sustainable use of its components. Art. 6(2)(e) and Art. 17(2) provide, evidence of the decision to grant prior informed consent be made available to the Access and Benefit-sharing Clearing-House and shall constitute an internationally recognized certificate of compliance, equal to non-parties in Art. 24.

The Food and Agriculture (FAO) projects that global agricultural demand in 2050 will be 60 percent higher than the three-year average for 2005—07. Global agricultural production has grown 2.5-3 times over the past century and can rightly be described as cornucopian, with enough food produced to feed the entire human family. As demand for agricultural products grew by 2.2 percent per year between 1961 and 2007, the extent of arable land grew much more slowly – just 14 percent for the entire period. To meet demand, farmers intensified production,

using mechanization, chemical fertilizer (in place of manure), new seed varieties, irrigation, and other advances to coax more from each hectare of land. Yet rates of growth of agricultural production are only half the 3 percent annual rate seen in developing countries in the past. The number of countries depend on grain imports (defined as importing 25 percent of more of domestic consumption) grew 57 percent between 1961 and 2013, to 77 nations – more than a third of the world's countries. Among developing countries, dependence on grain imports is greater than 50 percent in Central America, where land is relatively scarce, and in the Middle East and North Africa, where water is the chief constraint. Sub-Saharan Africa imports about 20 percent of its grain, and the low and middle-income nations of Asia import about 7 percent. Japan, with the wealth to outbid other nations in international markets, imports about 70 percent of its grain.

With 7.2 billion people on the planet and with the global population continuing to grow by around 75 million people per year, the challenge of feeding the planet is with us again. **Malnutrition** is a pervasive problem: around 40 percent of the world's population is malnourished in one way or another. The Food and Agriculture (FAO) defines chronic hunger as the insufficient intake of energy (calories) and proteins. Hundreds of millions of people are afflicted by chronic hunger and have only the energy for mere survival. The FAO estimated 870 million people for the years 2010-2012. There is also hidden hunger, or micronutrient insufficiency. The calories and proteins may be sufficient, but the micronutrients like vitamins or particular fatty acids are not adequately present in the diet. Key micronutrient deficiencies prevalent in many lo-income countries include vitamin A, vitamin B12, zin, iron, folate, omega-3 fatty acids, and iodine. The third kind of malnutrition, which is now at epidemic proportions in many parts of the world, especially the richest countries, is the excessive intake of calories leading to obesity, meaning weight is far too high for height. It is estimated that roughly one-third of all adults in the world are overweight, and around 10-15 percent are **obese**. Adding it all up, around 900 million people are chronically hungry. Perhaps another 1 billion more have enough macronutrients (calories and proteins) but suffer from one or more micronutrient deficiencies. Roughly 1 billion more are obese. In total, around 3 billion people are malnourished out of a world population of 7.2 billion people, meaning that a staggering 40 percent of the world is malnourished.

Chronic hunger is heavily concentrated in tropical Africa and in South Asia. More than one-third of the population in tropical Africa, especially central and southern Africa, is undernourished. In South Asia, between 20 and 33 percent of the population is chronically undernourished. Chronic undernourishment of young children is measured according to various indicators of severity. The first is stunting. **Stunting** means that a child has a very low height for his or her age. Specifically, children are assessed relative to a standard population distribution of height for age. Children who are more than two standard deviations below the norm are considered stunted. The second condition is even more urgent, and that is wasting – low weight for height. **Wasting** is often a sign of acute, life-threatening undernutrition, of the kind one often sees in a famine. Children may require high intensity nutritional foods designed to combat acute undernutrition and emergency procedures to help keep the children alive. There is a key distinction between chronic undernutrition (chronic insufficiency of calories and proteins) and acute undernutrition that may arise from wars, disasters, droughts and displacement of populations. When those acute episodes occur, there is not only massive suffering but also the risk of massive loss of life from starvation and disease. Violence and conflict often break out in hungry regions. **Obesity** marks the other end of the malnourishment spectrum and also causes a tremendous amount of disease and premature mortality. The United States, Mexico, Venezuela, Libya, Egypt, Saudi Arabia, South Africa and a few others have obesity rates above 30 percent.

Europe and Russia have an obesity rate between 20 and 30 percent. The obesity epidemic most likely results from a combination of too many calories, the wrong kinds of calories and the extreme physical inactivity of urban life. 200,000% annual inflation has fueled millions of Venezuelan refugees to lose more than ten kilograms of weight.

Permaculture is a term coined by Australian Bill Mollison and David Holmgren, in a book they wrote called *Permaculture One*. The books and very word Permaculture© are copyright. The word permaculture can be used by anyone adhering to the principles and ethics expressed herein. The only restriction on use is that of teaching; only graduates of a Permaculture Institute can teach 'Permaculture', and they adhere to agreed-on curricula developed by the College of Graduates of the Institutes of Permaculture. Permacultures, as a system of design for people in nature, has come a long way since 1974 when it was first proposed by Bill Mollison and David Holmgren. There are now more than 54 international teaching centers and over 80 teachers at work; students number some 6000, and are expanding exponentially. Permaculture gives priority to using existing wealth to rebuilding natural capital, especially trees and forests, as a proven storage of wealth to sustain humanity into a future with less fossil fuel. Permaculture emphasizes bottom-up "redesign" processes, starting with the individual and household as the drivers for change at the market, community and cultural level. Permaculture sees pre-industrial sustainable societies as providing models that reflect the more general system design principles observable in nature, and relevant to post-industrial systems. The word permaculture was coined to describe an "integrated evolving system of perennial or self-perpetuating plant and animal species useful to man". A more current definition of permaculture, is "Consciously designed landscapes which mimic the patterns and relationships found in nature, while yielding an abundance of food, fiber and energy for provision of local needs."

Almost all beginning gardeners who love their work **plant gardens** that are too large and then don't have time to tend them properly. Good French intensive gardeners can raise more on a hundred square feet than others can on three times that much space because they can concentrate water, soil nutrients and their labor on a smaller area. Thirty acres take the same amount of time that a large operator spends, with several workers, on a thousand acres, but costs will be lower because payroll is zero and tools cheaper, while production per acre is much higher. This economic truth becomes even truer as the number of acres farmed diminishes below twenty. As farms become smaller than three acres, yields start increasingly dramatically. Work is better achieved if there are many activities in progress, spread over the entire year. Biointensive methods work more practically with high value crops like vegetables. On raised beds of 100 square feet in size vegetable production can be increased from 2,000 to 14,000 pounds. Fruit trees are excellent trees to grow in fencerows where in addition to plenty of light, the grazing animals are handy for eating up the drops and surplus fruit. Scattering fruit trees out along forest edges and fencerows is less harmed by insect predation than the ones clustered in the more formal orchard. The key to successful small farming is marketing.

The idea behind permaculture is that **generalized principles** can be derived from the study of both the natural world and pre-industrial sustainable societies, and that these will be universally applicable to fast-track the post-industrial development of sustainable use of land and resources. These principles can be divided into ethical principles and design principles. Permaculture ethical principles were distilled from research of community ethics as adopted by older religious and cooperative groups. Since the emergence of permaculture, ethics – especially environmental ethics – has become a very active field of academic and wider study that lies at the heart of the manifold crisis facing humanity at the end of the second Christian millennium. The scientific foundation for permaculture design principles lies generally within the modern science of

ecology, and more particularly within the branch of ecology called systems ecology. Other intellectual disciplines, most particularly landscape geography and ethnobotany, have contributed concepts that have been adapted to design principles. The ethical principles of permaculture are (1) care for the earth, living soil, biodiversity and all living things, (2) care for people, setting limits on consumption and reproduction and redistributing surplus. The design principles are (1) observe and interact (2) catch and store energy, (3) obtain a yield, (4) apply self-regulation and accept feedback, (5) use and value renewable resources and services, (6) produce no waste, (7) design from patterns to details, (8) integrate rather than segregate, (9) use small and slow solutions, (10) use and value diversity, (11) use edges and value the marginal, (12) creatively use and respond to change, (13)

Design principle 1 **Observe and interact**. Good design depends on a free and harmonious relationship to nature and people, in which careful observation and thoughtful interaction provide the design inspiration, repertoire and patterns. It is not something that is done in isolation, but through continuous and reciprocal interaction with the subject. In hunter-gatherer and low-density agricultural societies, the natural environment provided all material needs, with human effort mainly required for harvesting. In preindustrial societies with high population densities, agricultural productivity depended on large and continuous inputs of fossil fuel energy to provide its food and other goods and services. Permaculture designers use careful observation and thoughtful interaction to reduce the need for both repetitive manual labor and for non-renewable energy and high technology. Thus, traditional agriculture was labor intensive, industrial agriculture is energy intensive, and permaculture-designed systems are information and design intensive.

Design Principle 2 **Catch and Store Energy**. Permaculture strategies of landscape development can be grouped as rebuilding the natural capital of landscapes in four key energy storages: water, living soil, trees and seed. Solar energy (in the form of visible light) is used by plants to transform water and carbon dioxide form the atmosphere into carbohydrates by the photosynthesis process. These carbohydrates are the start of the chemical energy supply chain that provides for the needs of all other living things, as well as (indirectly) creating the fossil fuels of coal, oil and gas. Solar energy also drives the weather and climate systems that delivery energy in the form of rain, wind, lightning and fire. Photosynthesis (in green plants) - Carbon dioxide + water + sunlight = carbohydrates + oxygen. Respiration (in plants and animals) - Carbohydrates + oxygen = carbon dioxide + water + metabolic energy.

