

# Hospitals & Asylums

Cancer HA-18-9-13, HA-17-3-21

By Anthony J. Sanders

- A. [Risk](#)
- B. [Diagnosis and Treatment](#)
- C. [Carcinogens](#)
- D. [Cost](#)

## I. [Histology](#)

- 1. [Skin](#)
- 2. [Hair and nails](#)
- 3. [Histologic tissues](#)

## II. [Dermatology](#)

- 1. [Eczema and Dermatitis](#)
- 2. [Burns](#)
- 3. [Acne, impetigo, leprosy, bacterial and mycobacterial infections](#)
- 4. [Warts, herpes and viral infections](#)
- 5. [Tinea and fungal infections](#)
- 6. [Lice, mites and parasitic infestations](#)
- 7. [Psoriasis](#)
- 8. [Lupus erythematosus](#)
- 9. [Pigmentary disorders](#)
- 10. [Hair loss, dandruff and nail infections](#)
- 11. [Hereditary disease and aging](#)

## III. [Oncology](#)

- 1. [Skin cancer](#)
- 2. [Tumors of the central nervous system](#)
- 3. [Lung cancer](#)
- 4. [Oropharyngeal, head and neck cancers](#)
- 5. [Vascular neoplasm](#)
- 6. [Cancer of esophagus and stomach](#)
- 7. [Cancer of the liver and pancreas](#)
- 8. [Colorectal and bowel cancer](#)
- 9. [Breast cancer](#)
- 10. [Uterine cancer](#)
- 11. [Cancer of the vulva and vagina](#)
- 12. [Male neoplasia](#)
- 13. [Transgender cancer risk](#)
- 14. [Urinary system cancer](#)
- 15. [Myeloma](#)
- 16. [Leukemia](#)

17. [Lymphoma](#)
18. [Sarcomas](#)
19. [Endocrine cancer](#)

#### IV. [Treatment](#)

1. [Diagnosis](#)
2. [Surgery](#)
3. [Radiation](#)
4. [Chemotherapy](#)
5. [Exercise](#)
6. [Diet](#)

#### Charts

- A.1 [Trends in cancer incidence rates \(2001- 2016\) and death rates \(2001- 2017\)](#)
- A.2 [Cancer death rate per 100,000 by race and sex](#)
- A.3 [Cancer incidence cases per 100,000 by race and sex](#)
- A.4 [Estimated Number of New Cancer Cases and Death, by site, US, 2020](#)
- A.5 [Invasive Cancer Risk at Selected Age Intervals by Sex and Site, US, 2014-2016](#)
- B.1 [Comprehensive Cancer Treatment](#)
- B.2 [Trends in the Five-Year Survival Rates of Certain Cancers 1960-2015](#)
- C.1 [Work Related Causes of Pneumonitis and Asthma](#)
- C.2 [Radiation Exposure Due to Medical Tests](#)
- C.3 [Toxicity profile for selected chemotherapeutic agents](#)
- I.1.1 [Skin](#)
- I.1.2 [Epidermis](#)
- I.1.3 [Dermis](#)
- I.1.4 [Race](#)
- I.2.1 [Hair](#)
- I.2.2 [Nails](#)
- I.2.3 [Fingerprints](#)
- I.3.1 [Tissues](#)
- I.3.2 [Slides of Epithelial Cells](#)
- I.3.3 [Slides of Connective Tissues](#)
- I.3.4 [Skeleton](#)
- I.3.5 [Bone Cross-Section](#)
- I.3.6 [Slides of Muscles Cells](#)
- I.3.7 [Muscles](#)
- I.3.8 [Slides of Neurons and Nerves](#)
- I.3.9 [Peripheral Nervous System](#)
- II.1.1 [Eczema](#)
- II.1.2 [Hives](#)
- II.1.3 [Systemic Lupus Erythematosus](#)
- II.1.4 [Actinic Keratosis](#)
- II.1.5 [Bullous Pemphigoid](#)
- II.1.6 [Canker Sores](#)
- II.2.1 [Degrees of Skin Burn](#)
- II.2.2 [Mesh Skin Graft](#)

[II.3.1 Types of Acne](#)  
[II.3.2 Impetigo](#)  
[II.3.3 Boil](#)  
[II.3.4 Leprosy](#)  
[II.4.1 Herpes simplex](#)  
[II.4.2 Chickenpox](#)  
[II.4.3 Types of Warts](#)  
[II.5.1 Athlete's foot](#)  
[II.5.2 Tinea versicolor](#)  
[II.5.3 Candidiasis \(thrush\)](#)  
[II.6.1 Lice and nits in hair](#)  
[II.6.2 Scabies](#)  
[II.7.1 Psoriasis](#)  
[II.8.1 Butterfly rash](#)  
[II.8.2 Monitoring for Lupus Medication Side-effects](#)  
[II.9.1 Chloasma](#)  
[II.9.2 Vitiligo](#)  
[II.9.3 Types of Skin Pigmentation](#)  
[II.9.4 Malignant Melanoma](#)  
[II.10.1 Male Pattern Hairloss](#)  
[II.10.2 Alopecia areata](#)  
[II.10.3 Periungual warts](#)  
[II.11.1 Ichthyosis](#)  
[II.11.2 Angioma](#)  
[II.11.3 Nevi](#)  
[II.11.4 Port Wine Hemangioma](#)  
[II.11.5 Melasma](#)  
[II.11.6 Cradle Cap](#)  
[II.11.7 Seborrheic eczema](#)  
[II.11.8 Aging Skin Conditions](#)  
[II.11.9 Wrinkles](#)  
[III.1.1 Types of Skin Cancer](#)  
[III.1.2 Squamous and Basal Cell Carcinomas of the Skin](#)  
[III.1.3 Mole Chart](#)  
[III.1.4 Mycosis Fungoides](#)  
[III.2.1 Symptoms of Central Nervous System Tumors](#)  
[III.2.2 Brain Anatomy](#)  
[III.2.3 CNS Tumor Treatment](#)  
[III.3.1 Chest X-ray of Lung Cancer](#)  
[III.3.2 Staging System for Lung Cancer](#)  
[III.3.3 Lung Biopsy](#)  
[III.3.4 Lung Cancer Treatment](#)  
[III.4.1 Anatomy of the Pharynx](#)  
[III.4.3 Staging System for Head and Neck Cancers](#)  
[III.5.1 Hemangiomas](#)  
[III.5.2 Hemangioma of the face](#)  
[III.5.3 Congenital hemangioma](#)  
[III.5.4 Kaposiform hemangioendothelioma](#)  
[III.6.1 Staging for Esophageal Cancer](#)

- [III.6.2 Gastric Cancer Staging](#)
- [III.7.1 Anatomy of the Liver and Pancreas](#)
- [III.8.1 Colon Cancer Staging](#)
- [III.9.1 Staging System for Breast Cancer](#)
- [III.10.1 Female Reproductive System](#)
- [III.10.2 Staging for Cervical Cancer](#)
- [III.10.3 Drugs Used to Treat Stage IVB Cervical Cancer](#)
- [III.10.4 Staging for Carcinoma of the Ovary](#)
- [III.10.5 Staging for Carcinoma of the Endometrium](#)
- [III.10.6 Staging of Gestational Trophoblastic Neoplasms](#)
- [III.11.1 Staging of Vaginal Cancer](#)
- [III.11.2 Anatomy of the Vulva](#)
- [III.11.3 Staging for Cancer of Vulva](#)
- [III.12.1 Anatomy of the Male Gonads](#)
- [III.12.2 Prostate Cancer Staging System](#)
- [III.12.3 Penile Cancer Staging System](#)
- [III.14.1 Anatomy of the Urinary System](#)
- [III.14.2 Renal Cell Cancer Staging System](#)
- [III.14.3 Bladder Cancer Staging System](#)
- [III.15.1 Common Laboratory Features of Plasma Cell Dyscracias and Myeloma](#)
- [III.15.2 Chemotherapy for Multiple Myeloma, Plasma Cell Dyscracias, Waldenström macroglobulinemia and Langerhans' cell histiocytoses](#)
- [III.16.1 Chemotherapy for Leukemia](#)
- [III.16.2 Differential Diagnosis of Leukemias](#)
- [III.17.1 Lymphoma Staging](#)
- [III.17.2 Chemotherapy for Lymphoma](#)
- [III.17.3 Non-Hodgkin's Lymphomas](#)
- [III.18.1 Staging System for Soft-Tissue Sarcomas](#)
- [IV.1.1 X-ray of Thoracic Tumor](#)
- [IV.1.2 Common Skin Diseases](#)
- [IV.1.3 Common Laboratory Stains](#)
- [IV.2.1 Wide Excision of Malignant Melanoma on Neck](#)
- [IV.3.1 Radiation Complications](#)
- [IV.3.2 Radiation Exposure Due to Medical Tests](#)
- [IV.4.1 Toxicity profile for selected chemotherapeutic agents](#)
- [IV.4.2 Herbal Remedies for Cancer](#)
- [IV.4.3 Equivalent Doses of Glucocorticoid Drugs](#)
- [IV.6.1 Vitamin and Mineral Deficiencies](#)

## [Work Cited](#)

### **A. Risk**

About 5 percent of the general population survive a **cancer diagnosis**. 0.5% of the population are diagnosed with cancer and 0.15% die from cancer annually. 30% of people diagnosed with cancer die from cancer. One out of every five people in the United States and many other countries in the world is expected to die of cancer. Any child born in the United States in 1985 has a more than one in three chance of eventually developing some form of invasive cancer. The average age at which all cancers are diagnosed in most Westernized countries is between 60

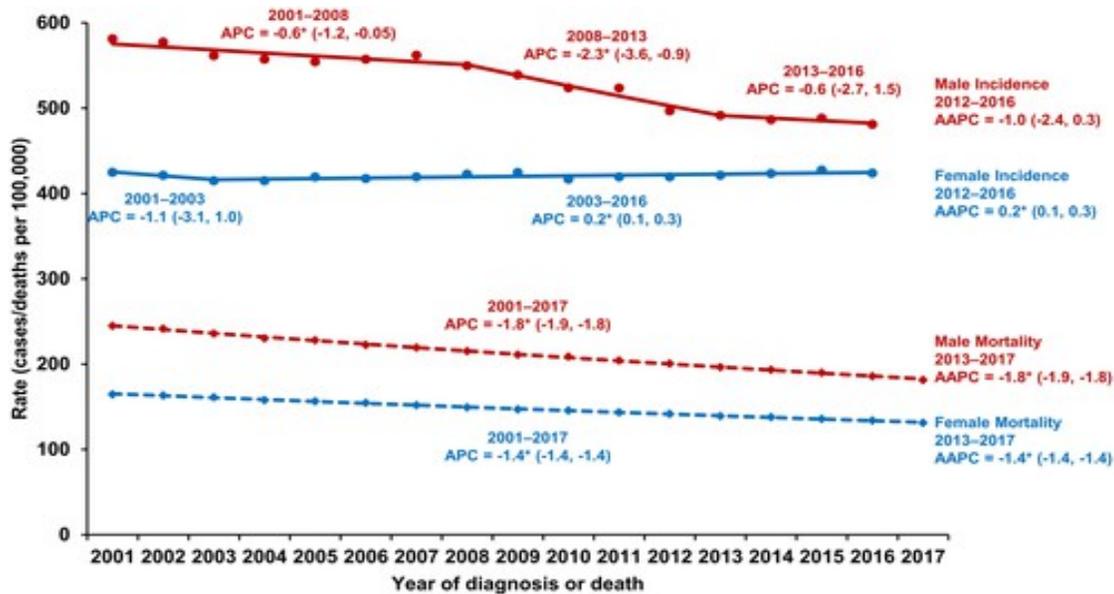
and 65. Of the more than 469,000 documented cases of deaths due to cancer in 1986 in the United States, the great majority (close to 90 percent) involved persons older than 55 (Friedberg '92: 55-57). About one in three people will at some time have an unwelcome diagnosis of cancer. Every day, around 1,500 Americans die of the disease. More than 1.6 million new cancer cases are diagnosed each year in the United States, and more than 550,000 die. Diagnosis are expected to rise to 2.3 million new cancer diagnoses per year by 2030 (Preidt '13). According to estimates from the International Agency for Research on Cancer (IARC), in 2018 there were 17.0 million new cancer cases and 9.5 million cancer deaths worldwide. With the eradication of infection and malnutrition as major causes of mortality, cancer has become more prominent as a life-threatening illness in children and the aging populace. Cancer has one biological property in common – the territorial expansion of a mutant clone (Greaves '00: 3). In the United States there is an increasing trend for cancers related to excess body weight and physical inactivity, including those for cancers of the female breast, uterus, kidney, liver, and pancreas (Henley '20).

American Cancer Society 2020 Facts and Figures reports: More than 16.9 million Americans have survived cancer as of January 1, 2019, most of whom were diagnosed many years ago and have no current evidence of cancer.. More than 1.8 million **new cancer cases** are expected to be diagnosed in 2020. This estimate does not include carcinoma in situ (noninvasive cancer) of any site except urinary bladder; nor does it include basal cell or squamous cell skin cancers because these types of skin cancer are not required to be reported to cancer registries. About 606,520 Americans are expected to die of cancer in 2020, 1,660 deaths per day. Cancer is the second most common cause of death in the US, exceeded only by heart disease. The overall age-adjusted cancer death rate rose during most of the 20th century, peaking in 1991 at 215 cancer deaths per 100,000 people, mainly because of smoking epidemic asbestos exposure. As of 2017, the rate had dropped to 152 per 100,000 (a decline of 29%) because of reductions in smoking, and asbestos, as well as improvements in early detection and treatment. 80% of all cancers in the United States are diagnosed in people 55 years of age or older. Certain behaviors also increase risk, such as smoking, having excess body weight, and drinking alcohol. In the US, an estimated 40 out of 100 men and 39 out of 100 women will develop cancer during their lifetime. The 5-year relative survival rate for all cancers combined has increased substantially since the early 1960s, from 39% to 70% among whites and from 27% to 64% among blacks. (ACS '20).