Design Principle 3 **Obtain a Yield**. All organisms and species obtain a yield form their environment adequate to sustain them. Those that fail in this task quickly disappear. There could hardly be a more fundamental lesson from nature, one that reinforces our basic survival instincts. Hardy and self-reliant species are important in any low-energy sustainable system. By selecting hardy, locally adapted and self-reproducing plants wherever possible, the designer can minimize the resources required to maintain gardens, farms and forests. These species can be thought of as “self-reliant” or “competent” in “obtaining yield”. Thus the first priority in healthy broadacre farm landscapes, rangelands and forests must be vigorous and self-reproducing plants. One interesting method of environmental accounting is the ecological footprint. This method coverts all consumed resources to a figure representing the area of land required to generate those resources and dispose of the wastes. Comparative figures show a global average of 2.9 hectares of productive land being used to support each person. Close to the top in consumption are the United States, at 12.2 hectares per person, and Australia, at 8.5 hectares per person. The EMERGY methodology is a powerful accounting system that has been continuously developed by Howard Odum and colleagues around the world since its beginnings in the late

1960s. One application of EMERGY accounting is the calculation of EMERGY yield ratio. A value greater than 1 indicates a net gain to the economy. A value over 4 is a high-value source. Annual crops have yield ratios little better than 1, while wood plantations yield 1.5 to 4, and 300 year-old rainforests yields.

Design Principle 4 **Apply Self-Regulation and Accept Feedback**. This principle deals with self-regulatory aspects of permaculture design that limit or discourage inappropriate growth or behavior. The self-controlling aspects of human culture, rather than the expansion of technology for resource exploitation and growth, represent the highest evolutionary development. The ways in which we apply these abilities to controlling excesses of growth and expansion over the next century will be greatest test of our evolutionary sophistication. Howard Odum described a "tripartite altruism" in nature: approximately one-third of captured energy is required for metabolic self-maintenance (of an individual or population); one-third is fed back to maintain lower-order system providers; and one-third is contributed upward to higher-order system controllers.

Principle 5 **Use and Value Renewable Resources and Services**. Renewable resources are those which are renewed and replaced by natural processes over reasonable periods without eh need for major non-renewable inputs. Permaculture design should aim to make best use of renewable natural resources to manage and maintain yields, even if some use of non-renewable resources is needed in establishing the system. Renewable services (or passive functions) are those we gain from plants, animals and living soil and water without them being consumed. The proverb "let nature take its course" reminds us that human intervention and complication of processes can make things worse and that we should respect and value the wisdom in biological systems and processes. In Nepal, one hectare of arable land used to be adequate to support a farmer and his family from rice production, vegetables, a few tree crops and livestock. However, this system required an additional seven hectares of common forest to provide the animal, fodder, fuel, construction materials and other special yields such as medicinal herbs. Given careful management, it is possible to harvest firewood, poles and sawlogs from native forests without reducing the capacity of the forest to continue its full range of ecological functions and to provide these yields to future generations. Total canopy cover in a forest is limited, but that canopy may exist as many thin saplings or a few large trees. Thinning of regrowth forest stands allows the remaining trees to grow faster and to a larger size. If the most desirable trees are removed, the value of the forest is degraded over time. If, in thinning, the least desirable trees are removed, the maturing forest will have increased values. By obtaining a yield of lower-quality, less useful wood (as firewood), we ensure there will be more useful wood in the future (as sawlogs). Put simply, "remove little trees to grow big trees".

Principle 6 **Produce No Waste**. This principle brings together traditional values of frugality and care for material goods the mainstream concern about pollution, and the more radical perspective that sees wastes as resources and opportunities. Bill Mollison defines a pollutant as "an output of any system component that is not being used productively by any other component of the system" In response to a question about plagues of snails in gardens dominated by perennials, Mollison was in the habit of replying that there was not an excess of snails but a deficiency of ducks. The earthworm is a suitable icon for this principle because it lives by consuming plant litter (wastes), which it converts into humus that improves the soil environment for itself, for soil micro-organisms and for the plants. Plants lose up to 10% of their primary chemical energy in carbohydrates through their roots, which appears at first to be wasteful. In fact the lost carbohydrates feed symbiotic and free-living micro-organisms in the soil, which supply the plant with critically needed mineral nutrients. Thus, what appears to be waste is actually exchange.

Nutrients in shed leaves are processed by soil organisms and converted to humus that can then feed the plant. This also has the effect of stimulating a very rich soil ecosystem and other plants. Deciduous trees tend to build humus-rich fertile soils more rapidly, at least partly because the quality of shed leaves is superior. Similarly, animal species vary in how efficiently they extract all the nutrients from their food. Carnivores and omnivores (such as dogs, fowls and people), which live on energy-rich and nutrient-rich food, are much less efficient than herbivores, which live on lower quality foods. Consequently, the manure from herbivores is a less concentrated source of mineral nutrients. Animal manure that takes at least a year to compost. In a Gi Gong breathing exercise. We are encouraged to imagine ourselves breathing in clear white light and breathing out toxic black smoke (Holmgrem '02: 111, 112, 124).

Principle 7 **Design from Patterns to Details**. Complex systems that work tend to evolve from simple ones that work, so finding the appropriate pattern for that design is more important than understanding all the details of the elements in the system. Whether designing a garden, a village, or an organization, we need a broad repertoire of familiar patterns of relative scale, timing and geometry that tend to recur in natural and sustainable human systems. The difference in scale between related systems is often an order of magnitude. For example, predators typically occupy 10 to 100 times (1 to 2 orders of magnitude) more territory than their prey and are proportionally less numerous. The permaculture concept began with the idea that natural ecosystems, especially forests, as models for agriculture. Forest ecosystems are dominated by large trees which grow tall through competition for light. They include understory species that can use the filtered light and stable microclimate created by the canopy. They have diverse habitats for both small and large animals. They are very effective at holding soil against landslips and other forms of instability. Many traditional agricultural societies recognized the value of forests for catchment protection and other long-term values. In some places, forest actually provided many of people's basic food needs. Corsica's "rural civilization" was supported by chestnut forests which provided, as well as the usual resources of fuel, timber and animal forage, the staple food of the people. This and other examples documented by Russell Smith in the 1930s and 1940s showed that food forests have been more productive and sustainable than grain agriculture in many parts of the world. The permaculture strategy of establishing "food forests" which are composed of a diversity of species that provide for people's needs, and yet have many of the characteristics of natural forests – is the best known application of this principle. These systems, especially in moist subtropical and tropical areas, have been productive and to a degree self-maintaining, but they have also been criticized as inappropriate from more traditional organic and biodynamic perspectives. In cool temperate climates most of the productive fruit and nut trees have evolved to flower and fruit and resist fungal diseases in more open environments than dense forests, whereas many subtropical species bear fruit under a shaded canopy and are well suited to forest systems. On a large scale, dense forests are only possible in high-rainfall areas or along streams and sources of abundant moisture. In low-rainfall regions, trees become more widely spaced, and a woodland structure is the norm. It would be unusual if weed-control strategies on a 10-hectare market garden applied to a 100 hectare cropping and grazing property. In fact, the farmer's crops and pastures may well be the market gardener's weeds. On large scales (1000 square meters and larger) it is rare for the whole garden to be managed intensively. Traditional orchards, animal runs and low input gardening can push out the scale of garden architecture another order of magnitude to 10,0000 square meters (1 hectare).

Principle 8 **Integrate Rather than Segregate**. In every aspect of nature, from the internal working of organisms to whole ecosystems, we find the connections between things are as important as the things themselves. By spacing vegetables widely, the conventional gardener

prevents competition for water sunlight and nutrients between plants. This allows all plants to grow to their maximum size, even though it require more land and more work in weed control. By eliminating weed growth in the garden, we reduce competition with our crops. These and similar efforts at reducing competition by segregation make our systems biologically simpler, increase valued yields and are easier to manage. But inadvertently they contribute to other problems, such as a breakdown in the free environmental services of maintaining soil fertility and controlling pests and diseases. A fundamental segregation tool is the garden fence, which excludes animals that would consume scratch out, or trample our food plants. Although permaculture gardening strategies focus on how to reintegrate animals, especially poultry, in gardens and orchards, fences and enclosures are generally needed to maintain segregation at appropriate times. Whether low-tech and socially accessible permaculture models or the high-tech corporate ways prevail, integration of previously segregated systems appears to be a fundamental principle driving post-industrial design. Integrated rural land uses, where every farm is to some degree a forest, were perhaps more central to the original permaculture vision than companion planting and guilds. Agroforestry, analog forestry, alley farming and other models for integrating trees with traditional farm land uses are examples of the ways that this vision is coming to fruition. Most pre-industrial societies had broadacre commons, and all community members had some, if varying, rights to use them.

The **Enclosure Act** in England began the global process of privatizing the commons, which is still proceeding in poorer countries. Reform of land tenure is one of the central sustainability and justice issues in Third World countries. However, first world governments and corporations have resisted any positive initiatives which might provide livelihoods and justice, let alone new models of collective management. In rich countries, our remaining commons in state forests, national parks, and so on are an unlikely source of innovative and creative models of community management. Their fate seems to be determined by bureaucratic and increasingly corporatized management structures and combative public policy compromises, this leads to carve-ups of territory and functions, and in many cases to privatization. Models for the management of public land are more likely to emerge from innovations in common land management within intentional communities. At present most large farms tend to be industrial monocultures, in energy descent, more diverse and integrated uses of farm land will develop, which will be much more labor-intensive. Large farms will again become communities of some sort. Within this structure it is possible to imagine highly integrated and ecologically sustainable land uses, and even benevolent owners who look after the interests of their workers .

Principle 9 **Use Small and Slow Solutions**. Systems should be designed to perform functions at the smallest scale that practical and energy-efficient for that function. Working to produce anything of value can be a painstaking experience when we are used to seeing things apparently appear from nowhere. Houses (made from prefabricated components) are knocked together in weeks or months, while owner-built houses using more labor-intensive methods typically take years. The idea of building something once to last tends to occur to builders and other practical people later in life, after they have reconstructed a few things they thought were good enough at the time. The small and slow approach is illustrated by using timber cut by small local sawmills and portable mills, which process logs at slower rates and thus get the best out of each unique tree. Home-produced food combined with infrequent bulk purchase of goods dramatically reduces food miles and speed. The use of site and local energies (passive solar and wood) illustrates small scale relative the centralized energies of gas and electricity. The permaculture ethic of recognizing and acknowledging limits provides a clear foundation for the slam and slow principle. In effect, “big is better” is a form of greed. The slogan “live simply so others may simply live” sums up this idea. The failure of agricultural research to tackle, or even recognize,

the myriad of small-scale and situation-specific opportunities for innovation illustrates the difficulties of the change from macro to micro scale. In agricultural research and development, the issues and opportunities that affect whole industries receive the majority of funding. Because most sustainable agriculture solutions are small-scale, they tend to fall through the net and are ignored. As Monsanto and other chemical giants have bought out all the established seed companies, new companies have sprouted to provide non-hybrid and non-GMO seeds to small farmers and gardeners. Desktop and Internet publishing have created explosive growth of the personal computer and the global Internet – despite the plans of the corporations for centralized super computer dominance of the information economy – is perhaps the most potent symbol of "small is powerful". Small size allows reallocation of available resources to flexibility, something widely recognized in relation to small business. The continued economic dominance of the global corporations can itself be attributed partly to their strategies to shed huge material and fixed assets (which reduce their flexibility) and move into controlling the capital and information flows that direct the production of goods and services.

10. Principle 10 **Use and Value Diversity**. The great diversity of forms, functions and interactions in nature and humanity are the source for evolved systemic complexity. The role and value of diversity in nature, culture and permaculture is itself complex, dynamic, and at times apparently contradictory. Diversity needs to be seen as a result of the balance and tension in nature between variety and possibility on the one hand, and productivity and power on the other. It is now widely recognized that monoculture is a major cause of vulnerability to pests and diseases, and therefore of the widespread use of toxic chemicals and energy to control these. Diversity in nature is a constant theme of biological science. With the gathering pace of biodiversity loss due to human impacts, it has become common to think of environmental issues as always involving a conflict between nature's drive for diversity and human demand for productivity. While permaculture incorporates strategies to conserve biodiversity, it also seeks a more fundamental redesign of all we do, so that biodiversity becomes a valued and functional. Tropical rainforests, which are some of the most stable ecosystems in the world, have high biodiversity. Much of the biodiversity is eliminated in temperate latitudes. Some apparently simple ecosystems appear to be very stable. For example, many forests go through successional stages, from pioneer stages involving a great number of initial species, to a very stable climax dominated by one species of slow-growing, long-lived trees. Examples are the yes (*Taxus*) forests in western Europe and myrtle beech (*Nothofagus*) forests in Tasmania. The structural diversity in the complex matrix of roots, litter and compost, trunk buttresses, faults and hollows, as well as a complex canopy structure, are features of yew and myrtle beech forests, which in turn support substantial insect and microbiological diversity. The potential lifespan of these trees is many hundreds of years in the case of myrtle beech and thousands in the case of yew. A diversity of crop varieties and species provides some degree of security or insurance against seasonal failures and pest or disease attack.

Principle 11 **Use Edges and Value the Marginal**. Within every terrestrial ecosystem the living soil – which may only be a few centimeters deep –is an edge or interface between non-living mineral earth and the atmosphere. For all terrestrial life, including humanity, this is the most important edge of all. Deep, well-drained and aerated soil is like a sponge, a great interface that supports productive and healthy plant life. Only a limited number of hardy species can thrive in shallow, compacted and poorly drained soil that has insufficient edge. Whatever the object is of our attention, we need to remember that it is at the edge of any thing, system or medium that the most interesting events take place; design that sees edge as an opportunity rather than problem is more likely to be successful and adaptable. In the process the negative connotations associated with the word "marginal" are discarded in order to see the value in elements that only

peripherally contribute to a function or system. On a global scale, coastal ecosystems are diverse and ecologically productive interfaces between terrestrial and oceanic domains. Within terrestrial landscapes, water bodies such as rivers, leaks and wetlands support freshwater aquatic and semi-aquatic ecosystems that are also diverse and productive. Vegetation immediately adjacent streams and waterways (riparian vegetation) is often more diverse in species and has greater density than vegetation further from the water. In contrast, where the sea and land meet at the abrupt edge of a sandy beach or cliff, the interface is minimal. Animal life living off the detritus delivered by those wild energies is predominant. In the tropics, the generally calm weather and moderate seas allow mangroves, the ultimate development of living interface between land and sea, to move out of the sheltered tidal estuaries and colonize part of the open seashore, especially rocky headlands. In bio-geography, an ecotone is edge between two bioregions where the distribution of species from both regions overlap, creating greater biodiversity than in either respective region. Ecotones generated by altitude may be quite narrow (less than 1 km); those generated by latitude or by distance from the sea (continental versus maritime) may be tens of kilometers in width. Changes in soil type, slope (break of slope) or aspect (ridges can create rapid transition in vegetation types over distances as small as a meter. Particularly distinct edges in wilderness landscapes are spiritually uplifting. Shelterbeds and hedgerows are traditional farm landscape examples of edge. Wide-spaced trees systems (agroforestry) completely integrates tree-growing with cropping or grazing to form a third land use. Most trees, even the hardiest, prefer to get established in a self-sheltering stand of dense young trees where the canopy suppresses grass, the worst enemy of young trees. The spacing of trees creates inner-row spaces that dictate the type of cropping or haymaking equipment that can be used. These problems naturally lead to the development of alley farming and shelterbelt forestry systems where the trees are concentrated in belts but there is still strong beneficial interaction between the trees and the cropland. Another example of use of edge in revegetation is the planting of shrubs along the edges of, rather than throughout, plantations.

Principle 12 **Creatively Use and Respond to Change**. This principle has two threads; designing to make use of change in a deliberate and co-operative way, and creatively responding or adapting to large-scale system change that is beyond our control or influence. The acceleration of ecological succession within cultivated systems is the most common expression of this principle in permaculture. When we intervene in systems over which we have some substantial design or management influence – gardens, farms, business, family – we can make use of change in ways that reflect our power and relationship to the system. This is top-down control. We appear to exercise arbitrary control in the garden when we plant, shift or remove plants, but other forces may also be planting, shifting (by reproduction) or removing species from our garden – for instance, wild birds, insects and diseases. When we act in co-operation with other agents, our effective power to change systems is amplified. The permaculture design process can be thought of as a top-down change management process. In the garden we are free to explore and experiment with top-down change processes because we can exercise great power (relative to other system elements) if and when we choose. The main consideration with building paths, or if your garden is big enough, roads, is to make them as much as possible from materials that are locally available. Pathways should be sufficiently hard wearing to stand the traffic which they are designed to take, and it is helpful if they are resistant to rain and snow. It also helps if they drain properly so that they don't become quagmires in wet weather. Ideally they should have a slightly sloping surface area so that they drain freely, and paths are themselves a very good system of drains if well designed. Any sort of crushed chippings or pebbles are useful for making pathways, provided that the surface is underlaid with some relatively impervious material to prevent deep rooting weeds form becoming a problem. Turf paths are relatively easy to maintain. Although they take time to mow, that is the only treatment

required to keep them in good shape. Planks and skids can be used to make temporary walkways. With two of them they can be moved to cover infinite distance. On slopes it is important to make a surface that is resistant to erosion, but which also affords safe footholds in wet conditions. Spare kerb stones are often useful. Some plants such as lawn chamomile actively thrive on pathways, and have the additional advantage of yielding very pleasant smells when walked on.