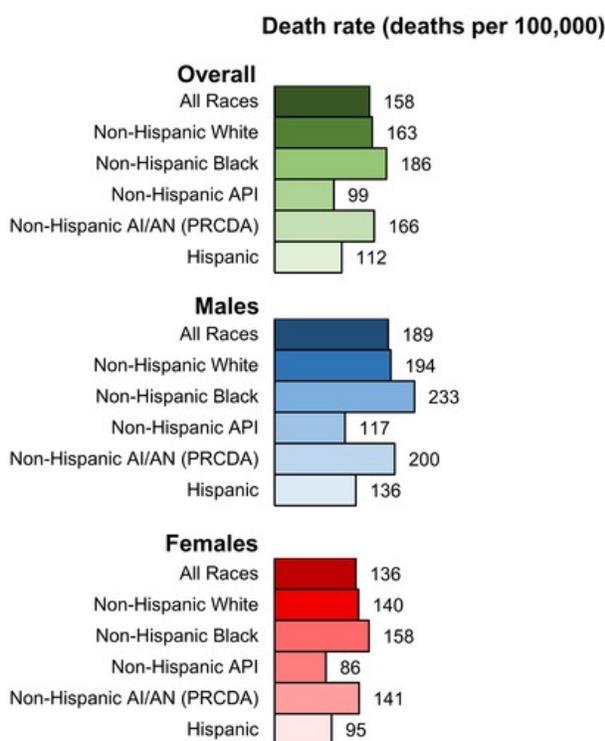
Cancer was the **second leading cause of death** after heart diseases and accounted for over 476,000 deaths, or more than 22 percent of fatalities from all causes in 1987. During the period between 1984 and 1986 cancer accounted for approximately 357 deaths per 100,000 people in the United States, very similar to other industrial nations. After accidents, the leading cause of death in children was cancer, accounting for nearly 1,700 deaths of 16,000 deaths from all causes in children between the ages of 1 and 14 (Friedberg '92: 44-48). In 1991 it was estimated that more 1 million new cases of cancer were diagnosed and there is about one new case of cancer for about every 150 people in the United States each year. According to the American Cancer Society, approximately 1.4 million Americans were diagnosed with cancer in 2006, and altogether some 10.5 million Americans alive today have had a cancer diagnosis at some time in their lives. In 2006 nearly 550,000 people died of cancer, which is second only to heart disease as the leading cause of death in the United States. 598,038 malignant neoplasms were 21.8% of the 2,744,248 total deaths in 2016. In 2017, malignant neoplasms remained the second leading cause of death. Malignant neoplasms caused 599,108, 21.3% of 2,813,503 deaths in 2017. Cancer caused 21.9% of deaths to males and 20.7% of deaths to females in 2017. In 2017, cancer was the first leading cause of death for the non-Hispanic API and Hispanic populations,

but it was the second leading cause for the non-Hispanic white, non-Hispanic black, and non-Hispanic AIAN groups. Cancer accounted for 25.1% of all deaths in the non-Hispanic API population, 21.4% in the non-Hispanic white population, 20.8% in the non-Hispanic black population, 20.6% in the Hispanic population, and 17.0% in the non-Hispanic AIAN population. On July 1, 2017 the total US population was estimated at 325,719,178, of the total 160,408,119 were male and 165,311,059 were female (Heron '19). American Cancer Society Facts and Figures estimate 1.8 million new cancer cases will be diagnosed and 606,520 will die from cancer in the United States, in 2020.

### Trends in cancer incidence rates (2001- 2016) and death rates (2001- 2017)

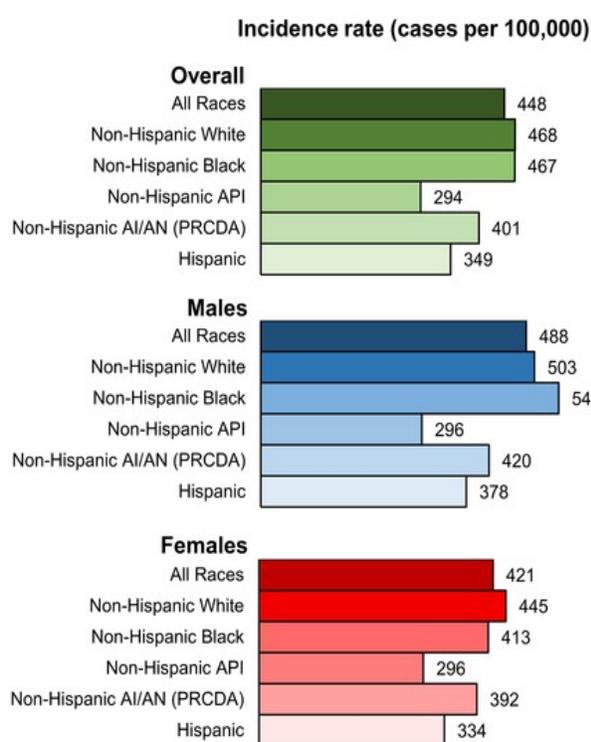


Source: 2020 Annual report to the nation on the status of cancer



According to official figures published in October 2006 in the Annual Report on the Nation on the Status of Cancer, 1975-2003, American's **risk of dying from cancer** has been steadily declining since the early 1990s, for both sexes and all races. From 1993 to 2003, a drop of 1.6 percent per year, double the decline of 0.8 percent per year in women. Somewhat paradoxically, however, the overall incidence of cancer diagnosis has been stable over this period and rates of diagnosis have actually increased for women (Mooney '07: 7-9). The 2020 Annual report to the nation on the status of cancer stated: Overall cancer death rates ranged from 125 to 195 deaths per 100,000 standard population. Overall, cancer death rates decreased 1.5% on average per year during 2001 through 2017, decreasing more rapidly among males -1.8% than among females -1.4%. Overall

cancer death rates decreased during 2013 through 2017 in every racial/ethnic group, decreasing the most among black persons –2.0% and the least among AI/AN persons –0.6%. The overall cancer death rate was highest among black persons. During 2013 through 2017, cancer death rates decreased in all states, decreasing 4.3% in Alaska and  $\geq 2\%$  per year in 6 additional states and the District of Columbia (Henley '20).



Overall, **cancer incidence rates** decreased 0.6% on average per year during 2012 through 2016, but trends differed by sex, racial/ethnic group, and cancer type. Among males, the decrease in cancer incidence rates since 2001 stabilized in 2013 and among non-Hispanic white males but decreased in other racial/ethnic groups. Overall the rate of cancer diagnosis in males declined from nearly 600 per 100,000 in 2001 to 500 per 100,000 in 2017. Rates increased for 5 of the 17 most common cancers, were stable for 7 cancers (including prostate), and decreased for 5 cancers (including lung and bronchus [lung] and colorectal). Among females, cancer incidence rates increased during 2012 to 2016 in all racial/ethnic groups, increasing on average 0.2% per year; rates increased for 8 of the 18 most common cancers (including breast), were stable for 6 cancers (including colorectal), and decreased for 4 cancers (including lung).

Historical declines in cigarette smoking have been reflected by declines in incidence of and mortality from several tobacco-related cancers, including lung, larynx, and bladder, which have greatly affected the overall incidence and death rates. Although the decrease in lung cancer was substantial, it continues to be the leading cause of cancer death, accounting for about one-quarter of all cancer deaths. Furthermore, these gains are being offset by increasing incidence trends for cancers related to excess body weight and physical inactivity, including those for cancers of the female breast, uterus, kidney, liver, and pancreas (Henley '20). In the US, an estimated 40 out of 100 men and 39 out of 100 women will develop cancer during their lifetime (ACS '20).

### Estimated Number of New Cancer Cases and Death, by site, US, 2020

	Estimated New Cases			Estimated Deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
All sites	1,806,590	893,660	912,930	606,520	321,160	285,360
Oral cavity & pharynx	53,260	38,380	14,880	10,750	7,760	2,990
Tongue	17,660	12,960	4,700	2,830	1,980	850
Mouth	14,320	8,430	5,890	2,660	1,690	970
Pharynx	17,950	14,630	3,320	3,640	2,820	820
Other oral cavity	3,330	2,360	970	1,620	1,270	350
Digestive System	333,680	187,620	146,060	167,790	97,560	70,230
Esophagus	18,440	14,350	4,090	16,170	13,100	3,070
Stomach	27,600	16,980	10,620	11,010	6,650	4,360

Small intestine	11,110	6,000	5,110	1,700	940	760
Colon	104,610	52,340	52,270	53,200	28,630	24,570
Rectum	43,340	25,960	17,380			
Anus, anal canal & ano-rectum	8,590	2,690	5,900	1,350	540	810
Liver & intra-hepatic bile duct	42,810	30,170	12,640	30,160	20,020	10,140
Gallbladder & other biliary	11,980	5,600	6,380	4,090	1,700	2,390
Pancreas	57,600	30,400	27,200	47,050	24,640	22,410
Other digestive organs	7,600	3,130	4,470	3,060	1,340	1,720
Respiratory system	247,270	130,340	116,930	140,730	76,370	64,360
Larynx	12,370	9,820	2,550	3,750	3,000	750
Lung & bronchus	228,820	116,300	112,520	135,720	72,500	63,220
Other respiratory organs	6,080	4,220	1,860	1,260	870	390
Bones & Joints	3,600	2,120	1,480	1,720	1,000	720
Soft tissue including heart	13,130	7,470	5,660	5,350	2,870	2,480
Skin (excluding basal and squamous)	108,420	65,350	43,070	11,480	8,030	3,450
Melanoma of the skin	100,350	60,190	40,160	6,850	4,610	2,240
Other non-epithelial skin	8,070	5,160	2,910	4,630	3,420	1,210
Breast	279,100	2,620	276,480	42,690	520	42,170
Genital system	317,260	203,740	113,520	67,830	34,210	33,620
Uterine cervix	13,800		13,800	4,290		4,290
Uterine corpus	65,620		65,620	12,590		12,590
Ovary	21,750		21,750	13,940		13,940
Vulva	6,120		6,120	1,350		1,350
Vagina & other genital, female	6,230		6,230	1,450		1,450
Prostate	191,930	191,930		33,330	33,330	
Testis	9,610	9,610		440	440	
Penis & other genital, male	2,200	2,200		440	440	
Urinary system	159,120	110,230	48,890	33,820	23,540	10,280
Urinary bladder	81,400	62,100	19,300	17,980	13,050	4,930
Kidney & renal pelvis	73,750	45,520	28,230	14,830	9,860	4,970
Ureter & other urinary organs	3,970	2,610	1,360	1,010	630	380
Eye & orbit	3,400	1,890	1,510	390	210	180
Brain & other nervous system	23,890	13,590	10,300	18,020	10,190	7,830
Endocrine system	55,670	14,160	41,510	3,260	1,600	1,660
Thyroid	52,890	12,720	40,170	2,180	1,040	1,140
Other endocrine	2,780	1,440	1,340	1,080	560	520

Lymphoma	85,720	47,070	38,650	20,910	12,030	8,880
Hodgkin lymphoma	8,480	4,690	3,790	970	570	400
Non-Hodgkin lymphoma	77,240	42,380	34,860	19,940	11,460	8,480
Myeloma	32,270	17,530	14,740	12,830	7,190	5,640
Leukemia	60,530	35,470	25,060	23,100	13,420	9,680
Acute lymphocytic leukemia	6,150	3,470	2,680	1,520	860	660
Chronic lymphocytic leukemia	21,040	12,930	8,110	4,060	2,330	1,730
Acute myeloid leukemia	19,940	11,090	8,850	11,180	6,470	4,710
Chronic myeloid leukemia	8,450	4,970	3,480	1,130	670	460
Other leukemia	4,950	3,010	1,940	5,210	3,090	2,120
Other unspecified sites	30,270	16,080	14,190	45,850	24,660	21,190

Source: American Cancer Society. Cancer Facts and Figures. 2020 pg. 4 Rounded to the nearest 10; cases exclude basal cell and squamous cell skin cancer and in situ carcinoma except urinary bladder. About 48,530 cases of female breast ductal carcinoma in situ and 95,710 cases of melanoma in situ will be diagnosed in 2020. Deaths for colon and rectal cancers are combined because a large number of deaths from rectal cancer are misclassified as colon.

Cancer death rates are the best measure of progress against the disease because they are less affected by detection practices than cancer incidence (new diagnoses) and survival rates. The overall age-adjusted cancer death rate rose during most of the 20th century, peaking in 1991 at 215 cancer deaths per 100,000 people, mainly because of the smoking epidemic. As of 2017, the rate had dropped to 152 per 100,000 (a decline of 29%) because of reductions in smoking, as well as improvements in early detection and treatment. This decline translates into more than 2.9 million fewer cancer deaths from 1991 to 2017, progress that has been driven by steady declines in death rates for the four most common cancer types – lung, colorectal, breast, and prostate. Cancer of the lungs, colo-rectal cancer and cancer of the prostate account for more than 50 percent of all cancers in men and cancer of the lung, colo-rectal cancer and cancer of the breast account for more than 50 percent of all cancers in women. Progress that has been driven by steady declines in death rates for the four most common cancer types – lung, colorectal, breast, and prostate (ACS '20). Cancer of the lung, colon and rectum, breast and prostate not only account for more than half of the total cancers, but they also account for over half of the death from cancer. This estimate does not include the most common of all cancers, carcinoma of the skin, although this type of skin cancer can be completely cure if properly treated, incidence of melanoma has tripled in the past three decades.

In the USA more people are dying of melanoma than ever before but there have been real improvements in early diagnosis and eradication by surgery. In the 1950s, only 50 percent of those with early-stage melanoma survived; today it's over 90 percent. Explanation, melanoma is five times more common now than it was 50 years ago. The mortality from cervical carcinoma in the US and western Europe has declined by some 50 percent since 1960, but the incidence has increased (Greaves '00: 238). 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. In both men and women the death rate from leukemia and cancers of the colon, bladder, liver and ovary has remained essentially unchanged for the past fifty years. Indeed, deaths due to cancer of the stomach have actually declined rather dramatically and in women deaths from cancer of the uterus and cervix have also decreased (Friedberg '92: 50-55).

There is the disturbing trend in the West of increasing rates of esophageal cancer, especially in men. Epidemiologically, the causal link is with alcohol consumption, especially when used in conjunction with smoking. As long ago as 1926, it was reported that there was an excess of deaths from esophageal cancers in the beer trade (innkeepers, bottlers, and cellar-men). Ethanol is broken down both by cells and resident oral bacteria into acetaldehyde, a DNA-binding carcinogen (Greaves '00: 262). Since 1975, the incidence of non-Hodgkin's lymphoma, melanoma, leukemia, and cancers of the lungs, thyroid, bladder and kidney has increased in women. The incidence of prostate and testicular cancer and cancers of the pancreas, kidney, liver and esophagus has risen in men, and overall incidence of childhood cancer has risen slightly. In both men and women the death rate from leukemia and cancers of the colon, bladder, liver and ovary has remained essentially unchanged for the past fifty years. Indeed, deaths due to cancer of the stomach have actually declined rather dramatically and in women deaths from cancer of the uterus and cervix have also decreased (Friedberg '92: 50-55).

While it may seem alarming that overall incidence of **child cancer** increased an average of 0.9% per year for adolescents and adolescents and young adults (AYAs) and 0.8% for children per year during 2012 through 2016; Child cancer death rates decreased an average of 1.0% per year among AYAs and an average of 1.4% per year among children during 2013-2017. Among children aged birth to 14 years, the incidence rate for all cancer sites combined was 16.8 cases per 100,000 standard population, ranging from 12.4 among AI/AN children to 17.8 among white children. The most common cancer types among children included leukemia, brain and ONS, and lymphoma, with increasing trends for each of these cancers during 2001 through 2016. Leukemia rates showed the most variability among racial/ethnic groups, ranging from 3.3 cases per 100,000 standard population among black children to 6.2 among Hispanic children. The cancer death rate among children was 2.1 deaths per 100,000 standard population and was highest among AI/AN children (2.6 deaths per 100,000) and lowest among API children (1.8 deaths per 100,000). Overall cancer death rates among children decreased an average of 1.4% per year during 2013 through 2017.