World Environmental Statistics

Area	Region	Surface area km2	Population Density per km2	% Urban	Agricultural Production Index	% Forested/ Agricultural	% of Agricultural Land: Arable/Permanent crops/ Pastures	Threatened species / Sites Protected %	CO_2 Emissions million tons / tons per capita	Energy Production, Petajoules / energy per capita (Gigajoules)
World		136,162,000	58.7	55.3	127	30.7 for		1,000,000 / 46.6	36,138.3 / 5	572,353/75
Africa		30,311,000	43.4	42.5	130	21.0				45,242/27
Americas		42,322,000	26.2			41.1				
Asia		31,915,000	146.5	49.9	135	19.1				263,383/62
Europe		23,049,000	33.6	74.5	110	45.9		n/a / 65.6		101,099/141
Oceania		8,564,000	4.9	68.2	109	20.4		n/a / 36.6		16,897/165
Afghanistan	Asia, South	652,864	55.7	25.5	125	2.1 / 58.1	20.5 / 0.37 / 79	42 / 6.1	9.8 / 0.3	60/4
Albania	Europe, South	28,748	107.1	60.3	143	28.2 / 42.9	52.4 / 6.8 / 40.7	130 / 67.0	5.7 / 2.0	87/32

Algeria	Africa, North	2,381,741	17.6	72.6	151	0.8 / 17.4	18 / 2.3 / 79.6	135 / 38.8	145.4 / 3.7	5,883/56
American Samoa	Oceania, Polynesia	199	278.4	87.2	116	87.7 / 21.8	61.2 / 38.8 / 0	92 / 61.5		
Andorra	Europe, South	468	163.7	88.1		34.2 / 44.5	13.4 / 0 / 86.6	13 / 26.1	0.5 / 6.4	1/124
Angola	Africa, Melanesia	1,246,700	24.7	65.5	192	46.4 / 47.5	8.3 / 0.5 / 91.2	146 / 28.4	34.8 / 1.4	4,137/24
Anguilla	Caribbean	91	167.2	100		61.1 / 0	0	52 / 0.2	0.1 / 9.8	0/151
Antigua & Barbuda	Caribbean	442	234.2	24.6	70	22.3 / 20.5	9.1 / 2.3 / 9.1	55 / 18.4	0.5 / 5.8	0 / 85
Argentina	America, South	2,780,400	16.3	91.9	131	9.9 / 53.9	13.9 / 0.4 / 39.6	256 / 33.2	204 / 4.7	3,100 / 83
Armenia	Asia, West	29,743	103.1	63.1	127	11.7 / 59.7	15.8 / 1.9 / 42	114 / 30.5	5.5 / 1.8	46 / 43
Aruba	Caribbean	180	587.1	43.4		2.3 / 11.1	11.1/0/0	32 / 47.8	0.9 / 8.4	1 / 123
Australia	Oceania	7,692,060	3.2	86	104	15.2 / 52.9	11.6 / 0.09 / 88.4	948 / 54.3	361 / 15.3	15,938 / 220
Austria	Europe, West	83,871	106.2	58.3	100	46.9 / 38.4	16.5 / 0.8 / 21.1	118 / 66.3	58.7 / 6.9	500/161
Azerbaijan	Asia, West	86,600	120.1	55.7	141	13.8 / 57.6	22.8 / 2.7 / 32.1	97 / 39.4	37.5 / 3.9	2,472 / 62

Bahamas	Caribbean	13,940	39.9	83	131	51.4 / 1.4	0.8 / 0.4 / 0.2	86 / 24.7	2.4 / 6.3	0 / 87
Bahrain	Asia, West	771	2,061.8	89.3	198	0.8 / 11.3	2.1 / 3.9 / 5.3	36 / 27.5	31.3 / 23.0	957 / 420
Bangladesh	Asia, South	147,570	1,278.1	36.6	144	11.0 / 70.1	59 / 6.5 / 4.6	151 / 48.0	73.2 / 0.5	1,509 / 11
Barbados	Caribbean	432	666	31.1	85	14.7 / 32.6	25.6 / 2.3 / 4.7	56 / 2.1	1.3 / 4.5	3 / 58
Belarus	Europe, Eeast	207,600	46.6	78.6	120	42.5 / 43.7	27.2 / 0.6 / 15.9	25 / 49.1	63.5 / 6.7	146 / 11
Belgium	Europe, West	30,528	379.7	98	101	22.6 / 44.1	27.2 / 0.8 / 16.1	37 / 80.8	93.4 / 8.3	444 / 197
Belize	America, Central	22,966	16.8	45.7	97	59.9 / 6.9	3.3 / 1.4 / 2.2	117 / 46.0	0.5 / 1.4	9 / 41
Benin	Africa, West	114,763	101.9	47.3	153	38.2 / 31.3	22.9 / 3.5 / 4.9	88 / 77.4	6.3 / 0.5	114 / 17
Bermuda	America, North	53	1,221.4	100	112	20 / 14.8	14.8 / 0 / 0		0.6 / 9.2	1 / 133
Bhutan	Asia, South	38,394	21.4	40.9	102	72.3 / 13.6	2.6 / 0.3 / 10.7	72 / 16.2	1.0 / 1.3	77 / 82
Bolivia	America, South	1,098,581	10.4	69.4	147	50.6 / 34.3	3.6 / 0.2 / 30.5	231 / 56.2	20.4 / 1.9	871 / 31
Bonaire, Sint Eustat	Caribbean		78.4	74.9				56 / 39.3	0.3 / 13.3	0 / 212

ius and Saba										
Bosnia & Herzegovina	Europe, South	51,209	68.7	48.2	118	42.7 / 42.2	19.7 / 2 / 20.5	91 / 12	22.2 / 5.8	257 / 87
Botswana	Africa, South	582,000	4.1	69.4	120	19.1 / 45.8	0.6 / 0 / 45.2	28 / 47.1	7.0 / 3.2	56 / 35
Brazil	America, South	8,515,767	25.2	86.6	136	59 / 0	0	990 / 47.6	530 / 2.6	11,456 / 59
British Virgin Islands	Caribbean	151	211.5	47.7	103	24.1 / 46.7	6.7 / 6.7 / 33.3	67 / 9.4	0.2 / 6.0	0 / 84
Brunei	Asia, South-east	5,765	82.4	77.6	169	72.1 / 2.5	0.8 / 1.1 / 0.5	193 / 62.9	9.1 / 21.6	673 / 269
Bulgaria	Europe, East	111,002	64.8	75	114	35.2 / 46.9	29.9 / 1.5 / 15.5	104 / 95.6	42.4 / 5.9	505 / 108
Burkina Faso	Africa, West	272,967	72.2	29.4	125	19.6 / 43	20.8 / 0.3 / 21.9	31 / 71.8	2.8 / 0.1	126 / 9
Burma (Myanmar)	Asia, South-east	676,577	82.4	30.6	137	44.5 / 19.2	16.5 / 2.2 / 0.5	321 / 22.9	21.6 / 0./4	1,141 / 16
Burundi	Africa, East	27,830	436.8	13	108	10.7 / 73.3	38.9 / 15.6 / 18.8	61 / 51.2	0.4 / 0	56 / 5
Cabo Verde	Africa, West	4,033	137.3	65.7	97	22.3 / 18.6	11.7 / 0.7 / 6.2	65 / 15.1	0.5 / 1.0	2 / 17

Cambodia	Asia, South-east	181,035	92	23.4	186	53.6 / 32.1	22.7 / 0.9 / 8.5	255 / 39.5	6.7 / 0.4	184 / 19
Cameroon	Africa, Middle	475,650	52.2	56.4	175	39.8 / 20.6	13.1 / 3.3 / 4.2	775 / 36.3	7.0 / 0.3	446 / 14
Canada	America, North	9,984,670	4.1	81.4	113	38.2 / 6.8	4.7 / 0.5 / 1.6	122 / 25.7	537 / 15.1	19,321 / 310
Cayman Islands	Caribbean	264	259.8	100	103	52.9 / 11.2	0.8 / 2.1 / 8.3	74 / 32.5	0.5 / 9.2	132 per capita
Central-African Republic	Africa, Middle	622,984	7.6	41.4	122	35.6 / 8.1	2.9 / 0.1 / 5.1	60 / 74.4	0.3 / 0.1	19 / 5
Chad	Africa, Middle	1,284,000	12.2	23.1	150	3.9 / 39.6	3.9 / 0 / 35.7	43 / 70.6	0.7 / 0	225 / 6
Channel Islands (UK)	Europe, North	180	874.1	30.9		4.2 /				
Chile	America, South	756,102	24.5	87.6	114	23.9 / 21.1	1.7 / 0.6 / 18.8	197 / 35.7	83 / 4.7	540 / 84
China	Asia, East	9,600,000	150.7	59.2	139	22.2 / 54.7	11.3 / 1.6 / 41.8	1,080 / 47.6	10,292 / 7.5	100,864 / 87

China, Hong Kong	Asia, East	1,106	7,75.1	100	59	0 / 5	3. / 0.9 / 0.9	64 / 56.7	46.2 / 6.4	80 G per capita
China, Macau	Asia, East	30	21,151.1	100	90			11 / 0	1.3 / 2.2	2 / 68
Colombia	America, South	1,141,748	44.6	80.8	115	52.7 / 37.5	1.4 / 1.6 / 34.5	835 / 38	84.1 / 1.8	5,593 / 31
Comoros	Africa, East	2,235	447.3	29	109	19.9 / 84.4	46.7 / 29.6 / 8.1	114 / 10.4	0.2 / 0.2	3 / 7
Congo, Republic of	Africa, Middle	342,000	15.8	66.9	138	65.4 / 31.1	1.6 / 0.2 / 29.3	134 / 72.1	3.1 / 0.7	623 / 24
Congo, Democratic Republic of the	Africa, Middle	2,344,858	37.1	44.5	109	67.3 / 11.4	3.1 / 0.3 / 8	349 / 40.1	4.7 / 0.1	1,218 / 16
Cook Islands	Oceania, Polynesia	236	72.5	75.1	91	62.9 / 8.4	4.2 / 4.2 / 0	75 / 22.4	0.1 / 3.4	0 / 41
Costa Rica	America, Central	51,100	97.0	79.3	129	54.0 / 37.1	4.9 / 6.7 / 25.5	340 / 45.3	7.8 / 1.6	110 / 43
Cote d'Ivoire	Africa, West	322,463	78.3	50.8	127	32.7 / 64.8	9.1 / 14.2 / 41.5	249 / 79.1	11 / 0.5	526 / 24
Croatia	Europe,	56,594	74.4	56.9	121	34.3 / 23.7	16 / 1.5 /	176 / 72	16.8 / 4.0	184 / 83

	South						6.2			
Cuba	Caribbean	109,884	107.9	77	103	30.8 / 60.3	33.8 / 3.6 / 22.9	339 / 73.4	34.8 / 3.0	212 / 42
Curacao	Caribbean	444	363.9	89.1		10 ag	10 / 0 / 0	51 / 40.4	5.9 / 37.8	0 / 592
Cyprus	Asia, West	9,251	128.7	66.8	79	18.7 / 13.4	9.8 / 3.2 / 0.4	72 / 57.8	6.1 / 5.2	5 / 73
Czechia	Europe, East	78,868	137.6	73.8	100	34.5 / 54.8	41 / 1 / 12.8	53 / 92.3	96.5 / 9.2	1,213 / 167
Denmark	Europe, North	42,921	135.6	87.9	101	14.6 / 63.4	58.9 / 0.1 / 4.4	47 / 89.7	33.5 / 5.9	662 / 118
Djibouti	Africa, East	23,200	41.9	77.8	133	0.2 / 73.4	0.1 / 0 / 73.3	98 / 0.9	0.7 / 0.8	4 / 11
Dominica	Caribbean	750	99.1	70.5	113	57.8 / 34.7	8 / 24 / 2.7	66 / 44.3	0.1 / 1.9	0 / 37
Dominican Republic	Caribbean	48,671	225.2	81.1	145	41.0 / 51.5	16.6 / 10.1 / 24.8	184 / 76.2	21.5 / 2.1	25 / 31
Ecuador	America, South	257,217	67.9	63.8	115	50.5 / 29.7	4.7 / 5.6 / 19.4	2,358 / 29	43.9 / 2.8	1,297 / 40
Egypt	Africa, North	1,002,000	99.8	42.7	124	0.1 / 3.6	2.8 / 0.8 / 0	156 / 39.6	201.9 / 2.2	3,051 / 38
El Salvador	America, Central	21,041	309.4	72	111	12.8 / 74.7	33.1 / 10.9 / 30.7	86 / 26.6	6.3 / 1.0	87 / 29
Equatorial Guine	Africa, Middl	28,052	46.8	72.1	115	55.9 / 10.1	4.3 / 2.1 / 3.7	177 / 100	5.3 / 6.5	879 / 84

a	e									
Eritrea	Africa, East	117,600	51.4	40.1	104	15.0 / 75.1	6.8 / 0 / 68.3	122 / 13.3	0.7 / 0.1	27 / 7
Estonia	Europe, North	45,227	30.8	68.9	128	52.7 / 22.2	14.9 / 0.1 / 7.2	23 / 94.9	19.5 / 14.8	233 / 176
Eswatini	Africa, South	17,363	80.9	23.8	113	34.1 / 68.3	9.8 / 0.8 / 57.7	34 / 30.3	1.2 / 1.0	38 / 38
Ethiopia	Africa, East	1,104,300	107.5	20.8	164	12.5 / 36.3	15.2 / 1.1 / 20	148 / 19.8	11.6 / 0.1	1,334 / 15
Falkland Islands (Malvinas)	America, South	12,173	0.2	77.7	96	0 / 92.4	0 / 0 / 92.4	23 / 10.9	0.1 / 18.9	0 / 257
Faroe Islands	Europe, North	1,393	35.5	42.1	101	0.1 / 2.1	2.1 / 0 / 0	21 / 6.7	06 / 12.4	1 / 188
Fiji	Oceania, Melanesia	18,272	49.9	56.2	84	55.7 / 23.3	9 / 4.7 / 9.6	291 / 4.9	1.2 / 1.3	8 / 43
Finland	Europe, North	338,440	18.2	85.4	97	73.1 / 7.5	7.4 / 0 / 0.1	36 / 72.6	47.3 / 8.6	734 / 245
France	Europe, West	551,500	119.1	80.4	96	31.0 / 52.7	33.4 / 1.8 / 17.5	278 / 81.2	303.3 / 4.7	5,720 / 155
French Guiana	America, South	83,534	3.5	85.3	127	98.9 for		73 / 67.4	0.7 / 2.8	3 / 46
French Polyn	Oceania, Polyn	4,000	78.1	61.8	102	42.3 / 12.5	0.7 / 6.3 /	175 / 5.4	0.8 / 2.9	1 / 41

esia	esia						5.5			
Gabon	Africa, Middle	267,668	8.0	89.4	123	89.3 / 19	1.3 / 0.6 / 17.2	270 / 61.7	5.2 / 3.1	556 / 62
Gambia	Africa, West	11,295	213.8	61.3	106	48.2 / 56.1	41 / 0.5 / 14.6	67 / 34.6	0.5 / 0.3	7 / 7
Georgia	Asia, West	69,700	56.2	58.6	74	40.6 / 35.5	5.8 / 1.8 / 27.9	120 / 28.4	9.0 / 2.2	58 / 49
Germany	Europe, West	357,376	236.1	77.3	107	32.7 / 48	34.1 / 0.6 / 13.3	116 / 78.6	719.9 / 8.9	5,007 / 160
Ghana	Africa, West	238,537	129.5	56.1	153	41 / 69.1	20.7 / 11.9 / 36.5	238 / 85	14.5 / 0.6	372 / 12
Gibraltar	Europe, South	6	3,473.3	100		0 / 0	0	31 / 35	0.5 / 16.5	272 G per capita
Greece	Europe, South	131,957	86.4	79.1	93	31.5 / 63.4	19.7 / 8.9 / 34.8	374 / 73.2	67.3 / 6.1	355 / 90
Greenland (Denmark)	America, North	2,166,086	0.1	86.8	98	0 / 0.6	0 / 0 / 0.6	23 / 30.3	0.5 / 9/0	2 / 158
Grenada	Caribbean	345	318.6	36.3	128	50 / 32.3	8.8 / 20.6 / 2.9	54 / 42.7	0.2 / 2.3	0 / 38
Guadeloupe	Caribbean	1,785	265.8	98.5	92	43 for		73 / 80.8	2.6 / 5.5	5 / 71
Guam	Oceania, Micronesia	549	306.9	94.8	78	46.3 / 33.4	1.9 / 16.7 / 14.8	99 / 40.2		
Guate	Ameri	108,8	160.9	51.1	158	33.0 /	14.2 /	290 /	18.3 /	316 /

mala	ca, Central	89				41.2	8.8 / 18.2	30.8	1.1	29
Guinea	Africa, West	245,857	53.1	36.1	135	25.9 / 58.1	11.8 / 2.8 / 43.5	185 / 76.4	2.4 / 0.2	116 / 12
Guinea-Bissau	Africa, West	36,125	67.8	43.4	143	70.1 / 44.8	8.2 / 6.9 / 29.7	77 / 52.6	0.3 / 0.1	25 /16
Guyana	America, South	214,969	4.0	26.6	130	84 / 8.4	2.1 / 0.1 / 6.2	94 / n/a	2.0 / 2.6	7 / 45
Haiti	Caribbean	27,750	403.2	55.3	156	3.5 / 66.4	38.5 / 10.2 / 17.7	205 / 10.5	2.9 / 0.3	139 / 17
Holy See	Europe, South	0	1,820.5	100				1 / n/a		
Honduras	America, Central	112,492	84.2	57.1	124	41 / 28.8	9.1 / 4 / 15.7	301 / 65	9.5 / 1.2	113 / 29
Hungary	Europe, East	93,024	107.0	71.4	88	22.9 / 58.9	48.5 / 2 / 8.4	66 / 82.9	42.1 / 4.3	471 / 107
Iceland	Europe, North	103,000	3.4	93.8	126	0.5 / 18.7	1.2 / 0 / 17.5	27 / 18	2.0 / 6.1	285 / 950
India	Asia, South	3,287,263	455.4	34	145	23.8 / 60.5	52.8 / 4.2 / 3.5	1,052 / 26.1	2,238 / 1.7	23,538 / 28
Indonesia	Asia, South-east	1,910,931	147.3	55.3	143	50.2 / 31.2	13 / 12.1 / 6.1	1,281 / 23.5	464.2 / 1.8	17,926 / 37
Iran	Asia, South	1,628,750	50.4	74.9	110	6.6 / 30.1	10.8 / 1.2 /	134 / 48.6	649.5 / 8.3	13,637 /