The most common cancer deaths among children were from brain and CNS cancer (0.7 deaths per 100,000) and leukemia (0.5 deaths per 100,000). During 2001 through 2017, death rates among children for brain and ONS cancer were stable, whereas death rates from leukemia declined 2.8% per year. Among young adults (AYAs) aged 15 to 39 years, the incidence rate for all cancer sites combined was 75.5 cases per 100,000 standard population, ranging from 54.8 per 100,000 among API AYAs to 84.1 among white AYAs. The cancer death rate among AYAs was 8.9 deaths per 100,000 standard population and was highest among black AYAs (11.4 deaths per 100,000) and AI/AN AYAs (11.0 deaths per 100,000) and lowest among API AYAs (6.9 deaths per 100,000). The most common cancer deaths among AYAs were from female breast cancer (2.2 deaths per 100,000 standard population), brain and CNS cancer (1.0 deaths per 100,000), leukemia (0.9 deaths per 100,000), and colorectal cancer (0.9 deaths per 100,000) (Henley '20).

An estimated 11,050 new cancer cases will be diagnosed among children ages 0 to 14 years in the US in 2020, and an estimated 1,190 children will die of the disease. One in 389 children will be diagnosed with cancer by age 15, and it is the second-leading cause of death among children ages 1-14 years after accidents. Childhood cancer incidence rates have slowly increased each year since at least 1975. From 2007 to 2016, rates increased on average by 0.8% annually. The death rate for cancer in children ages 0-14 years declined by more than half from 1975 (4.9 per 100,000) to 2017 (2.0 per 100,000), largely due to improvements in treatment and high rates of participation in clinical trials. However, the pace of decline slowed from about 3% annually during the late 1970s through the early 1990s to 1.3% annually since then. There are few known risk factors for childhood cancer. Most cancers in children are believed to arise spontaneously due to random cell mutations, with no external cause. Exposure to ionizing radiation, such as that from prior radiotherapy, increases the risk of childhood leukemia and possibly other cancers. Solid organ transplant recipients are at increased risk for non-Hodgkin lymphoma, largely because of drugs that suppress the immune system to prevent organ rejection. Cancer risk is also increased in children with certain genetic syndromes (e.g., Down syndrome, Li-Fraumeni syndrome, and Beckwith-Wiedemann syndrome) (ACS '20: 12).

In 2020, there will be approximately 89,500 new cancer cases and 9,270 cancer deaths in **adolescents and young adults (AYAs)** ages 15 to 39 years in the United States. These patients are often grouped with younger or older patient populations, which masks important differences in cancer distribution, tumor biology, and survivorship. For example, an increasing body of evidence indicates that several types of cancer in AYAs are molecularly distinct from those that occur in other age groups, suggesting possible differences in how cancers in this age group develop and are most effectively treated. In addition, for some cancer types, AYAs are more likely to be diagnosed at a late stage because of both delays in diagnosis due to the rarity of cancer in this age group and higher uninsured rates and higher prevalence of aggressive disease. AYA patients also have a high risk of long-term and late effects, including infertility, sexual dysfunction, heart problems, and future cancers. The **most common cancers among AYAs** vary substantially by age. Adolescents (15- to 19-year-olds) have a unique cancer profile that includes childhood cancers (e.g., acute lymphocytic leukemia), adult cancers (e.g., thyroid and melanoma of the skin), and a disproportionately high burden of lymphoma. For example, Hodgkin lymphoma accounts for 13% of cancer cases in adolescents compared to 9% in ages 20-29 years and 3% in ages 30-39 years. Conversely, adults 20-39 years have a higher proportion of solid tumors. In 2020, the most commonly diagnosed cancers will be thyroid, testicular germ cell tumors (GCTs), and melanoma of the skin in ages 20-29 years and female breast, thyroid, and melanoma in ages 30-39 years (ACS '20: 29, 30).

Although the majority of cases in AYAs occur in the absence of a known hereditary predisposition, certain genetic syndromes are strongly linked to early-onset cancers, such as: Lynch syndrome and colorectal, ovarian, and endometrial cancers. Familial adenomatous polyposis and colorectal cancer, Li-Fraumeni syndrome and several cancer types, including breast, sarcoma, brain, and leukemia. MEN2 familial syndrome and medullary thyroid cancer. In addition, a history of cancer in a parent or sibling increases the risk of being diagnosed with cancer at a younger age, especially if the relative was diagnosed at a young age. For example, men with a first-degree relative with a history of a testicular GCT are four times more likely to develop the disease compared to those without this medical history. Exposure to infectious agents is another important risk factor among AYAs. Infections associated with cancers in AYAs include human papillomavirus, Epstein-Barr virus, human immunodeficiency virus (HIV), and human herpesvirus 8. Importantly, although smoking-related cancers other than cervical are

generally uncommon in AYAs, cigarette smoking increases susceptibility to these cancer-related infections.

During 2012-2016, **cancer incidence rates** for all sites combined were similar in females and males ages 15-19 years (23 versus 24 cases per 100,000, respectively) but 30% higher in females compared to males ages 20-29 years (55 versus 42 per 100,000) and nearly double in females ages 30-39 years (161 versus 84 per 100,000).<sup>11</sup> Higher incidence rates in women ages 20-39 years are primarily driven by breast cancer, as well as higher rates of thyroid cancer and melanoma of the skin. For example, thyroid cancer incidence rates among women in their 20s are more than fivefold those among men (15 versus 3 per 100,000 during 2012-2016, respectively). Notably, although lung cancer is rare in AYAs, incidence rates in women in their 30s are higher than those in men, in contrast to higher rates among men compared to women 50 years of age and older. Higher lung cancer rates in young women are not fully explained by smoking prevalence. Testicular GCTs are the most commonly diagnosed cancer among young adult men, with rates peaking in the 30-39 age group (13 per 100,000 during 2012-2016). Conversely, ovarian GCTs are rare and rates peak during adolescence (0.8 per 100,000). In contrast to incidence, **cancer mortality** in males is slightly higher than in females among adolescents and young adults in their 20s, primarily reflecting higher incidence rates among males for cancers with lower survival (e.g., brain tumors and soft tissue and bone sarcomas). Leukemia is the leading cause of cancer death in both males and females ages 15-29 years, whereas brain and breast cancers are the leading causes of death in males and females, respectively, ages 30-39 years. Although cervical cancer is highly preventable, it is the second-leading cause of cancer death among women ages 20-39 years.

Overall **5-year survival** has increased since the mid-1970s among AYAs with the exception of a decline during the HIV/AIDS epidemic among young adult men. Five-year relative survival rates for AYA patients diagnosed during 2009-2015 were generally similar across age groups (83%-86%) and comparable to that in children (84%), but substantially higher than that in adults 40 years of age and older (66%). High overall survival in AYAs reflects 5-year relative survival rates of 94% or greater for many of the most common cancers, such as thyroid and testicular cancer, melanoma, and Hodgkin lymphoma, but masks lower rates for leukemias, brain tumors, and bone and soft tissue sarcomas. Importantly, overall AYA cancer survival may be artificially inflated as a result of overdetection of thyroid cancer, which has >99% 5-year survival. **Fertility counseling** and preservation are crucial components in the management of AYA cancer because many cancer treatments directly or indirectly affect fertility. The American Society for Clinical Oncology (ASCO) clinical practice guidelines recommend that fertility preservation be discussed with all new patients at the time of diagnosis because efforts such as sperm banking and embryo/oocyte cryopreservation (the freezing of fertilized or unfertilized eggs) should be started in advance of treatment. In one study of AYA cancer survivors, 18% of males and 38% of females had not made such fertility preservation arrangements because they were not aware of these options (ACS '20: 29-39). Gonadotrophic cancer patients should have their cancers surgically removed and should not try to preserve reproductive function, in favor of wide excision and sexual function, if possible.

In some countries particular cancers are more of a problem than in others. For example, in the United States about 42 people per 100,000 died of cancer of the colon and rectum during the period 1984 to 1986. But in New Zealand about 62 people per 100,000 died of this type of cancer, and in Ecuador only 9 per 100,000 did. Similarly, in England and Wales 36 women per 100,000 died of breast cancer, but in Ecuador only about 6 per 100,000 did. Different death rates

suggest that in different parts of the world there are different causative and genetic factors at work (Friedberg '92: 44-48). The cancer-related mortality rate for African-American women, is 28 percent higher than for white women. The U.S. latino population, is more likely than non-Hispanics to suffer from several cancers of infectious origins: human papilloma virus (HPV) in cervical cancer, *Helicobacter pylori* (treated with metronidazole) in stomach cancer and hepatitis B and C in liver cancer. Latino children also have a higher incidence of leukemia, retinoblastoma and osteosarcoma (Mooney '07: 7-9).

During the three-year period 1984 to 1986 in Switzerland slightly more than 33 men per 100,000 died of prostatic cancer, compared with about 23 men per 100,000 in the United States. However, in Japan only about 5 men per 100,000 died of this disease. But when Japanese men immigrate to the United States their incidence of prostatic cancer rises. Cancer of the skin is two hundred times more common in Queensland, Australia than in Bombay, India due to different levels of ultraviolet radiation from the sun that penetrate through the ozone layer in these two parts of the world, and the protection of having dark skin affords against skin cancer caused by sunlight. Cancer of the esophagus is three hundred times more common in northeast Iran than in Nigeria. Genetic factors may be partly responsible for this, but more likely, people in northeast Iran are eating something that people in Nigeria are not. Even within a single country, such as the United States, the cancer death rates differ from one state to another. The total death rate for all types of cancer is highest in New York, Connecticut, Rhode Island and Massachusetts, and is lowest in Idaho, Wyoming and Utah (Friedberg '92: 103, 101, 102).

Cancer usually **develops in older people**; 80% of all cancers in the United States are diagnosed in people 55 years of age or older. Certain **behaviors** also increase risk, such as smoking, having excess body weight, and drinking alcohol. In the US, an estimated 40 out of 100 men and 39 out of 100 women will develop cancer during their lifetime. These estimates are based on cancer occurrence in the general population and may differ for individuals because of exposures (e.g., smoking), family history, and/or genetic susceptibility. For many types of cancer, risk is higher with a **family history** of the disease. This is thought to result primarily from the inheritance of genetic variations that confer low or moderate risk and/or similar exposures to lifestyle/ environmental risk factors among family members. Inheritance of genetic alterations that confer a very high risk occurs much more rarely. **Relative risk** is the strength of the relationship between exposure to a given risk factor and cancer. It is measured by comparing the rate of cancer in a group of people with a certain exposure or trait to the rate in a group of people without this characteristic. For example, men and women who smoke are about 25 times more likely to develop lung cancer than nonsmokers, so the relative risk of lung cancer among smokers is 25. Most relative risks are not this large. For example, the relative risk of breast cancer among women who have a mother, sister, or daughter with a history of breast cancer is about 2.

#### **Invasive Cancer Risk at Selected Age Intervals, by Sex and Site, US, 2014-2016**

		Birth to 49	50 to 59	60 to 69	70 and older	Birth to death
All sites	Male	3.5 (1 in 29)	6.2 (1 in 16)	13.3 (1 in 8)	32.7 (1 in 3)	40.1 (1 in 2)
	Female	5.8 (1 in 17)	6.4 (1 in 16)	10.2 (1 in 10)	26.7 (1 in 4)	38.7 (1 in 3)
Breast	Female	2.0 (1 in 49)	2.4 (1 in 42)	3.5 (1 in 28)	7.0 (1 in 14)	12.8 (1 in 8)
Colon &	Male	0.4 (1 in	0.7 (1 in	1.1 (1 in 90)	3.3 (1 in 30)	4.4 (1 in 23)

Rectum		262)	143)			
	Female	0.4 (1 in 274)	0.5 (1 in 190)	0.8 (1 in 126)	3.0 (1 in 33)	4.1 (1 in 25)
Kidney & Renal Pelvis	Male	0.2 (1 in 415)	0.4 (1 in 266)	0.7 (1 in 153)	1.4 (1 in 74)	2.2 (1 in 46)
	Female	0.2 (1 in 661)	0.2 (1 in 551)	0.3 (1 in 317)	0.7 (1 in 136)	1.2 (1 in 82)
Leukemia	Male	0.3 (1 in 391)	0.2 (1 in 550)	0.4 (1 in 249)	1.5 (1 in 69)	1.9 (1 in 54)
	Female	0.2 (1 in 499)	0.1 (1 in 838)	0.2 (1 in 433)	0.9 (1 in 109)	1.3 (1 in 77)
Lung & Bronchus	Male	0.1 (1 in 730)	0.6 (1 in 158)	1.8 (1 in 57)	6.0 (1 in 17)	6.7 (1 in 15)
	Female	0.2 (1 in 499)	0.6 (1 in 169)	1.4 (1 in 70)	4.8 (1 in 21)	6.0 (1 in 17)
Melanoma of the skin	Male	0.4 (1 in 228)	0.5 (1 in 197)	0.90 (1 in 109)	2.6 (1 in 38)	3.6 (1 in 28)
	Female	0.6 (1 in 156)	0.4 (1 in 245)	0.5 (1 in 194)	1.2 (1 in 86)	2.5 (1 in 41)
Non-Hodgkin lymphoma	Male	0.3 (1 in 367)	0.3 (1 in 340)	0.6 (1 in 176)	1.9 (1 in 53)	2.4 (1 in 41)
	Female	0.2 (1 in 529)	0.2 (1 in 463)	0.4 (1 in 238)	1.4 (1 in 72)	1.9 (1 in 52)
Prostate	Male	0.2 (1 in 441)	1.8 (1 in 57)	4.7 (1 in 21)	8.2 (1 in 12)	11.6 (1 in 9)
Thyroid	Male	0.2 (1 in 449)	0.1 (1 in 694)	0.2 (1 in 558)	0.2 (1 in 405)	0.7 (1 in 144)
	Female	0.9 (1 in 112)	0.4 (1 in 252)	0.4 (1 in 273)	0.4 (1 in 251)	1.9 (1 in 52)
Uterine cervix	Female	0.3 (1 in 367)	0.1 (1 in 831)	0.1 (1 in 921)	0.2 (1 in 595)	0.6 (1 in 159)
Uterine corpus	Female	0.3 (1 in 323)	0.6 (1 in 157)	1.0 (1 in 95)	1.5 (1 in 69)	3.1 (1 in 33)

Source: American Cancer Society Cancer Facts and Figures, US, 2020 pg, 14

At least 42% of newly diagnosed cancers in the US – about 750,000 cases in 2020 – are **potentially avoidable causes**, including the 19% of all cancers that are caused by **smoking** and the 18% caused by a combination of excess body weight, alcohol consumption, poor nutrition, and **physical inactivity**. Certain cancers caused by infectious agents, such as human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Helicobacter pylori* (*H. pylori*), could be prevented through behavioral changes or vaccination to avoid the infection, or treatment of the infection. Many of the more than 5 million skin cancer cases that

are diagnosed annually could be prevented by protecting skin from excessive sun exposure and not using indoor tanning devices (ACS '20). It is estimated: Around 15 percent of the total cancer burden worldwide can be linked to persistent infection with common **viruses** such as HPV, HBV, HCV, EBV, HHV8 and HTLV-1 (Greaves '00: 171-173, 168). **Dioxin**, from red meat, fish, and dairy products, may be responsible for 12 percent of human cancers in industrialized societies (Robbins '01: 42 143, 144). Adding all of this comes to 69 percent. 31 percent **other potentially treatable** occupational and accidental overexposure to carcinogens including the sun (6%), radiation, bacterial and fungal infections. Persons whose cancer was caused by **radiation exposure**, such as from the laser of a defective CD ROM or DVD drive, must not be treated with invariably lethal dose radiation treatment. **Epsom salt bath** or swim in a saline or chlorine pool, or ocean, treats internal and external methicillin resistant *Staphylococcus aureus* (MRSA) lesions preventing potentially carcinogenic **toxic shock syndrome** in combination with *Streptococcus* spp. **Ampicillin** (Principen) treats pneumonia, sinusitis and meningitis. **Pneumovax** is effective against *Streptococcus pyogenes*, probable cause of rheumatic heart disease, and many pneumonias. **Metronidazole** (Flagyl ER) treats antibiotic resistant *Clostridium difficile* and carcinogenic *Helicobacter pylori* and is the best medical treatment for *Escherichia coli* bottled water detox. **Hydrocortisone crème** treats *Aspergillus niger* that elaborates a carcinogenic aflatoxin and can contaminate tobacco and peanut products. Coronavirus, mold allergies and mite infestations are treated with hydrocortisone, eucalyptus, lavender or peppermint (HELP).

## **B. Diagnosis and Treatment**

**General symptoms** caused by many different types of cancer are (1) persistent tiredness for no obvious reason, (2) progressive loss of weight for no obvious reason, (3) progressive paleness of the tongue or fingernail beds, especially if accompanying fatigue, can signify anemia from blood loss, (4) persistent loss of appetite, (5) fracture of a bone without any obvious trauma. **Cancer of the colon and rectum** exhibit (1) persistent diarrhea, (2) blood in the stool can be bright red to dark brown or black if aged, (3) stools that are narrower than normal, (4) loss of weight for no apparent reason, (5) a feeling that one has not emptied one's bowel completely, (6) general discomfort in the stomach area, such as bloating, fullness or cramps, or gas pains. **Cancer of the breast** exhibits (1) a lump or bump or even a feeling of thickening in the breast or in the armpit, (2) a change in the texture of the nipple or the pink tissue (often brown in women who have had children) called the areola, which immediately surrounds the nipple, (3) any discharge from the nipple, and (4) any change in the shape of one breast. **Cancer of the lung** exhibits (1) a persistent cough not associated with a cold or the flu, (2) persistent chest pain, which may or may not be related to coughing, (3) persistent hoarseness, (4) coughing up blood, (5) shortness of breath for no apparent reason, (6) frequent and persistent respiratory infections, such as bronchitis or pneumonia. **Cancer of the stomach** exhibits (1) persistent and unexplained abdominal pain or discomfort, including indigestion and heartburn, (2) vomiting, especially vomiting blood. **Cancer of the cervix or uterus** exhibits (1) bleeding between normal menstrual periods, (2) bleeding after intercourse or after a pelvic examination, (3) a persistent discharge from the vagina. Cancer of the pancreas is problematic because it tends not to exhibit early symptoms and particular attention must be paid to (1) persistent pain in the abdomen, particularly if it spreads to the back, (2) a yellow discoloration of the skin and the whites of the eyes, called jaundice. This can be caused by cancer of the pancreas blocking the duct (tube) through which bile normally flows, (3) persistent loss of appetite and (4) persistent nausea.

Cancer of the lymph glands (**Lymphoma**) exhibits (1) painless swelling of the lymph glands in the neck, armpits, or groin, (2) heavy sweating during the night, (3) persistent itching of the skin for no apparent reason, (4) the development of red patches on the skin and (4) persistent and unexplained nausea and vomiting. **Leukemia** in adults exhibits (1) enlarged lymph glands, (2) persistent bone pain, (3) a tendency to bleed or bruise easily, (4) a sense of heaviness or fullness under the left ribs, due to enlargement of the spleen, and (5) frequent infections anywhere in the body. **Melanoma** of the skin exhibits (1) change in the size, shape, or color of a mole, (2) a tendency for a mole to bleed or ooze, or to become tender, painful or itchy, or (3) the appearance of a new mole. **Cancer of the bladder** exhibits (1) bleeding with urination, with or without pain. **Cancer of the testicles** exhibits (1) a lump in either of the testicles, (2) persistent pain or discomfort in the testicles, (3) a sudden collection of fluid in the scrotum, (4) enlargement or swelling of either testicle, (5) persistent pain or dull ache in the groin or lower abdomen, or (6) enlargement or tenderness of the breasts resulting from hormonal imbalances caused by certain cancers of the testicle (Friebberg '92: 12-16).

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 many 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 gluconeogenesis 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). Meat proteins subjected to high-temperature pyrolysis (burnt) generate carcinogens, including mutagenic amines, as natural breakdown products 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 polycyclic hydrocarbon (Greaves '00:185-189). A vegan diet is prescribed for cancer patients (Gerson '90).

**Early diagnosis of childhood cancer** is often hampered by nonspecific symptoms shared by common childhood conditions. Parents should ensure that children have regular medical checkups and be alert to unusual, persistent symptoms, including an unusual mass or swelling; unexplained paleness or loss of energy; a sudden increase in the tendency to bruise or bleed; a persistent, localized pain or limping; a prolonged, unexplained fever or illness; frequent headaches, often with vomiting; sudden eye or vision changes; and excessive, rapid weight loss. Following are more specific symptoms for the major categories of pediatric cancer according to the International Classification of Childhood Cancer (ICCC); the distribution of each cancer type provided in parentheses is among all cancers in children ages 0 to 14 years in the US, including benign and borderline malignant brain tumors and cancers not classified by the ICC. **Leukemia** (28% of all childhood cancers) may cause bone and joint pain, fatigue, weakness, pale skin, bleeding or bruising easily, fever, or infection. **Brain** and other central nervous system tumors

(26%) may cause headaches, nausea, vomiting, blurred or double vision, seizures, dizziness, and difficulty walking or handling objects. **Neuroblastoma** (6%), a cancer of the peripheral nervous system that is most common in children younger than 5 years of age, usually appears as a swelling in the abdomen. **Wilms tumor** (5%), also called nephroblastoma, is a kidney cancer that may appear as swelling or a lump in the abdomen. **Non-Hodgkin lymphoma** (5%; includes Burkitt lymphoma) and Hodgkin lymphoma (3%), often cause lymph nodes to swell and appear as a lump in the neck, armpit, or groin; other symptoms can include fatigue, weight loss, and fever. **Rhabdomyosarcoma** (3%), a soft tissue sarcoma that can occur in the head and neck, genitourinary area, trunk, and extremities, may cause pain and/or a mass or swelling. **Retinoblastoma** (2%), an eye cancer that usually occurs in children younger than 5 years of age, is often recognized because the pupil appears white or pink instead of the normal red color in flash photographs or during an eye examination. **Osteosarcoma** (2%), a bone cancer that most often occurs in adolescents, commonly appears as sporadic pain in the affected bone that may worsen at night or with activity and eventually progresses to local swelling. Ewing sarcoma (1%), another cancer usually arising in the bone in adolescents, typically appears as pain at the tumor site (ACS '20: 12, 13)..

Childhood cancers are treated based on the type and stage of cancer. **Treatment** is coordinated by a team of experts, including pediatric oncologists and nurses, social workers, psychologists, and others trained to assist children and their families. Outcomes are most successful when treatment is managed by specialists at a children's cancer center. If the child is eligible, placement in a clinical trial, which compares a new treatment with the best currently available treatment, should be considered. Overall, childhood cancer survival has improved markedly over the past 40 years due to new and improved treatments. The 5-year relative survival for all ICCC groups combined during the most recent time period (2009-2015) is 84%, although rates vary considerably depending on cancer type and stage, patient age, and other characteristics. For example, the 5-year survival for Hodgkin lymphoma is 98%; for retinoblastoma it is 96%; Wilms tumor, 93%; non-Hodgkin lymphoma, 91%; leukemia, 87% (91% for acute lymphocytic leukemia and 66% for acute myeloid leukemia); neuroblastoma, 81%; Ewing sarcoma, 76%; brain and other central nervous system tumors (excluding benign brain tumors), 74%; rhabdomyosarcoma, 71%; and osteosarcoma, 69%. Pediatric cancer survivors may experience treatment-related side effects long after active treatment, including impairment in organ function (e.g., cognitive defects) and new cancers. The Children's Oncology Group (COG) has developed guidelines for screening for and managing late effects in survivors of childhood cancer (ACS '20: 13) .

Lumps, bumps and swelling of all types are extremely common. They are called **tumors** and can happen for all sort of reasons that have nothing to do with the uncontrolled growth of cells. For instance, a spider bite, a harmless large swollen bruise under the skin, called a **hematoma**, no one calls insect bites or hematomas tumors, but by strict medical definition they are, and lesions such as that caused by *Staphylococcus aureus* or chicken pox are also not generally considered cancer but with a co-occurring fungal invasion enough mutations might be caused to generate uncontrolled cellular growth near the septic necrosis that might be entirely absorbed into the cancerous human cells. The correct name for a swelling that is caused by the uncontrolled growth of cells is neoplasm. A tumor is generally used to refer to a collection of cells that develops as the result of the uncontrolled growth of cells somewhere in the body. Some tumors are made up of cancer cells. These are called **malignant tumors** and only these tumors have the special ability to invade the surrounding tissue and spread by metastasis to various parts of the body. Benign tumors are genuine neoplasms, consisting of cells in which growth is not properly

regulated and they grow progressively. Most of them grow very slowly with a relative lack of seriousness in terms of one's health. For example, many women lead perfectly healthy lives with benign tumors of the womb (called fibroids) and thousands of perfectly healthy people have benign tumors of the fatty tissue under the skin (called lipomas), frequently on the back.

Common warts and moles are also examples of **benign tumors** of the skin. Although benign tumors don't spread, they can cause serious disease and even death if they grow in a vital organ such as the brain or the heart. But because they never spread, most benign tumors are not harmful and their removal almost always results in a complete cure. Some benign tumors can and quite frequently do undergo malignant change. A notable example is a type of benign tumor of the large bowel called an intestinal polyp. Intestinal polyps can eventually become malignant, giving rise to cancer of the large bowel (colon). Cancer of the colon is one of the most common forms of cancer in both men and women. Pigmented moles can also become malignant. Simple freckles are collections of cells deep in the skin that contain a brown pigment called melanin that is present in cells all over the skin and is very important in protecting the skin from the harmful effects of sunlight. In addition to freckles there are also other small brown or black spots called moles. These sometimes form a discrete little swelling or tumor in the skin. Most are harmless and benign but rarely some of them can become cancerous, giving rise to a very serious type of malignant tumor called a melanoma, which can spread to other parts of the body extremely rapidly, although it remains quite tiny in the skin. Moles in the palms of the hands, the soles of the feet or the skin of the scrotum tend to become malignant most often. The majority of cancer (malignant tumors) do not first go through an extended benign stage, they are malignant from the beginning (Friedberg '92: 22, 23, 26, 28, 29).

A cancer in a vital organ such as the brain may be the size of a pea when it begins to interfere with brain functions. On the other hand cancer of the intestine may be much larger before one is aware of any disturbance in health. The presence of a **progressively enlarging cancer** in the breast or the skin really doesn't impair one's health because it doesn't affect any function that is absolutely needed for good health. But cancer also spread to other parts of the body, becoming just as large and invasive as at the original site. So the problem with cancer of the intestine, breast or skin is not so much the effect that an expanding mass of cancer cells has on those particular organs, but the fact that cancer cells spread to other parts of the body, so that life-sustaining organs, such as the brain, lungs, liver, heart and kidneys become compromised and are no longer able to function properly. The phenomenon of spread to other parts of the body constitutes the single most important problem in the diagnosis and the effective treatment of cancer. It is extremely difficult to eradicate every single cancer cell in the body once spread has occurred. Cancer cells are able to invade the tiny blood vessels that are present everywhere in the body. When this happens, some of the cancer cells are swept into the bloodstream and travel in the circulating blood and are deposited in many different organs.

In these new locations the cancer cells begin to grow in exactly the same way they grew in the part of the body where they originated in a process called **metastases**. Metastases may be limited to a few selected places, or they may be rampant in many organs or tissues. The lungs, brain, liver and bones are particularly frequent sites at which cancer cells spread. Cancer cells can also spread through the lymphatic system. Located at various intervals along the lymphatic circulation are lymph nodes (or lymph glands) where the lymph gets filtered and purified. If cancer cells penetrate the lymphatic system they are transported to the nearest lymph node and begin to grow in them, causing them to become enlarged. **Metastasis to lymph nodes** is a very frequent means of spread of cancer. The spread of cancer to the lymph nodes can increase the

chances of the cancer spreading to other parts of the body. This can happen if the lymphatic circulation eventually empties into the blood circulation or if cancer cells grow in a lymph gland and break through the node and invade surrounding tissues. There are thousands of tiny lymph nodes scattered all over the body and as any of them become occupied by cancer cells each affected lymph node constitutes a possible new center of metastatic growth from which further spread of the disease can occur. In summary, cancer cells in any organ or tissue of the body can metastasize to other organs and tissues through the blood circulation and through the lymphatic circulation. There are no benign lymphatic tumors. And that is how cancer, the process of uncontrolled growth of cells, causes progressive deterioration of the health and, in many cases, death (Friedberg '92: 16-20).

Cancer is not a single disease, but rather a single disease entity comprising many different individual disease or cancers. Virtually every cell type in the body can become cancerous. The cells that line all the surfaces of the body are called **epithelial cells**. The entire skin is a surface and is covered by a sheet of epithelial cells called the epithelium, tubes are also lined with epithelial cells. Carcinomas, leukemias, lymphomas and the various sarcomas account for more than 95 percent of all human cancers. It is important to remember that because every organ consists of different cell types, that organ can be the seat of several types of cancers. For example, cancer of the colon could be a cancer of the epithelial cells of the colon (carcinoma of the colon), or of connective tissue cells of the colon (fibrosarcoma of the colon), or even of the muscle cells in the colon (leiomyosarcoma of the colon). Most cancers of the colon are carcinomas. When epithelial cells anywhere in the body become cancerous such cancers are called **carcinomas**. A carcinoma of the lung means a malignant tumor that develops because of cancerous changes in cells lining the air passages. Similarly a carcinoma of the colon means malignant tumor cells line the inside of the large intestine. Benign tumors of epithelial cells are called **adenomas**. Thus benign polyps of the intestine are adenomas of the colon or adenomatous polyps of the colon. Carcinomas are the most common forms of cancer. Another common type of cancer is **leukemia**. When white blood cells, produced in the bone marrow, become cancerous they give rise to leukemia. **Bone marrow** is soft and pulpy because it contains large numbers of cells that are in various stages of maturation to fully formed red and white blood cells, which are then released into the bloodstream. Leukemias are actually cancers of the bone marrow. When lymphocytes and the lymph nodes become cancerous it is known as **lymphoma**.