							18.1			126
Iraq	Asia, West	435,052	90.6	70.5	75	1.9 / 18.1	8.4 / 0.5 / 9.2	72 / 6.1	168.4 / 4.8	7,565 / 55
Ireland	Europe, North	69,797	69.7	63.2	110	10.9 / 66.1	15.4 / 0 / 50.7	50 / 89.9	34.1 / 7.3	80 / 118
Isle of Man	Europe, North	572	148.8	52.6		6.1 / 74.7	43.8 / 0 / 30.9	3 / n/a		0 / 3
Israel	Asia, West	22,072	390.6	92.4	109	7.6 / 23.8	13.7 / 3.8 / 6.3	174 / 15.7	64.6 / 8.1	308 / 118
Italy	Europe, South	302,073	201.6	70.4	92	31.6 / 47.1	22.8 / 8.6 / 15.7	359 / 78	320.4 / 5.4	1,509 / 107
Jamaica	Caribbean	10,990	267.7	55.7	105	31 / 41.4	11.1 / 9.2 / 21.1	311 / 22.3	7.4 / 2.7	8 / 39
Japan	Asia, East	377,930	348.9	91.6	92	68.5 / 12.5	11.7 / 0.8 / 0	404 / 68.5	1,214 / 9.6	1,269 / 142
Jordan	Asia, West	89,318	111.6	91	145	1.1 / 11.4	2 / 1 / 8.4	113 / n/a	26.5 / 3.6	8 / 48
Kazakhstan	Asia, Central	2,724,902	6.8	57.4	139	1.2 / 77.4	8.9 / 0 / 68.5	82 / 16.3	248 / 14.3	7,338 / 185
Kenya	Africa, East	591,958	89.5	27	126	7.8 / 48.1	9.8 / 0.9 / 37.4	480 / 37.5	14.3 / 0.3	761 / 21
Kiribati	Oceania, Micronesia	726	146.2	54.1	61	15 / 42	2.5 / 39.5 / 0	104 / 52.5	0.1 / 0.6	0 / 8
Korea, Democratic	Asia, East	120,538	212.7	61.9	102	41.8 / 21.8	19.5 / 1.9 / 0.4	78 / 10.2	40.5 / 1.61	788 / 13

People's Republic										
Korea, Republic of	Asia, East	100,284	526.2	81.5	103	63.4 / 18.1	15.3 / 2.2 / 0.6	111 / 36.6	587. / 11.7	2,116 / 226
Kosovo	Europe, South	10,887				41.7 / 52.8	27.4 / 1.9 / 23.5			
Kuwait	Asia, West	17,818	235.5	100	191	0.4 / 8.5	0.6 / 0.3 / 7.6	49 / 59	95.4 / 25.4	7,003 / 375
Kyrgystan	Asia, Central	199,949	32	36.4	117	3.3 / 55.4	6.7 / 0.4 / 48.3	44 / 22.6	9.6 / 1.7	75 / 28
Laos	Asia, South-east	236,800	30.2	35	219	81.3 / 10.6	6.2 / 0.7 / 3.7	209 / 45.5	2.0 / 0.3	185 / 28
Latvia	Europe, North	64,573	31.0	68.1	139	54 / 29.2	19.6 / 0.1 / 10.5	30 / 97.3	7.0 / 3.5	98 / 91
Lebanon	Asia, West	10,452	595.7	88.6	89	13.4 / 63.3	11.9 / 12.3 / 39.1	87 / 13.1	241 / 4.3	8 / 53
Lesotho	Africa, South	30,355	74.5	28.2	96	1.6 / 76.1	10.1 / 0.1 / 65.9	18 / 15.3	2.5 / 1.2	31 / 27
Liberia	Africa, West	111,369	50.4	51.2	113	43.4 / 28.1	5.2 / 2.1 / 20.8	172 / 16.4	0.9 / 0.2	76 / 20
Libya	Africa, North	1,676,198	3.7	80.1	117	0.1 / 8.8	1 / 0.2 / 7.6	63 / 4.6	57 / 9.1	1,496 / 163

Liechtenstein	Europe, West	160	238.5	14.3	97.4	43.1 / 37.6	18.8 / 0 / 18.8	6 / 75.8	0 / 1.1	1 / 76
Lithuania	Europe, North	65,286	45.9	67.7	131	34.8 / 44.8	34.9 / 0.5 / 9.4	26 / 91.6	12.8 / 4.4	76 / 102
Luxembourg	Europe, West	2,586	227.9	91	103	33.5 / 50.7	24 / 0.6 / 26.1	11 / 78.7	9.7 / 17.3	6 / 278
Macedonia	Europe, South	25,713	82.7	58	123	39.6 / 44.3	16.4 / 1.4 / 26.5	110 / 21.1	7.5 / 3.6	58 / 57
Madagascar	Africa, East	587,295	45.1	37.2	118	21.4 / 71.1	6 / 1 / 64.1	1,324 / 24.3	3.1 / 0.1	132 / 7
Malawi	Africa, East	118,484	203.3	16.9	146	33.4 / 59.2	38.2 / 1.4 / 19.6	176 / 81.6	1.3 / 0.1	68 / 5
Malaysia	Asia, South-east	330,323	97.5	76	123	67.6 / 23.2	2.9 / 19.4 / 0.9	1,272 / 39.5	242.8 / 8.1	3,748 / 113
Maldives	Asia, South	300	1,480.9	39.8	67	3.3 / 23.3	10 / 10 / 3.3	75 / 0	1.3 / 3.7	0 / 52
Mali	Africa, West	1,240,192	15.7	42.4	171	3.9 / 34.1	5.6 / 0.1 / 28.4	42 / 33.8	1.4 / 0.1	55 / 5
Malta	Europe, South	315	1,350.3	94.6	90	1.1 / 32.3	28.4 / 3.9 / 0	39 / 99.4	2.3 / 5.6	1 / 65
Marshall Islands	Oceania, Micronesia	181	295.4	77	104	49.3 / 50.7	7.8 / 31.2 / 11.7	101 / 25.4	0.1 / 1.9	0 / 42
Martinique (France)	Caribbean	1,128	363.3	89	79	45.8%		48 / 99.1	2.3 / 5.8	1 / 79

Mauritania	Africa, West	1,030,700	4.4	53.7	120	0.2 / 38.5	0.4 / 0 / 38.1	85 / 14.6	2.7 / 0.7	30 / 13
Mauritius	Africa, East	1,969	624.8	40.8	92	19 / 43.8	38.4 / 2 / 3.4	257 / 10.4	4.2 / 3.3	12 / 52
Mayotte	Africa, East		692.5	46.1		15.6 for		88 / 54.1		0 / 21
Mexico	America, Central	1,964,375	67.3	80.2	126	34 / 54.9	11.8 / 1.4 / 41.7	1,162 / 33.4	480 / 3.8	35,079 / 33.4
Micronesia, Federated States of	Oceania, Micronesia	702	151.8	22.7	101	91.8 / 25.5	2.3 / 19.7 / 3.5	157 / 1.3	0.2 / 1.4	0 / 22
Moldova	Europe, East	32,891	104.5	42.6	111	11.9 / 74.9	55.1 / 9.1 / 10.7	35 / 23.6		15 / 21
Monaco	Europe, West	2	26,105.4	100		0 / 1	0 / 1 / 0			
Mongolia	Asia, East	1,564	2.0	68.4	161	8.1 / 73	0.4 / 0 / 72.6	41 / 43.7	20.8 / 7.2	654 / 92
Montenegro	Europe, South	13,812	46.8	66.8	66	61.5 / 38.2	12.9 / 1.2 / 24.1	96 / 11.9	2.2 / 3.5	30 / 68
Montserrat	Caribbean	103	52	9.1	104	25 / 30	20 / 0 / 10	55 / 30.6	0 / 9.6	149 G per capita
Morocco	Africa, North	446,550	81.1	62.5	122	12.6 / 67.5	17.5 / 2.9 / 47.1	207 / 43	60 / 1.7	59 / 23
Mozambique	Africa, East	799,380	38.8	36	149	48.2 / 56.3	6.4 / 0.3 / 49.6	309 / 31.3	8.4 / 0.3	810 / 19
Nami	Africa	824,1	3.1	50	93	8.4 /	1 / 0 /	115 /	3.8 /	20 /