**Connective tissue**, a delicate sheet of white tissue with a fibrous consistency which is present immediately underneath the epithelial linings of the body, such as tendons and ligaments, that connect the epithelium to deeper tissues, such as muscles for example. Cells that are present in connective tissue are called **fibroblasts**. Cancers that arise from cells in this general scaffold of connective tissue are called **sarcomas**. For example, a cancer from bone cells is called an osteosarcoma and a cancer from the muscle cells is called rhabdomyosarcoma. **Sarcomas** are tumors of supporting tissues. **Osteosarcoma** is a malignant and osteoma a benign tumor of bone cells. **Rhabdomyosarcoma** is a malignant and rhabdomyoma benign tumor of the muscle cells. **Fibrosarcoma** is malignant and fibroma benign tumor of the fibroblasts in the connective tissue. **Liposarcoma** is a malignant and lipoma benign tumor of the fat cells. **Chondrosarcoma** is a malignant and chondroma benign tumor of cartilage cells. **Angiosarcoma** is malignant and angioma is benign tumor of blood vessel cells (Friedberg '92: 32-36).

**Cancer** is a process during which cells in the body grow in an uncontrolled fashion. The average adult person consists of about three trillion cells. Cells are very tiny. Atypical living cell is only about one five-hundred thousandth of an inch long, requiring a microscope to see. If

these cells were laid out they would be about 375 miles long. During the growth of a child individual cells do not get bigger, they increase in number. Cells increase in numbers by a process whereby one cell (called the parent cell) divides and gives rise to two cells (called daughter cells). These two cells in turn become parents and each gives rise to two new daughters so that we now have four cells, and so on. This process is called cell division. During cell division all of the components of the cell are duplicated so that when the cell divides – splits in two – each new cell gets every component that its parent had and so the two cells are identical. In the human body, loss and renewal of cells is a constant process. In an adult person consisting of about three trillion cells, an estimated 350 billion of them divide every day. Each day millions of cells are shed from the skin, from the lining of the intestines, the lining of the airways and from various other parts of the body. During the process of menstruation millions of cells are shed from the lining of the womb each month and a new lining of cells forms. All of these lost cells must be replaced by new ones, which arise by the regulated (controlled) growth of their parent cells. In addition to the particular growth problems that occur before birth and which result in congenital birth defects or malformations, any time after a normal infant is born some aspect of the complicated programs that control the growth of cells can go wrong and cells in the body can begin to grow when they shouldn't – this is called cancer the uncontrolled growth of cells. If a cancer cell is only about one five hundred thousandth of an inch long, a cancer consisting of one thousand cells somewhere in the body would be smaller than the head of a pin. People with such a tiny cancer are totally unaware of its presence in their bodies. They feel in perfect health because at this stage the tiny cancer usually causes no ill effects whatsoever. But as the cancer cells continue to multiply, ignoring the controls that regulate the growth of normal cells, the cancer gets progressively bigger until it begins to make its presence felt in some way, by producing symptoms. Cancer cells don't respect territorial boundaries. They invade their immediate surroundings, literally shoving normal neighboring cells out of the way in a process called invasion. No tissues are protected from this invasive process. Even tissue as hard as bone can be invaded by cancer cells. By the time a cancer is big enough to actually be felt as a lump or a bump it consists of many millions of cells (Friedberg '92: Xiii, 2, 35, 6, 8, 9).

Cancer is thought of as a process that involves **multiple independent mutations** that alter the function of multiple independent genes and hence of multiple proteins that provide for the normal growth of cells. Mutations however only occur in about one in one million cells exposed to carcinogens such as cigarette smoke. Because mutations are rather rare and because six to ten particular genes among the fifty thousand genes in a cell must be affected to result in cancerous changes it takes a long time for cancer to develop. In the face of continued exposure the DNA of cells eventually suffers permanent alterations. However once cancer cells have arisen in the body they can sometimes be eliminated by natural processes. The immune system treats foreign cells as invaders that do not belong and kills them. The immune system hunts down the invading bacteria, fungus or viruses, recognizes them as foreign to the body, and disposes of them. This special ability to tell the difference with foreign cells also triggers the rejection of transplanted organs, tissues and bone marrow. Some people repair DNA better than others, and some people are born with a severely reduced ability to carry out DNA repair. One of the most dramatic examples is a disease called xeroderma pigmentosum (XP) found in about one in 200,000 people in North America and Western Europe who have an extremely high probability of developing a variety of skin cancers but some 700,000 new cases of skin cancer are diagnosed, so be careful of the summer sun (Friedberg '92: 66-69, 87, 90, 94).

Since **mutations** represent permanent alterations in genes, they are passed on to all the descendants of that particular cell, however mutations in a lung cell or a breast cell cannot be

passed on to one's children. One can be born with a "cancer gene" that is mutated at the outset of life, predisposing the person to acquire the other two or nine mutations. Some children are born with a defective "cancer gene" they inherited from their parents. Even though they carry this mutated gene in every cell in their body, this particularly "cancer gene" predisposes them uniquely to retinoblastoma of the cells in the retina of the eye. Some people are born with a disease called hereditary multiple polyposis in which they have many hundreds sometimes even thousands of intestinal polyps and they have a much higher chance of getting colon cancer than people who don't have the disease. The ability to identify genes that predispose to cancer in the population is a very exciting and very recent advance. Cancer researchers call these "cancer genes" **oncogenes**. The technology of isolating genes from cells and making multiple identical copies of them is called gene cloning. Treatments or prevention strategies for cancer are based on disrupting or eliminating whatever it is that particular protein does in cells to produce cancer. Aside from age and family history, which strongly suggest the operation of genetic factors, the risk of breast cancer in women is also influenced by the age at which menstruation started and the age when their first baby was born. The earlier the age of first menstruation, the greater the risk of cancer. And women who have their first child later in life are at an increased risk for breast cancer compared to women who have their first child earlier (Friedberg '92: 94-98).

Up to 50 percent of advanced, metastatic cancers have deletions or mutations resulting in loss of normal function in the **p53 molecule** (cellular detector of DNA damage and conductor of the cell death program). Cells of all vertebrate species have a gene that encodes a protein called p53 (p for protein, 53 for 53K daltons molecular weight). Some individuals have the Li-Fraumeni syndrome which includes an increased risk of several forms of cancer (breast carcinomas, sarcomas, and leukemias) relatively early in life. Some 50 percent of non-familial, common, cancers have abnormalities of one of both copies of the p53 gene (mutated or deleted) in the cancer cell clone. P53 is the most commonly altered gene in human cancer. Absence of p53 function can allow cells to survive the otherwise deleterious impact of other mutations that compel persistent proliferation, allows cells to survive anoxic conditions, for example, in poorly vascularized tumors, allows some cancer-causing viruses to replicate, for example, papilloma virus 16 in cervical cancer and allows cells to survive and continue to divide in the presence of DNA damage, for example, cells in sunburnt skin. The presence of a genetic abnormality in the p53 gene in a cancer biopsy suggests a poor clinical outcome of systemic chemotherapy or radiotherapy, probably because cell death is not fail-safe (Greaves '00: 241, 242, 64, 64).

The earlier any cancer is diagnosed the sooner treatment can begin. Unfortunately it is not possible to **diagnose** every type of cancer at a stage before it has spread to other parts of the body. Cancers in many parts of the body that cannot be easily felt can be seen on an X-ray film. CAT (computerized axial tomography) scanning, MRI (magnetic resonance imaging) and ultrasound are even more sensitive. Ultrasound is so safe and accurate it is now routinely used for examining babies in the womb. A mammogram is a special type of X-ray examination of the breast that is extremely helpful in diagnosing many cases of breast cancer early. Some cancer cells produce substances that normal cells don't make or the cancer cells produce substance in higher amounts than normal. Drawing a small amount of blood and carrying out special chemical tests on it sometimes allow certain types of cancer to be diagnosed, or at least suspected. For instance, prostate specific antigen (PSA) can be a useful blood test for the early diagnosis of cancer of the prostate. The definitive determination that cancer is present in any part of the body and the diagnosis of the particular type of cancer are usually made by removing a small amount of the tumor and examining it under a microscope. This process is called biopsy.

**Biopsies** are usually carried out because different tumors are treated differently. Once a small piece of tissue is removed it is carefully examined by a pathologist, a physician who is specially trained to recognize the look of cancer cells under the microscope, and who can also tell what particular type of cells the cancer came from and therefore give it the appropriate designation. Sometimes the biopsy and formal diagnosis of cancer and its treatment by surgical removal are carried out at the same time. The patient is given a general anesthetic in the operating room and an operation is carried out to biopsy the tumor. The pathologist, stationed nearby, uses a process specially designed to provide a diagnosis within a matter of minutes. The process employs the rapid freezing of the tissue so that it can be cut into very thin slices (or sections) for examination under the microscope, the procedure is called a frozen section. If cancer is identified by frozen section the surgeon will frequently go ahead and remove it there and then, provided it is operable. The best way to examine the extent of lymphoma called staging is by operating on the patient to directly examine the different lymph nodes in the belly (Friedberg '92: 38-41).

Although diagnosis of prostate cancer is only about 0.2 percent for men age 70 and older on autopsy **prostate cancer** (usually very small) is present in as many as 20 percent. A very common form of cancer in women develops in a part of the womb called the **cervix**, which forms the entrance to the womb or uterus. Epithelial cells in the lining of the cervix become cancerous rather frequently wherefore women have been encouraged to have frequent Pap smears named for its inventor, Dr. George Papanicolaou, to evaluate scrapings of cervical cells for cancer. Pap smears have led to the discovery that very early cancer of the cervix, at a stage before any cancer cells have invaded the surrounding tissues, occurs most frequently in women who are about thirty-five to forty-five years old. On the other hand, cancer of the cervix that has already invaded the surrounding tissues by the time it is first diagnosed occurs most frequently in women aged about forty-five to fifty – five because it takes about ten years for the noninvasive form of cancer of the cervix to become the invasive form (Friedberg '92: 75, 76).

As a cancer grows, it advances through the multiple steps of tumor progression. It starts with a single cancer cell, growing into many thousands of cancer cells, then invading the immediate surroundings and eventually spreading to other parts of the body. As it grows, its ability to interfere with the health of the patient increases in inverse proportion to its ability to be cured by treatment. When an initial diagnosis of cancer is made, the pathologist who examines the cancer biopsy attempts to determine the state of cancer growth by **grading and staging**. Pathologists grade the severity of the mutation of cancer cells based on the extent to which they deviate from normal cells, the more the cancer cells resemble the normal cells from which they arose the less aggressively the cancer is growing – grade 1 cancers are considered to be the least aggressive, grade 4 cancers the most aggressive. In many cases the grade of cancer is not a particularly reliable indicator of how rapidly and aggressively it will grow and many grade 4 cancers still respond well to treatment and don't grow noticeably faster than grade 1 cancers. Much more important from the point of view of the outlook for successful treatment is the stage of the cancer.

The Union Internationale Contre Cancer (IUCC), uses three primary criteria for **staging**- the size of the cancer, spread to neighboring lymph nodes and metastasis to other sites in the body, known as TNM (Tumor, Nodes, Metastases) Staging. The American Joint Committee on Cancer Staging uses a slightly different variation that includes a staging rank of 0-4. Stage 1 – a cancer that measures less than two inches in diameter with no spread to lymph nodes or to distant parts of the body. Stage 2 – a cancer that measures less than two inches in diameter with spread to lymph nodes but not to distant parts of the body. Stage 3 – A cancer of any size with spread to

the skin of the breast, or to the muscles of the chest or the chest wall and involvement of lymph nodes, but no spread to distant sites. Stage 4 – any cancer that has spread to distant parts of the body. Different criteria may be applied for the staging of other types of cancer but they fundamentally all take into account a very commonsense and rational way of assigning a score to the cancer based on how rapidly the cancer has grown and how far it has progressed (Friedberg '92: 77-80). The staging system is useful to understand how particular cancers progress but many people with solitary nodules and local disease are denied oral chemotherapy which is reserved for un-resectable patients in the literature, although chemotherapy is a more probable cure for many cancers.

Cancer is treated by **surgery, radiation and chemotherapy**. If tumors are relatively small, detectable, and in convenient sites, then surgeons can remove, them, much as Leonides of Alexandria performed mastectomies for breast cancer in AD 180. That excision alone can eradicate the problem in some cases is not in doubt. But clearly it can and does fail. The real problem in cancer treatment comes from the spread of disease throughout and between tissues. Once a cancer clone has evolved to this stage of territorial exploration, the knife is redundant and the blunter instruments of ionizing radiotherapy and chemotherapy are used (Greaves '00: 239). Surgical treatment can result in a complete cure if the surgeon is able to remove every single cancer cell, this is easiest to achieve if the cancer is completely confined to a single tumor. In many cases, surgery is a very effective way of treating cancer, especially if the cancer is located in an accessible part of the body, so that the surgeon can reach all of the cancer and can safely remove a generous amount of the surrounding normal tissue, just to be certain. Cancer of the breast is often treated this way. Sometimes a cancer may be inoperable because of where it is growing. Tumors that have metastasized widely are also inoperable. Under such circumstances it is impossible to surgically remove all the cancerous tissue. A third condition that can make cancer inoperable is that the patient's general health is not adequate to survive the ordeal of major surgery.

### Comprehensive Cancer Treatment

Skin Cancer	Treatment
Squamous cell carcinoma	Excision. Red sap from bloodroot ( <i>Sanguinaria Canadensis</i> ).
Basal cell carcinoma	Excision. topical 5-fluorouracil (5-FU) is effective, 1% to 5% 5-FU cream or gel is applied twice daily for 10 to 21 days or longer until marked erythema and crusting develop in the treated skin; the lesions are then allowed to slough and re-epithelialize.
Malignant melanoma	Lesions that are 1.69 mm or less can be safely excised with margins of 1 cm to 2 cm, whereas thicker lesions should be excised with 3 cm margins. Cytotoxic systemic therapy for patients with disseminated malignant melanoma has been of limited palliative benefit. Dacarbazine (DTIC) is one of the more active single agents. A typical schedule involves 5 days of intravenous treatment each 3 weeks. However, a response rate of only 14% was noted compared with polychemotherapy. The nitrosoureas (BCNU, CCNU or methyl-CCNU) are also active against DMM with regression occurring in 15%. Bleomycin, Vincristine, Lomustine, and Dacarbazine (BOLD) with Interferon. Carmustine, Cisplatin, Dacarbazine, and Tamoxifen (Dartmouth Regimen).

Mycosis fungoides	Radioresistant. Corticosteroids are quite helpful, especially for the first two stages . Radiation therapy of the superficial type is very effective for plaque and small tumor lesions; electron beam radiation therapy can be administered to the total body, either early or late in the disease. Systemic chemotherapeutic agents include the alkylating agents cyclophosphamide (Cytosan), chlorambucil (Leukeran), and nitrogen mustard; the plant alkaloid vincristine (Oncovin); the antimetabolite methotrexate; the antibiotic doxorubicin (Adriamycin); and the antibiotic derivative bleomycin (Blenoxane). Monoclonal antibodies are also being used for therapy
Warts	Trichloroacetic acid solution (saturated) or Salicylic acid (10%) in flexible collodion 30.0 may be applied to warts every night for 5 to 7 nights. The dead tissue can then be removed with scissors. Moist warts (condylomata acuminata) are treated with Podophyllum resin in alcohol (25% solution). Apply once to the warts, cautiously. For plantar warts fluorinated corticosteroid-occlusive dressing therapy is applied to the wart(s) at night and covered with Saran Wrap, Handi-Wrap, or Blenderm Tape. Leave on for 12 to 24 to 48 hours and reapply.
Cysts	Surgical excision and suturing
Actinic and seborrheic keratosis	Currettement, followed by a light application of trichloroacetic acid, (or doxycycline powder). Fluorouracil is useful for the patient with multiple superficial actinic keratoses. Fluroplex 1% cream 30.0 or Efugex 2% solution 10.0 applied to area twice a day, with fingers, for two weeks. A corticosteroid cream may hasten healing. Treatment may need to be repeated in several months or years.
Hemangiomas	Systemic corticosteroids and excision have been used successfully.
Choriocarcinoma Hydatidiform mole, invasive mole)	Patients with invasive mole or choriocarcinoma or metastases require immediate chemotherapy. Single-agent chemotherapy has been most commonly used. Intramuscular methotrexate, 0.4 mg/kg daily for 5 days every 2 weeks, or IV actinomycin D, 10 to 12µg/kg daily for 5 days every 2 weeks as necessary. There is less toxicity with intramuscular methotrexate, 1 mg/kg daily for 4 days, with intramuscular leucovorin, 0.1 mg/kg on alternate days, is associated with a high cure rate and low toxicity. Patients with high-risk tumors are initially treated with combination chemotherapy. The most common regimen used includes intramuscular methotrexate, 0.3 mg/kg, IV actinomycin D, 10µg/kg and chlorambucil, 10 mg orally daily for 5 days, with repeated courses as necessary.
<b>Central Nervous System (CNS) Tumor Type</b>	<b>Treatment</b>
<b>Malignant Glial Tumors</b>	
Astrocytoma (Kernohan Grades I and II) and	Methotrexate (oral) or 5-fluorouracil. Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy.
Glioblastoma	Postoperative radiation to approximately 60 Gy in 1.8 to 2 Gy fractions

(Kernohan Grades III and IV)	delivers as a 45 Gy whole brain plus 15 Gy tumor boost, or as 60 Gy to the tumor volume plus a 2 cm to 3 cm margin. BCNU, 60 mg to 80 mg/m <sup>2</sup> / for 3 days (total: 180 mg to 240 mg/m <sup>2</sup> ) every 6 weeks, or lomustine (CCNU), 110 mg to 130 mg/m <sup>2</sup> orally every 6 weeks or every 6-week combination CCNU, 110 mg/m <sup>2</sup> orally on day 1, procarbazine, 60 mg/m <sup>2</sup> for 14 days (days 8 to 21), and vincristine, 2 mg intravenously on days 8 and 29. Treatment for up to 1 year after maximal tumor response is recommended. Cisplatin, 100 mg/m <sup>2</sup> every 3 to 4 weeks, is an alternative therapy. Combination therapy with Gleevec and Hydrea resulted in complete or partial disappearance of the tumor in 20% of patients. Half of the patients survived for at least 19 weeks. Thirty-two percent of patients survived for six months without a worsening of their tumor, and 16% survived for two-years.
Oligodendroglioma	Methotrexate (oral) or 5-fluorouracil. Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy.
Ependymoma	Radiosensitive tumors. 5 year survival improves from 2% with surgery alone to 50% with surgery plus radiation
<b>Adult Nonglial Malignant Tumors</b>	
Primary CNS lymphoma (microglioma)	Dexamethasone, 10 mg initially, and 4 mg every 6 hours orally or intravenously. For spinal cord compression doses equivalent to dexamethasone, 50 mg per day Oral methotrexate. Oral therapy. PCV combination plus steroids or vincristine, 1.5 mg/m <sup>2</sup> intravenously weekly, doxorubicin (Adriamycin), 75 mg/m <sup>2</sup> intravenously on days 1 and 22, and prednisone, 40 mg/m <sup>2</sup> for 21 days, repeated every 6 weeks (APO) for 1 to 2 years or standard CHOP lymphoma chemotherapy. Additional intrathecal therapy with methotrexate or cytarabine (ara-C) may be needed for CSF seeding.
Malignant meningioma (sarcomatous/angioblastic)	Poorly responsive to surgery alone. Radiation of 50 Gy to 60 Gy. Doxorubicin (Adriamycin) and other "sarcoma regimens".
<b>Malignancies of Childhood</b>	
Medulloblastoma	Oral methotrexate. Craniospinal radiation of 45 Gy to 50 Gy to the posterior fossa and cervical cord, 35 Gy to the supratentorium and 35 Gy to 40 Gy to the spinal axis. Vincristine-based combination chemotherapy such as the PCV combination, MOPP with or without prednisone or vincristine, CCNU plus intrathecal methotrexate.
Germinoma (pineal)	Germ cell tumors are radiosensitive; resection may be unnecessary. Radiation to 50 Gy to 60 Gy is reported to produce up to 60% 5 year survival. Standard vinblastine, bleomycin, cisplatin germ cell treatment.
Brain stem glioma	Methotrexate (oral) or 5-fluorouracil. Complete resection curative. Incompletely resected tumors irradiated with 40Gy to 45Gy. BCNU, 60 mg to 80 mg/m <sup>2</sup> / for 3 days (total: 180 mg to 240 mg/m <sup>2</sup> ) every 6 weeks, or lomustine (CCNU), 110 mg to 130 mg/m <sup>2</sup> orally every 6 weeks or every 6-week combination CCNU, 110 mg/m <sup>2</sup> orally on day 1, procarbazine, 60 mg/m <sup>2</sup> for 14 days (days 8 to 21), and vincristine, 2

	mg intravenously on days 8 and 29. Treatment for up to 1 year after maximal tumor response is recommended. Cisplatin, 100 mg/m <sup>2</sup> every 3 to 4 weeks, is an alternative therapy.
Low-grade tumors: optic glioma, cystic cerebellar astrocytoma, juvenile pilocytic astrocytoma	Benign lesions treated with surgery alone even at recurrence.
<b>Histologically Benign Tumors</b>	
Meningioma	Rarely recur if completely resected. Radiation to incompletely resected lesions.
Schwannoma (acoustic neuroma)	Rarely recur if completely resected. Radiation to incompletely resected lesions.
Pituitary adenoma	Focal radiation alone or surgery with radiation for incompletely resected tumors.
Craniopharyngioma	Resection followed by radiation.
Cancers of the Neck	
Cancer of the Neck and Head	<p><b>Methotrexate</b> is generally given at 40 mg/m<sup>2</sup> intravenously weekly, and is also available in oral table 2.5 mg once a week. Two commonly used regimens are (1) Cisplatin, 50 mg/m<sup>2</sup> on day 6, methotrexate, 40 mg/m<sup>2</sup> on days 1 and 15; Bleomycin 10 mg on days 1, 8, 15; response rate is 61%. (2) Cisplatin, 100 mg/m<sup>2</sup> on day 1; 5-FU, 1000 mg/m<sup>2</sup> for 4 days, response rate is 70%. Cisplatin and Continuous Infusion Fluorouracil (CF). Docetaxel and Carboplatin (AUC=6)(DC). Docetaxel and Cisplatin (DP). Docetaxel, Cisplatin and Fluorouracil (DCF). Docetaxel, Cisplatin and Fluorouracil (TCF). <b>Radiotherapy</b> for head and neck cancer is usually done with either teletherapy, brachytherapy or hyperthermia. In <b>teletherapy</b>, treatment with a linear accelerator (4-6 MeV energy) is preferred. Cobalt-60 units are acceptable if they operate at 80 SSD (source-to-skin distance). A combination of lateral opposed fields, anterior and lateral wedged fields, or isocentric multiple fields is used for the primary tumor site. A single anterior field with a midline block can be used to treat the neck, and lower neck fields should match the primary field at the skin. The accepted dose rate is 180 cGy to 200 cGy per day. The dose to tumor volume for primary treatment is approximately 6600 cGy to 7000 cGy in 6 to 7 weeks. The dose to a tumor bed following resection is 5500 cGy in 5 to 5 ½ weeks for negative margins, 6000 cGy for close margins and 6600 cGy-7000 cGy for positive margins. The maximum dose to the spinal cord should be no more than 4000 cGy when 200 cGy fractions are used. Postoperative radiation should not begin until postoperative healing is satisfactory (about 2 weeks).</p>
Cancer of the Salivary Glands	Treatment of minor salivary gland cancers includes a wide excision. Most would recommend postoperative radiation for patients with high-grade cancers, positive margin, perineural invasion, deep lobe involvement, and regional lymph node metastases, at a minimum dose of 5000 cGy to 5500 cGy or 6600 cGy for positive margins. Primary

	radiotherapy is reserved for inoperable patients. The best single agents are cisplatin, doxorubicin, 5-FU and methotrexate. Overall responses have been noted in up to 60% of patients.
Lung Cancer	Carboplatin and Etoposide (CE). Cisplatin and Pemetrexed. Docetaxel and Capecitabine (DC). Docetaxel and Cisplatin (DP). Etoposide and Cisplatin (GC). Irinotecan and Carboplatin (IC). Irinotecan and Cisplatin (IP). Paclitaxel and Carboplatin (PC or TC). Pemetrexed and Carboplatin (PC). Vinorelbine and Cisplatin (VC)
Small cell lung cancer	Chemotherapy for small cell lung cancer is effective, achieving an 80% initial response rate and increasing mean survival from 13 weeks to 13 months. It has been reported that up to 5% are potentially cured. Chemotherapy programs utilized in SCLC generally include three or four drugs selected from known active single agents such as cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide (VP-16), cisplatin, or a nitrosourea such as moustine (CCNU).
Non-small cell	Chemotherapy for non-small cell carcinoma is disappointing. Response rates vary from 10% to 40%. Potentially curative radiotherapy is customarily administered to a total dose of 55 Gy to 60 Gy (5500-6000 rad) in continuous fractionation using megavoltage equipment.
Vascular Neoplasms	
Angiosarcomas	Usually treated with the antiangiogenic drugs paclitaxel (Taxol), docetaxel (Docetaxel, Taxotere), sorafenib (Nexavar), or bevacizumab (Avastin).
Lymphangiosarcoma	Chemotherapeutic drugs such as paclitaxel, doxorubicin, ifosfamide, and gemcitabine exhibit antitumor activity. Bevacizumab, may be effective in treating lymphangiosarcoma. Investigation of bevacizumab in combination with other chemotherapy agents is underway.
Abdominal cancer	Gastrointestinal: Gemcitabine and Capecitabine (Biliary, Gallbladder). Irinotecan and Cisplatin (IP) (Gastroesophageal). Colon/Colorectal: Capecitabine plus Oxaliplatin (XelOx/CapOx). Fluorouracil, Leucovorin and Irinotecan (FOLFIRI). High-Dose Fluorouracil and Leucovorin. Irinotecan, Fluorouracil and Leucovorin. Leucovorin, Fluorouracil and Oxaliplatin (FOLFOX4). Leucovorin, Fluorouracil and Oxaliplatin (FOLFOX 6 & 7). Protracted Venous Infusion Fluorouracil. Weekly Fluorouracil and Leucovorin.
Esophageal cancer	Docetaxel and Capecitabine (DC). Docetaxel and Cisplatin (DP). Irinotecan and Cisplatin (IP). Chemotherapy regimens utilizing combination of 5-fluorouracil (5-FU) (1000 mg/m <sup>2</sup> per day, IV continuous infusion on days 1 to 4; repeat on days 29 and 32) and cisplatin (75 mg/m <sup>2</sup> , 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.
Adenocarcinoma of the stomach	Patients who have undergone gastrectomy should receive vitamin B <sub>12</sub> , 100 µg monthly, to avoid megaloblastic anemia. Single-agent chemotherapy response rates are less than 30%. Doxorubicin (25%),

	<p>5-Fluorouracil (21%), Mitomycin-C (30%), Hydroxyurea (19%), BCNU (18%), Chlorambucil (13%), Mechlorethamine (13%), Methyl-CCNU (8%), Cisplatin (22%), Triazinate (15%) and Methotrexate (11%) are indicated for gastric cancer. The most widely applied combination regimen is the FAM program, consisting of 5-fluorouracil, doxorubicin (Adriamycin) and mitomycin-C. A review of 300 patients documented an overall response rate of 35%. The FAP program, consisting of 5-FU, doxorubicin and cisplatin produced a complete response in 12% to 15% of patients, who survived more than 4 years. Docetaxel and Capecitabine (DC). Docetaxel and Cisplatin (DP). Docataxel, Cisplatin and Fluorouracil (DCF). Epirubicin, Cisplatin and Capecitabine (ECX). Epirubicin, Cisplatin and Fluorouracil (ECF). Fluorouracil, Doxorubicin and Mitomycin (FAM). Irinotecan and Cisplatin.</p>
Gastrointestinal sarcomas of the small bowel	<p>Single agent doxorubicin, 70 mg/m<sup>2</sup> has a response rate of 15% to 35%. DTIC 1 g. m<sup>2</sup> every 3 weeks has a single agent response rate of 17%. Response rates improved in combination doxorubicin, 70 mg/m<sup>2</sup> and DTIC 1 g. m<sup>2</sup> every 3 weeks but so nausea and vomiting increased. Trials of ifostamide in previously untreated patients yield response rates of 20% to 40%. A study of a combination doxorubicin, ifosfamide, and DTIC with mesna uroprotection yielded a response rate of 48% with 13% complete response.</p>
Colon cancer	<p>The 1 g/m<sup>2</sup>/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, streptozotocin 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%. The first-line treatment for metastatic colorectal cancer appears to be the fluorouracil + folinic acid combination (LV-5FU2 protocol) plus either oxaliplatin (FOLFOX protocol) or irinotecan (FOLFIRI protocol)</p>
Anal cancer	<p>5-FU 1000 mg/m<sup>2</sup> per day, as continuous infusion on days 1 to 4, repeat on days 28 to 31; Mitomycin-C, 15 mg/m<sup>2</sup> 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% complete response.</p>
Pancreatic cancer	<p>Fluorouracil, Doxorubicin and Mitomycin (FAM). Gemcitabine and Capecitabine. 5-FU alone is the most appropriate chemotherapy choice for pancreatic cancer. The median survival for all patients treated with radical surgery (Whipple procedure) 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<sup>2</sup>) therapy for a total treatment time of 2 years. Patients undergoing this combined modality approach had a median survival of approximately</p>