bia	, South	16				47.2	46.2	85.4	1.6	31
Nauru	Oceania, Micronesia	21	565.6	100	114	0 / 20	0 / 20 / 0	82 / 0	0 / 4.8	0 / 65
Nepal	Asia, South	147,181	206.7	19.7	140	25.4 / 28.8	15.1 / 1.2 / 12.5	104 / 54.6	8 / 0.3	430 / 18
Netherlands	Europe, West	41,542	506.7	91.5	118	11.2 / 55.1	29.8 / 1.1 / 24.2	40 / 91.4	167.3 / 9.9	1,990 / 179
New Caledonia	Oceania, Melanesia	18,575	101.4	70.7	105	45.9 / 10.4	0.4 / 0.2 / 9.8	526 / 66.4	4.3 / 16.5	2 / 240
New Zealand	Oceania	268,107	18.0	86.5	117	38.6 / 43.2	1.8 / 0.3 / 41.1	199 / 44.3	34.7 / 7.7	775 / 209
Nicaragua	America, Central	130,373	52.2	58.5	132	25.9 / 42.2	12.5 / 2.5 / 27.2	144 / 73.7	4.9 / 0.8	92 / 27
Niger	Africa, West	1,267,000	17.6	16.4	173	0.9 / 35.1	12.3 / 0.1 / 22.7	34 / 42.7	2.1 / 0.1	99 / 5
Nigeria	Africa, West	923,768	215.1	50.3	119	7.7 / 78	37.3 / 7.4 / 33.3	361 / 79.6	96.3 / 0.6	10,603 / 32
Niue	Oceania, Polynesia	260	6.2		101	69.6 / 19.1	3.8 / 11.5 / 3.8	52 / 95.3	0 / 5.7	0 / 64
Northern Mariana Island	Oceania, Micronesia	457	120	91.6		64.1 / 6.6	2.2 / 2.2 / 2.2	102 / 40.6		

s										
Norway	Europe, North	386,194	14.7	82.2	107	33.2 / 2.7	2.2 / 0 / 0.5	64 / 55.9	47.6 / 9.2	8,615 / 234
Oman	Asia, West	309,500	15.6	84.5	144	0 / 4.7	0.1 / 0.1 / 4.5	99 / 11.5	61.2 / 14.4	3,481 / 285
Pakistan	Asia, South	796,095	260.5	36.7	128	1.9 / 35.2	27.6 / 1.1 / 6.5	140 / 36.6	166.3 / 0.9	2,451` / 18
Palau	Oceania, Micronesia	459	47.7	79.9		97.6 / 10.8	2.2 / 4.3 / 4.3	182 / 36.6	0.3 / 12.4	147 G per capita
Palestine	Asia, West	6,020	839.3	76.2	87	1.5 / 43.3	7.4 / 11 / 24.9	31 / 2.5	2.8 / 0.6	9 / 16
Panama	America, Central	75,320	56	67.7	112	62.1 / 30.5	7.3 / 2.5 / 20.7	383 / 38.8	8.8 / 2.3	36 / 44
Papua New Guinea	Oceania, Melanesia	462,840	18.6	13.2	122	74.1 / 2.6	0.7 / 1.5 / 0.4	493 / 7.3	6.3 / 0.8	168 / 21
Paraguay	America, South	406,752	17.4	61.6	164	38.6 / 53.8	10.8 / 0.2 / 42.8	59 / 23.3	5.7 / 0.5	329 / 39
Peru	America, South	1,285,216	25.4	77.9	150	57.8 / 18.8	3.1 / 1.1 / 14.6	685 / n/a	52 / 2.0	961 / 30
Philippines	Asia, South-east	300,000	357.2	46.9	113	27 / 41	18.2 / 17.8 / 5	783 / 41.7	105.7 / 1.1	999 / 20
Poland	Europe, East	312,679	124.4	60.1	113	30.8 / 48.2	36.2 / 1.3 / 10.7	58 / 88.1	285.7 / 7.4	2,834 / 104

Portugal	Europe, South	92,226	112.4	65.2	108	34.7 / 39.7	11.9 / 7.8 / 20	281 / 73.9	45.1 / 4.3	222 / 88
Puerto Rico (USA)	Caribbean	8,868	412.5	93.6	102	55.9 / 22	6.6 / 5.6 / 9.8	126 / 34		1 / 16
Qatar	Asia, West	11,607	232.1	99.1	166	0 / 5.6	1.1 / 0.2 / 4.3	39 / 50	107.9 / 41.1	9,225 / 848
Reunion	Africa, East	2,513	353.3	99.6	102	35.1 for		130 / 45.8	4.2 / 4.9	9 / 69
Romania	Europe, East	238,391	85.1	54	95	29.8 / 60.7	39.1 / 1.9 / 19.7	104 / 77.3	70 / 3.6	1,116 / 69
Russia	Europe, East	17,098,246	8.8	74.4	139	49.8 / 13.1	7.3 / 0.1 / 5.7	235 / 26.9	1,705 / 12	56,024 / 205
Rwanda	Africa, East	26,338	506.7	17.2	140	19.5 / 74.5	47 / 10.1 / 17.4	62 / 45.7	0.8 / 0.1	85 / 8
Saint Helena	Africa, West	308	10.4	39.8		5.1 / 30.8	10.3 / 0 / 20.5	100 / 54.8	0 / 3.1	0 / 37
Saint Kitts & Nevis	Caribbean	261	214.8	30.8	39	42.3 / 23.1	19.3 / 0.4 / 3.5	52 / 29.2	0.2 / 4.2	0 / 60
Saint Lucia	Caribbean	539	294.5	18.7	65	33.3 / 17.4	4.9 / 11.5 / 1	62 / 46	0.4 / 2.2	0 / 33
Saint Pierre and Miquelon	America, North	242	27.6	90.2	115	12.2 / 8.7	8.7 / 0 / 0	12 / n/a	0.1 / 12.2	0 / 175
Saint Vince	Carib	389	282.6	52.2	110	69.2 /	12.8 / 7.7 /	58 /	0.2 /	0 / 31

nt and the Grenadines	bean					25.6	5.1	42.7	1.9	
Samoa	Oceania, Polynesia	2,842	69.9	18.2	118	60.4 / 12.4	2.8 / 7.8 / 1.8	93 / 36.5	0.2 / 1.0	1 / 29
San Marino	Europe, South	61	559.3	97.2		0 / 16.7	16.7 / 0 / 0	1 / n/a		
SaoTome e Principe	Africa, Middle	964	217.5	72.8	109	55.8 / 50.7	9.1 / 40.6 / 1	94 / 58	0.1 / 0.6	1 / 14
Saudi Arabia	Asia, West	2,206,714	15.6	83.8	106	0.5 / 80.7	1.5 / 0.1 / 79.1	131 / 21	601 / 19.5	28,571 / 354
Senegal	Africa, West	196,712	84.6	47.2	145	43 / 46.8	17.4 / 0.3 / 29.1	123 / 41.2	8.9 / 0.6	80 / 11
Serbia	Europe, South	88,499	100.2	56.1	105	31.1 / 57.9	37.7 / 3.4 / 16.8	71 / 30.2	38 / 4.3	449 / 69
Seychelles	Africa, East	457	207	56.7	99	88.4 / 6.5	2.2 / 4.3 / 0	439 / 19.7	0.5 / 5.2	0 / 65
Sierra Leone	Africa, West	72,300	107	42.1	195	42.2 / 56.2	23.4 / 2.3 / 30.5	177 / 80.3	1.3 / 02	54 / 10
Singapore	Asia, South-east	719	8,274	100	115	23.1 / 1	0.9 / 0.1 / 0	293 / 21.1	56.4 / 10.2	28 / 220
Sint Maarten (Dutch)	Caribbean	34	1,192.7	100				51 / 6.4	0.7 / 19.5	305 G per capita

Slovakia	Europe, East	49,035	113.3	53.7	98	40.3 / 40.1	28.9 / 0.4 / 10.8	54 / 83.6	30.7 / 5.6	265 / 125
Slovenia	Europe, South	20,273	103.3	54.5	88	62 / 22.8	8.4 / 1.3 / 13.1	143 / 88.7	12.8 / 6.2	142 / 133
Solomon Islands	Oceania, Melanesia	28,896	22.3	23.7	113	78.1 / 3.9	0.7 / 2.9 / 0.3	245 / 9.5	0.2 / 0.4	3 / 10
Somalia	Africa, East	637,657	24.2	45	108	10.1 / 70.3	1.8 / 0 / 68.5	175 / 0	0.6 / 0.1	129 / 13
South Africa	Africa, South	1,221,037	47.3	66.4	117	7.6 / 79.4	9.9 / 0.3 / 69.2	581 / 37.7	489.8 / 9.1	7,049 / 117
Spain	Europe, South	505,944	93	80.3	104	36.8 / 54.1	24.9 / 9.1 / 20.1	617 / 56.3	234 / 5.1	1,368 / 106
Sri Lanka	Asia, South	65,610	334.1	18.5	128	33 / 43.5	20.7 / 15.8 / 7	587 / 49.8	18.4 / 0.9	181 / 21
Sudan	Africa, North	1,861,484	23.5	34.6		100 ag	100 pasture	133 / 25	15.4 / 0.4	658 / 16
Sudan, South	Africa, East	658,841	21.1	19.6		100 ag	15.7 / 0.2 / 84.2	49 / 33.6	1.5 / 0.1	321 / 2
Suriname	America, South	163,820	3.6	66.1	146	98.3 / 0.5	0.4 / 0 / 0.1	83 / 51.2	2.0 / 3.7	40 / 54
Swaziland	Africa, South	17,363	79.5	21.3	114	33.8 for		34 / 57.4	1.2 / 1.0	
Sweden	Europe, North	438,574	24.4	87.4	100	68.9 / 7.5	6.4 / 0 / 1.1	54 / 58.8	43 / 4.5	1,408 / 193
Switz	Europ	41,29	216.2	73.8	101	31.7 /	10.2 /	74 /	35 /	509 /