	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.
Insulinoma	Diazoxide in doses of 300 mg to 800 mg daily inhibits release of insulin and also has a peripheral hyperglycemic effect, a benzothiadiazine diuretic should be given with diazoxide. Propranolol and glucocorticoids have also been used.
Carcinoid tumors	Medical management of the carcinoid syndrome includes use of alpha- or beta-adrenergic blockers (propranolol, phenoxybenzamine), antiserotonin agents (cyproheptadine), phenothiazines (chlorpromazine), and corticosteroids. Propranolol, a beta-blocking agent, has been reported to decrease the frequency and intensity of carcinoid-related flushing. The doses usually used are 10 mg, three times a day, given orally. Phenoxybenzamine, 20 mg/daily, has also been reported to decrease the frequency and severity of flushing and diarrhea. The phenothiazine chlorpromazine has been known to alleviate carcinoid flushing, the optimal dose used was 25 mg, four times daily. Cyproheptadine (Periactin), 4 mg to 8 mg four times daily. In patients with bronchial carcinoids, prednisone, 10 mg to 20 mg per day. Diphenoxylate hydrochloride (Lomotil), one to two tablets two to four times per day, is useful for controlling the diarrhea associated with both carcinoid and islet cell tumors. A long-acting analogue of somatostatin (Sandostatin, SMS 201-995) is quite effective in aborting a carcinoid crisis, including severe hypertension, among patients undergoing surgery, in this setting, intravenous (IV) therapy of 150µg to 300µg is given to stop the crisis. More routine use of SMS 201-995 is self-administered as a subcutaneous injection. Treatment is usually started as 150µg twice a day and then increased to 150µg three times daily. A large majority of patients (77%) have had prompt relief of symptoms associated with the carcinoid syndrome.
Hepatic cancer	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.
Female Cancers	
Breast Cancer	CMF+/-P: Cyclophosphamide, Methotrexate, 5-Fluorouracil, and Prednisone; CMF: Cyclophosphamide, Methotrexate, 5-Fluorouracil; FAC: 5-Fluorouracil, Doxorubicin, Cyclophosphamide; AC Doxorubicin, Cyclophosphamide; and PF Phenylalanine mustard, 5-Fluorouracil, Cyclophosphamide, Doxorubicin and Fluorouracil (CAF, FAC). Cyclophosphamide, Methotrexate and Fluorouracil (CMF). Docetaxel and Capecitabine (DC). Docetaxel and Carboplatin (AUC=6)(DC). Docetaxel and Cisplatin (DP). Docetaxel, Doxorubicin and Cyclophosphamide (TAC). Dose Dense Doxorubicin and Cyclophosphamide Followed by Paclitaxel. Doxorubicin and Cyclophosphamide. Doxorubicin and Cyclophosphamide followed by Docetaxel. Doxorubicin and Docetaxel. Fluorouracil, Epirubicin and Cyclophosphamide (FEC50)(FEC)(FEC100)(FEC). Gemcitabine and

	Capecitabine. Ixabepine and Capecitabine. Lapetinib and Capecitabine. Paclitaxel and Gemcitabine. Pemetrexed and Carboplatin (PC)
Cervical cancer	Most advanced tumors are managed entirely by external irradiation, delivering 5500 cGy to 6000 cGy to the whole pelvis over 5 to 6 weeks. Patients treated with cisplatin, 50 mg/m <sup>2</sup> every 3 weeks, reported an overall response rate of 38%. Methotrexate, bleomycin and cisplatin has 89% response rate, doxorubicin may be added for cure in 29%. Docetaxel and Carboplatin (AUC=6)(DC)(Cervical).
Carcinoma of the ovary (serous cystadenocarcinoma, mucinous sytadenocarcinoma, endometrioid, undifferentiated and clear cell carcinoma)	Treatment of early ovarian cancer includes surgery alone, surgery plus pelvic radiation therapy, surgery plus total abdominal radiation therapy, surgery plus intraperitoneal radioisotopies and surgery and surgery followed by chemotherapy. Oral methotrexate 2.5 mg once a week should be prescribed before expensive surgical, radiation or combination intravenous chemotherapy treatments are tried for methotrexate resistance. Docetaxel and Carboplatin (AUC=6)(DC). Docetaxel and Carboplatin (AUC=5)(DC). Docetaxel and Cisplatin (DP). Liposomal Doxorubicin. Pemetrexed and Carboplatin (PC).
Germ cell tumor of the ovary	Germ cell tumors of the ovary comprise only 5% to 10% of the total but are important because of their aggressiveness, their lack of successful management with surgery and radiation therapy, and their high degree of curability with combination chemotherapy. A four drug combination termed Hexa-CAF (hexamethylmelamine, cyclophosphamide, methotrexate, and 5-fluourouracil produced an increase in response rate (75% versus 54%), more complete remissions (33% versus 16%) and significantly longer median survival (29 months versus 17 months) versus single-agent melphalan. Oral methotrexate 2.5 mg once a week might suffice.
Carcinoma of the endometrium (adenocarcinoma in about 67% of patients, 13% are adenosquamous carcinomas. Rarely <1% purely squamous carcinoma. Also rare <1% are clear cell carcinomas with a particularly poor prognosis.	Either hysterectomy or medical management depending on the patient's desire for childbearing. Hysterectomy strongly advised to prevent recurrent cancer. When childbirth is desired, ovulation can be produced with clomiphene. Commonly used agents include hydroxyprogesterone (Delalutin, deoxyprogesterone (Provera, and the oral agent megestrol (Megace), with response rates up to 30%. Tamoxifen also appears to induce progesterone-receptor activity. Doxorubicin (Adriamycin) has shown the most activity, Adriamycin, 60 mg/m <sup>2</sup> IV every 3 weeks, has produced a 37% response rate in 43 patients, 26% of whom had clinically complete regression of disease. Cisplatin also appears to produce a significant response rate (46%) when used at doses of 10 mg/m <sup>2</sup> IV every 4 weeks. Combination chemotherapy has not been studied extensively and does not seem to show results better than single-agent therapy. Docetaxel and Cisplatin (DP(Urothelial), Docetaxel and Carboplatin (AUC=6)(DC)(Cervical).
Carcinoma of the vulva Ninety percent of the invasive tumors are squamous carcinoma. Three	Herpes simplex type II and human papilloma virus have been identified in vulvar cancers and vulvar condyloma. Topical chemotherapy, usually 5-FU, has been utilized, three 7 day treatment courses of 5% 5-FU given two weeks apart. Topical dinitrochlorobenzene has also been used with similar results

percent of the tumors are basal cell carcinomas. Less commonly seen are adenocarcinoma of the Bartholin duct, Paget's disease, melanoma, and sarcomas.	
Carcinoma of the vagina	Many carcinomas of the vagina are not surgically resectable. Radiation therapy is the more common management approach. Carcinoma <i>in situ</i> and carcinomas limited to the vaginal wall (Stage I) are generally treated with intracavitary or interstitial radiation therapy. Cesium-137 needles are commonly used. When lesions are located high in the vagina, intrauterine tandems and vaginal colpostats are used. Five year survival for Stage I and II carcinomas has generally been reported at 35%.
Gestational Trophoblastic Neoplasm	Etoposide, Methotrexate, Actinomycin, Cyclophosphamide and Vincristine (EMA/CO). Hydroxyurea, Dactinomycin, Vincristine, Leucovorin, Cyclophosphamide, and Doxorubicin (Modified Bagshawe Regimen).
Male Cancers	
Adenocarcinoma of the prostate and transitional cell carcinoma of the respond to chemotherapy protocols for bladder cancer and are unresponsive to hormonal manipulation. Rare tumors include endometroid cancer and carcinoma sarcomas; and lymphomas.	Standard therapy for advanced prostatic adenocarcinoma is hormone manipulation, which can be accomplished by orchiectomy or the administration of exogenous hormones such as diethylstilbesterol (DES), 1 mg daily (up to 3 mg) to suppress testosterone levels, antiandrogens (i.e., flutamine or cyproterone acetate), progestins combined with estrogens (megestrol, 40 mg three times daily, with low-dose DES or estinyl), and luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide. Levels of testosterone will drop to castration levels. Hormonal manipulation will induce remission in approximately 40% to 80% of patients depending on the criteria employed. Complete disappearance of the disease is rare. Surgery and radiation therapy produce 5, 10 and 15 years survival rates for State B disease of 75%, 50% and 30% to 50% for C and D1 disease, survival is 55% and 15% respectively. Seventy-percent survival for interstitial and external radiation is expected at 5 years, while 50% to 30% is reported for 10 and 15 years for Stages B2-C disease. When one excludes disease stabilization as a response category multi-drug chemotherapy has less than 5% response rate. The most frequently employed agents are doxorubicin, given in a dose of 45 mg to 60 mg/m <sup>2</sup> every 3 weeks or 20 mg/m <sup>2</sup> weekly, cyclophosphamide, 5-fluourouracil and cisplatin with doxorubicin. Prednisone, initially in a dose of 40 mg daily progressively decreased by 5 mg weekly, can improve quality of life by increasing appetite and weight and decreasing bone pain. Docetaxel and Capecitabine (DC). Docetaxel and Estamustine. Doxetaxel and Prednisone (DP). Gemcitabine and Capecitabine. Mitoxantrone and Prednisone (MP). Taxanes and Estramustine.

<p>Squamous cell (epidermoid) <i>carcinoma in situ</i> of the penis, erythroplasia of Queyrat and soft-tissue sarcomas</p>	<p>Soft-tissue sarcomas requires a total penectomy but no lymph node dissection. Therapy for carcinoma <i>in situ</i> is complete local incision. For erythroplasia of Queyrat, topical 5-fluourouracil twice daily has been effective; radiation therapy has not. Locally invasive penile lesions with clinically enlarged inguinal nodes are observed in 75% of cases at presentation, and after removal of the primary tumor, such nodes will have metastatic involvement. The 5 year survival rate for Stage 3 is more than 50%. Methotrexate, bleomycin, and cisplatin all have response rates in the 10% to 30% range; long-term complete remission is uncommon. Combinations have not been proven more effective. Laser therapy has been curative for some superficial lesions.</p>
<p>Germ cell tumors of the testicles</p>	<p>Germ cell tumors are the most curable malignancy. Cisplatin-based chemotherapy has results in the cure of 70% of 80% of patients with metastatic disease. For patients failing to achieve a complete remission or relapsing from complete remission, Etoposide (VP-16), 100 mg/m<sup>2</sup> IV for 5 days, plus cisplatin 20 mg/m<sup>2</sup> IV for 5 days is the standard treatment, that only cures 15% to 25% of those relapsing from complete remission. Bleomycin, Etoposide and Cisplatin (BEP). Cisplatin and Ifosfamide with either Vinblastine or Etoposide (VIP). Etoposide and Cisplatin.</p>
<p>Kidney and Bladder Cancer</p>	
<p>Renal cell carcinoma (hypernephroma) Uncommon tumors include adult Wilms', and soft-tissue sarcomas</p>	<p>Early diagnosis is mandatory, and therapy with irradiation and corticosteroids can prevent a major decrease in quality of life. Hypercalcemia is usually a terminal event and may be controlled for a limited time with hydration, mithramycin and rarely, by a prostaglandin inhibitor. Radical nephrectomy with lymph node dissection is the only appropriate therapy for locoregional renal cell carcinoma. If there is invasion of the renal vein and inferior vena cava, urologists may consider tumor embolectomy to remove all residual disease. Partial nephrectomy is performed in selected cases presenting with a grade I renal cell carcinoma and patients with a single kidney. When synchronistic or metachronous tumors occur bilaterally, renal transplantation can be considered. Pre-operative or postoperative radiation therapy has limited value. Chemotherapy is also ineffective, with transient tumor regression occurring in less than 5% to 10%. The most commonly used agents are vinblastine and a nitrosourea. Progestins produce tumor regression in less than 2% to 8% of cases and should never be employed as surgical adjuvants. Alpha-interferon induces responses in 13% to 20% of cases; however responses have been atrial and of limited duration.</p>
<p>Transitional (epidermoid) cell carcinoma of the bladder, over 90% of urothelial tumors, squamous cell (6%-8%), adenocarcinoma</p>	<p>Therapy for superficial lesions (Stages 0, A and sometimes B1) is endoscopic resection and fulguration with cystoscopy repeated every 3 months. When lesions recur frequently or are diffuse, the standard therapy is thiophosphoramidate (thiotepa) 60 mg/60 ml normal saline IV for 2 hours, weekly for 6 consecutive weeks. Approximately 30% to 40% of patients will respond, particularly those with low-grade lesions, but severe myelosuppression may occur. BCG 120 mg/50 ml of normal saline has also been found to be extremely efficacious when given</p>

<p>and urachal carcinoma (2%), clear cell, and mixed varieties. Embryonal rhabdomyosarcoma tends to occur in children.</p>	<p>weekly for 6 weeks, resulting in 60% of cases achieving complete remission. Other agents include mitomycin-C, 20 mg to 60 mg/20 ml to 40 ml, and doxorubicin 20 mg to 60 mg; however both of these agents cause severe bladder irritation. Radical cystectomy is considered for diffuse or recurrent Tis lesions, a procedure resulting in a 5 year survival rate of more than 90%. Standard therapy for Stages B-C disease is radical cystectomy with resection of local pelvic nodes. Overall 5 year survival rates for Stages B-C range from 30% to 50% in patients presenting with papillary low-grade lesions, survival is 60% to 75%. When surgery is medically contraindicated, supervoltage irradiation, 6000 cGy to 7000 cGy in 6 to 8 weeks, can produce 5 year survival rates of approximately 20% to 30% or higher for B1-2 and C disease. The most active single chemotherapeutic agents are cisplatin and methotrexate, and to a lesser extent, doxorubicin, vinblastine and mitomycin-C. Single agents induce response in 15% to 30% of cases; few responses are complete. Combination chemotherapy programs have reported complete remission in 16% to 40% of cases, and partial response in an additional 15% to 30%. Most combinations employ cisplatin and doxorubicin, frequently with cyclophosphamide (CISCA), cisplatin and methotrexate together and with vinblastine (CMV) and doxorubicin (M-VAC). Such regimens seem to be efficacious against transitional cell carcinoma but not for Tis, squamous cell, or adenocarcinoma. Long-term remission has been reported in patients with metastatic disease. CMV induces a 28% complete remission rate leading to a 1 month median survival for patients with complete remission; a few are surviving more than 2 years. M-VAC has induced complete remission in 39% of patients with 58% surviving 22 to 47 months or more. Intravesical Doxorubicin. Intravesical BCG. Intravesical Gemcitabine. Intravesical Mitomycin. Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC).</p>
<p>Myeloma</p>	<p>Chemotherapy in the form of alkylating agents induces remission in 50 to 70% of patients, but the median survival is still a dismal 3 years. Autologous and allogenic bone marrow transplantation after intensive chemotherapy offers the promise of cure. High serum levels of cytokine IL-6 is associated with a poor prognosis. Bortezomib and Dexamethasone (BD). Liposomal Doxorubicin and Bortezomib. Melphalan and Prednisone (MP). Melphalan, Prednisone and Thalidomide (MPT). Thalidomide and Dexamethasone (TD). Vincristine, Doxorubicin and Dexamethasone (VAD).</p>
<p>Multiple Myeloma and Plasma Cell Dyscracias</p>	<p>Oral Thalidomide, with dexamethasone, a corticosteroid. Others: Bortezomib, Carfilzomib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Doxil (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride Liposome, Dox-SL (Doxorubicin Hydrochloride Liposome), Evacet (Doxorubicin Hydrochloride Liposome), Kyprolis (Carfilzomib), Lenalidomide, LipoDox (Doxorubicin Hydrochloride Liposome), Mozobil (Plerixafor), Neosar (Cyclophosphamide), Plerixafor Pomalidomide (Pomalyst), Pomalyst, Revlimid (Lenalidomide), Synovir (Thalidomide), Thalidomide, Thalomid (Thalidomide), Velcade (Bortezomib),</p>