erland	e, West	1				38.7	0.6 / 27.9	35.2	4.3	123
Syria	Asia, West	185,180	99.6	54.2	79	2.7 / 75.8	25.4 / 5.8 / 44.6	132 / 1.1	30.7 / 1.7	196 / 23
Taiwan	Asia, East	32,260	729.9	78.2		22.7 ag	16.9 / 5.8			
Tajikstan	Asia, Central	142,600	65.1	27.1	159	3.0 / 34.7	6.1 / 0.9 / 27.7	45 / 21	5.2 / 0.6	82 / 13
Tanzania	Africa, East	947,303	66.7	33.8	165	52 / 43.7	14.3 / 2.3 / 27.1	1,082 / 57	11.6 / 0.2	958 / 20
Thailand	Asia, South-east	513,120	135.4	49.9	118	32.1 / 41.2	30.8 / 8.8 / 1.6	611 / 71.7	316.2 / 4.7	2,929 / 80
Timor-Leste	Asia, South-east	14,919	89	30.6	111	46.1 / 25.1	10.1 / 4.9 / 10.1	24 / 38.7	0.5 / 0.4	147 / 7
Togo	Africa, West	56,785	146.9	41.7	142	3.5 / 67.4	45.2 / 3.8 / 18.4	80 / 97	2.6 / 0.4	113 / 20
Tokelau	Oceania, Polynesia	12	131.9	0	115	0 / 60	0 / 60 / 0	49 / 2.6		
Tonga	Oceania, Polynesia	747	151.4	23.1	137	12.5 / 43.1	22.2 / 15.3 / 5.6	79 / 9.3	0.1 / 1.1	0 / 16
Trinidad & Tobago	Caribbean	5,127	267.6	53.2	96	45.7 / 10.6	4.9 / 4.3 / 1.4	69 / 40.7	46 / 34	1,577 / 600
Tunisia	Africa, North	163,610	75	68.9	117	6.7 / 64.8	18.3 / 15.4 / 31.1	96 / 40.8	28.8 / 2.6	260 / 40

Turkey	Asia, West	783,562	106.4	75.1	129	15.2 / 49.7	26.7 / 4 / 19	388 / 2.3	346 / 4.5	1,314 / 68
Turkmenistan	Asia, Central	488,100	12.5	51.6	102	8.8 / 72	4.1 / 0.1 / 67.8	54 / 14.6	68.4 / 12.9	3,407 / 216
Turks & Caicos	Caribbean	948	37.9	93.1		36.2 / 1.1	1.1 / 0 / 0	60 / 28	0.2 / 6.1	0 / 84
Tuvalu	Oceania, Polynesia	26	376.2	62.4	111	33.3 / 60	1.1 / 0 / 0	96 / n/a	0	0 / 14
Uganda	Africa ,East	241,550	221.6	23.8	92	10.4 / 71.2	34.3 / 11.3 / 25.6	196 / 72	5.2 / 0.1	595 / 17
Ukraine	Europe, East	603,500	76	69.4	153	16.7 / 71.2	56.1 / 1.5 / 13.6	102 / 23.7	227.3 / 5.1	2,552 / 84
United Arab Emirates	Asia, West	83,600	114.1	86.5	101	3.9 / 4.6	0.5 / 0.5 / 3.6	56 / 30.8	211.4 / 23.2	9,682 / 392
United Kingdom	Europe, North	242,495	275.2	83.4	103	13.0 / 71	25.1 / 0.2 / 45.7	102 / 84.4	419.8 / 6.5	4,926 / 116
United States	America, North	9,835,517	35.7	82.3	117	33.9 / 44.5	16.8 / 0.3 / 27.4	1,513 / n/a	5,254.3 / 16.2	84,007 / 282
Uruguay	America, South	173,626	19.8	95.3	118	10.5 / 87.2	10.1 / 0.2 / 76.9	106 / 20.8	6.7 / 2.0	126 / 62
Uzbekistan	Asia, Central	448,969	76.1	50.5	167	7.6 / 62.6	10.1 / 0.8 / 51.7	59 / 15.9	105.2 / 3.6	2,344 / 60

Vanuatu	Oceania, Melanesia	12,189	23.1	25.3	124	36.1 / 15.3	1.6 / 10.3 / 3.4	137 / 6.4	0.2 / 0.6	1 / 11
Venezuela	America, South	912,050	36.7	88.2	109	52.9 / 24.5	3.1 / 0.8 / 20.6	328 / 67.4	185.2 / 6.1	7,337 / 79
Viet Nam	Asia, South-east	330,967	311.2	35.9	138	47.6 / 34.8	20.6 / 12.1 / 2.1	616 / 40.9	166.9 / 1.8	3,043 / 32
Virgin Islands USA)	Caribbean	347	299.8	95.7	107	50.3 / 11.5	2.9 / 2.9 / 5.7	58 / 39.4		0 / 1
Wallis and Futuna	Oceania, Polynesia	142	83.4	0	112	41.6 / 42.8	7.1 / 35.7 / 0	89 / 0	0 / 1.6	26 G per capita
Western Sahara	Africa, North	266,000	2.1	86.7	107	2.7 / 18.8	0 / 0 / 18.8	49 / n/a		
Yemen	Asia, West	527,968	54.8	36.6	141	1.0 / 44.5	2.2 / 0.6 / 41.7	298 / 31.1	22.7 / 0.9	172 / 5
Zambia	Africa, East	752,612	23.7	43.5	183	65.4 / 31.7	4.8 / 0 / 26.9	88 / 48.3	4.5 / 0.3	385 / 27
Zimbabwe	Africa, East	390,757	43.7	32.2	100	36.4 / 42.5	10.9 / 0.3 / 31.3	89 / 85.9	12.0 / 0.8	449 / 30

Source: World Statistics Pocketbook. 2018 ed. UN Department of Economic and Social Affairs; CIA World Factbook

The United Nations Secretary-General warned in mid-October that the organization is facing a "cash crisis" if member states do not pay the annual dues they owe: $1.3 billion in payments are outstanding. As of October 9, the UN regular budget was $386 million overdrawn, and by the end of the month it will surpass last year's record cash deficit of $488 million. As of the end of September, member states had paid just 70% of what they owe for the regular budget for the 2019 fiscal year. At the same time last year, that figure was 78%. By Tuesday, October 8, 64 states had yet to pay their assessments in full – among them the United States, the U.N.'s largest

contributor. Each year, the regular budget has cut into extra funds earlier and earlier, and 2019 is the second year in a row in which the organization exhausted all regular budget reserves and is staying afloat with funds left over from closed peacekeeping missions. The UN general budget allocates $955 million in spending for the last quarter of 2019. But with only $147 million of cash left to draw from closed peacekeeping missions, the organization needs $808 million to stay in operation. A single payment from the United States would cover that, and more. The U.S. owes $674 million for 2019, and $381 million from previous budgets, a spokesman for the Secretary-General confirmed to NPR. The United States is currently responsible for $1.1 billion ($1,055 million) of the unpaid fees to the general budget, a portion of which is carried over from prior years. This is roughly 75% of money owed to the general budget. The US also owes $2.4 billion to the peacekeeping budget, some of which is a build-up of late payments from previous years. The US Congress capped its contribution to the peacekeeping budget in 1994, and has regularly passed special measures since then to pay its bill in full. Since 2017, however, the US has enforced the cap and now owes nearly $1.1 billion in missing payments. The U.S. generally makes its dues payments in October, and an official from the U.S. mission told NPR that it will pay "the vast majority of what we owe to the regular budget this fall."

The Secretary of State must pay $2.1 billion (FY 20) to restart P.L. 480 International Agricultural Assistance Program. The USA also owes $1.1 billion to settle UN regular budget arrears and current year contribution. $1 billion more arrears are owed dues to discrimination against United Nations Educational, Scientific and Cultural Organization and United Nations Relief (UNESCO) and Works Administration for the Relief of Palestine Refugees in the Near East (UNRWA) FY11 and FY19. State Department program levels must be re-estimated from $56.0 billion FY 16, to $60.5 billion FY 20 including arrears for the regular budget, UNESCO and UNRWA, $61.6 billion FY 20 to also pay arrears for peacekeeping, and begin to stabilize annual Department spending growth at 2.5% for all programs, 3% for P.L. 480. State Department Security Assistance costs, and total, may be reduced by $6 billion when International Military Assistance, International Military Education, International Narcotic Control and Law Enforcement and non-UN peacekeeping, are terminated, but whereas it takes one year advance notice under the Constitution, the costs of these treasonous programs inflate the FY 20 total and can be internally turned into undistributed offsetting receipts to reduce the deficit and pay for legitimate programs in the next year budget, on the basis of the human rights. Congress must vote, due to mounting arrears, the Secretary of State, who has never produced a budget of his own, must immediately authorize the Treasury to pay $61.6 billion FY 2020 for the Foreign Service budget. Congress must vote to terminate $6 billion armed resistance FY 21. Congress must vote pay $61.6 billion FY 20 including all arrears, $60.6 billion or $54.6 billion FY 21. To settle 2.6% annual growth for the Cabinet Agency 2.5% for all programs, 3% for P.L. 480, from FY 16 program levels before the illegal budget cuts, had to be translated into leeks by Hebrew, in *State Department, Foreign Relations and Related Organizations FY 20* total to overrule prior FY 19 settlement estimates under Art. 19 of the UN Charter.

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