	Zoledronic Acid Zometa (Zoledronic Acid).
Waldenström macroglobulinemia	Fludara (fludarabine) and Leustatin (cladribine) first to try. Cytosan (cyclophosphamide) may be added. Other commonly used chemotherapy drugs are Luekeran (chlorambucil) and prednisone, usually given together, or Adriamycin (doxorubicin). Rituxan (rituximab). Campath (alemtuzumab) has also been an effective treatment, as has Velcade (bortezomib).
Langerhans' cell histiocytoses	Oral methotrexate (20 mg/m <sup>2</sup> ) weekly for 6 months or Oral thalidomide 50 mg to 200 mg nightly, with prednisone are taken for low risk disease or vinblastine IV and prednisone for patients with more complicated cases requiring radiation and surgery.
Acute Leukemias	
Acute lymphoblastic leukemia (ALL)	Abitrexate (Methotrexate), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Arranon (Nelarabine), Asparaginase Erwinia chrysanthemi, Cerubidine (Daunorubicin Hydrochloride), Clafen (Cyclophosphamide), Clofarabine, Clofarex (Clofarabine), Clolar (Clofarabine), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine), Cytosan (Cyclophosphamide), Dasatinib, Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Erwinaze Asparaginase Erwinia Chrysanthemi), Folex (Methotrexate), Folex PFS (Methotrexate), Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Imatinib Mesylate, Marqibo (Vincristine Sulfate Liposome), Methotrexate, Methotrexate LPF (Methorexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Nelarabine, Neosar (Cyclophosphamide), Oncaspar (Pegaspargase), Pegaspargase, Ponatinib Hydrochloride, Rubidomycin (Daunorubicin Hydrochloride), Sprycel (Dasatinib), Tarabine PFS (Cytarabine), Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, Vincristine Sulfate Liposome, Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone Alternating with Methotrexate and Cytarabine (Hyper-CVAD). Prednisone, Asparaginase, Vincristine, Daunorubicin, Cyclophosphamide, Cytarabine, Thioguanine, Mercaptopurine and Methotrexate (Hoelzer Regimen). Prednisone, Vincristine, Daunorubicin, and Asparaginase (PVDA).
Acute myeloblastic leukemia (AML)	Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Arsenic Trioxide, Cerubidine (Daunorubicin Hydrochloride), Clafen (Cyclophosphamide), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine), Cytosan (Cyclophosphamide), Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Neosar (Cyclophosphamide), Rubidomycin (Daunorubicin Hydrochloride), Tarabine PFS (Cytarabine), Trisenox (Arsenic Trioxide), Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, combination; ADE. Cytarabine and Daunorubicin (7 plus 3). Cytarabine and Idarubicin (7+3). Fludarabine, Cytarabine and Filgrastim (FLAG). High-Dose Cytarabine (HIDAC). High-Dose Cytarabine (HDAC) Plus Danorubicin.
Myelodysplastic syndromes	

Chronic myeloid leukemia (CML)	Bosulif (Bosutinib), Bosutinib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine) Cytoxan (Cyclophosphamide), Dasatinib, Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Imatinib Mesylate, Neosar (Cyclophosphamide), Nilotinib, Omacetaxine Mepesuccinate, Ponatinib Hydrochloride, Sprycel (Dasatinib), Synribo (Omacetaxine Mepesuccinate), Tarabine PFS (Cytarabine), Tassigna (Nilotinib)
Chronic lymphocytic leukemia (CLL)	Alemtuzumab, Ambochlorin (Chlorambucil), Ambochlorin (Chlorambucil), Arzerra (Ofatumumab), Bendamustine Hydrochloride, Campath (Alemtuzumab), Chlorambucil/Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Fludara (Fludarabine Phosphate), Fludarabine Phosphate, Leukeran (Chlorambucil), Linfovizin (Chlorambucil), Neosar (Cyclophosphamide), Ofatumumab Treanda (Bendamustine Hydrochloride), combinations Chlorambucil-Prednisone CVP. Cyclophosphamide, Fludarabine, and Rituximab (CFR, FCR). Cyclophosphamide, Vincristine and Prednisone. Lymphomas.
Meningeal Leukemia	Cytarabine, Cytosar-U (Cytarabine), Tarabine PFS (Cytarabine), Methotrexate
Hairy cell leukemia	Cladribine (2-chlorodeoxyadenosine, 2-CdA), Pentostatin
Polycythemia vera	Anagrelide (Agrylin), Ruxolitinib (Jakafi)
Lymphoma	
Hodgkin's lymphoma	Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Ambochlorin (Chlorambucil), Bleomycin (Bleomycin), Bleomycin, Brentuximab Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Dacarbazine, Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Leukeran (Chlorambucil), Linfovizin (Chlorambucil), Lomustine, Matulane (Procarbazine Hydrochloride), Neosar (Cyclophosphamide), Procarbazine Hydrochloride, Velban (Vinblastine Sulfate), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, combinations; ABVD, ABVE, ABVE-PC, BEACOPP, COPP, ICE, MOPP, STANFORD and VAMP. Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone (BEACOPP baseline and escalated). Doxorubicin, Bleomycin, Vinblastine and Dacarbazine (ABVD). Mechlorethamine, Vincristine, Procarbazine and Prednisone (MOPP). MOPP/ABVD and Selected MOPP/ABV(D) Hybrid Regimens. Mechlorethamine, Doxorubicin, Vinblastine, Vincristine, Bleomycin, Etoposide and Prednisone (Stanford V).
Non-Hodgkin's lymphoma	Abitrexate (Methotrexate), Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Ambochlorin (Chlorambucil), Arranon (Nelarabine), Bendamustine Hydrochloride, Bexxar (Tositumomab and Iodine I 131 Tositumomab), Bleomycin (Bleomycin), Bleomycin, Bortezomib, Brentuximab

	<p>Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Denileukin Diftitox, DepoCyt (Liposomal Cytarabine), Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Folex (Methotrexate), Folex PFS (Methotrexate), Folutyn (Pralatrexate), Ibritumomab Tiuxetan, Intron A (Recombinant Interferon Alfa-2b), Istodax (Romidepsin), Leukeran (Chlorambucil), Linfolizin (Chlorambucil), Liposomal Cytarabine, Matulane (Procarbazine Hydrochloride), Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Mozobil (Plerixafor), Nelarabine, Neosar (Cyclophosphamide), Ontak (Denileukin Diftitox), Plerixafor, Pralatrexate, Recombinant Interferon Alfa-2b, Rituxan (Rituximab), Rituximab, Romidepsin, Tositumomab and Iodine I 131 Tositumomab, Treanda (Bendamustine Hydrochloride), Velban (Vinblastine Sulfate), Velcade (Bortezomib), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, Vorinostat, Zevalin (Ibritumomab Tiuxetan), Zolinza (Vorinostat) and combinations CHOP, COPP, CVP, EPOCH, ICE, R-CHOP. Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP). Dexamethasone, Cytarabine and Cisplatin (DHAP). Etoposide, Prednisone, Vincristine, Cyclophosphamide and Doxorubicin (EPOCH). Etoposide, Methylprednisolone, Cytarabine and Cisplatin (ESHAP). Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone Alternating with Methotrexate and Cytarabine (Hyper-CVAD). Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP)</p>
Soft-tissue and bone sarcomas	Mesna uroprotection, Doxorubicin, Ifosfamide and Dacarbazine (MAID).
Osteosarcoma	<p>The most active single agent in OS include doxorubicin, 60 mg to 90 mg/m<sup>2</sup> (21% response rate); methotrexate 8g to 12 g/m<sup>2</sup> with leukovorin rescue (30% to 40%); cisplatin, 100 mg/m<sup>2</sup> (25%) and ifosfamide, 5 g to 10 g/m<sup>2</sup>. Cyclophosphamide, melphalan, mitomycin C and dacarbazine (DTIC) all have response rates of about 15%. Between 20% and 40% of patients with OS who undergo resection of pulmonary metastases are cured. Chondrosarcoma, fibrosarcoma, malignant giant cell tumors of bone, and malignant fibrous histiocytoma (MFH) are less responsive to chemotherapy and are generally treated as soft-tissue sarcomas. Cisplatin, Doxorubicin, and High-Dose Methotrexate. Doxorubicin and Cisplatin. Doxorubicin, Cisplatin, High-Dose Methotrexate and Ifosfamide.</p>
Ewing's sarcoma	<p>Initial treatment consists of vincristine, actinomycin D, cyclophosphamide and doxorubicin (VACA). Doxorubicin is the most effective single agent. Although higher and lower dose schedules exist, doses used in the Intergroup Ewing Sarcoma Study were vincristine, 1.5 mg/m<sup>2</sup>/week, weeks 1 to 6 and 8 to 13; actinomycin D, 0.15 mg/kg daily, days 1 to 5 every 12 weeks; cyclophosphamide, 500 mg/m<sup>2</sup>/week; and doxorubicin, 30 mg/m<sup>2</sup> daily, says 1 to 3 every 3 weeks. Radiotherapy of about 6000 cGy to the primary (begun during the fourth or fifth cycle of chemotherapy controls local disease in most</p>

	patients.
Soft-tissue sarcomas	Wide re-excision after local failure should be followed by 6600 cGy radiotherapy. Local control rate (90+%) and overall disease-free survival (60%) in limb-sparing surgery are similar to that after amputation or radical resection. The local failure rate where radiotherapy was not used was 30%. An initial dose of 5000 cGy in 200 cGy fractions should be delivered to the entire compartment and surgical field with at least a 5 cm margin. A boost to a shrinking field to the tumor bed with an additional 1000 cGy and 600 cGy more to the scar is also indicated, with sparing of one third of the circumference of the extremity, at least 2 cm to 4 cm on the forearm, or thigh, to prevent lymphedema. Despite advances in surgery and radiation therapy 40% to 60% of patients with high-grade tumors die of metastatic disease despite primary control. Single-agent doxorubicin has a response rate of 15% to 35%. A dose-response relationship has been observed with higher response rates at doses greater than 50 mg/m <sup>2</sup> every 3 weeks. Doxorubicin may be less cardiotoxic when administered by continuous infusion over 4 days. DTIC has a single agent response rate of 17%. An improved response rate of the combination of DTIC and doxorubicin has been noted. However nausea and vomiting is increased. Phase II trials of ifosfamide in previously treated patients yield response rates of 20% to 40%. A phase I and II study of combination of doxorubicin, ifosfamide and DTIC with mesna uroprotection in 56 patients yielded a response rate of 48% with 13% complete response. Cyclophosphamide, Vincristine, Doxorubicin and Dacarbazine (CYVADIC). Gemcitabine and Docetaxel (GD). Ifosfamide, Carboplatin and Etoposide (ICE).
Rhabdomyosarcoma (malignancy of the striated muscle)	Variations of the vincristine, actinomycin D, cyclophosphamide, and doxorubicin (VACA) chemotherapy regiment are used. Mesna, Doxorubicin, Ifosfamide and Dacarbazine (MAID).
Gastrointestinal sarcomas are generally leiomyosarcomas smooth muscle tumors	Response rates to chemotherapy appear equivalent to that of soft-tissue sarcomas in other locations. Mesna, Doxorubicin, Ifosfamide and Dacarbazine (MAID).
Gynecologic sarcomas	Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the treatment of choice for localized disease. Pre- or post operative radiotherapy decreases the local recurrence rate but does not affect survival and frequently precludes delivery of adequate doses of chemotherapy. Mesna, Doxorubicin, Ifosfamide and Dacarbazine (MAID).
Kaposi's sarcoma	Interferon-alfa was the first drug specifically approved for the <b>treatment of Kaposi's</b> . It is of particular interest because of its antiproliferative, antiviral (anti-HIV), antiangiogenic, and immune-modulating properties. Etoposide (VP-16) has been evaluated as both an oral and an intravenous treatment for KS. As an oral agent, VP-16 has been evaluated primarily in patients who have undergone prior treatment with multiple cytotoxic agents. When VP-16 is given

	<p>intravenously (150 mg/m<sup>2</sup> on days 1 to 3 every 4 weeks), high response rates (78%) have been reported in patients without prior treatment and with good prognosis (no history of opportunistic infection and no constitutional symptoms). In patients with KS of poor prognosis, bleomycin given intramuscularly (5 mg/day for 3 days) or as a 4-day continuous infusion (6 mg/m<sup>2</sup>/day) produced a 48% partial response rate. Results of a small, single-institution study in which bleomycin was given as a 72-hour infusion (20 mg/m<sup>2</sup>/day) to 17 patients indicated a partial response rate of 65%. Bleomycin toxicity appears to be acceptable, with neutropenia an infrequent complication. Doxorubicin (also known by its trade name Adriamycin) is a component of the most widely used combination regimen for HIV-associated KS. In one trial, however, weekly treatment with doxorubicin (25 mg/m<sup>2</sup>) in patients with AIDS-related KS achieved a partial response rate of only 10%. Alternating vincristine and vinblastine weekly achieves a response rate of 33%. Toxicity includes vincristine-induced neurotoxicity (which limits its usefulness as a single agent) and vinblastine-induced myelosuppression. Paclitaxel A partial response was reported in 13 of 20 patients (65%), with 5 of 6 patients with known pulmonary KS responding, as well as 6 previously treated patients with nonpulmonary KS achieving a partial response. In a second trial, of the 30 evaluable patients, 16 (53%) achieved a partial response. The time to response was short (median of three cycles of treatment). Dramatic improvement in symptomatic lymphedema was noted in 25 of 26 patients. Therapy was well tolerated. Two liposomal agents are currently approved for the treatment of KS: liposome-encapsulated daunorubicin (DaunoXome) and liposome-encapsulated doxorubicin (Doxil).</p>
Endocrine cancers	
<p>Thyroid cancer (papillary (80%), follicular (15%), Hürthle cell (6%), medullary (50% familial), anaplastic (7%) and other such as soft-tissue sarcomas, lymphomas, epidermoid carcinoma occur rarely as primary tumors of the thyroid, but the thyroid can serve as a site of metastasis from other sites).</p>	<p>The preferred initial therapy for metastatic thyroid cancer is Radioactive iodine (RAI) in full therapeutic doses. In preparation for therapy, thyroid replacement with T4 or T3 is discontinued, and after 4 to 6 weeks elapse and a hypothyroid state has been induced, tracer is administered to establish that the metastatic tumor does indeed concentrate RAU significantly. A 40% cure rate of patients with metastatic disease has been observed with RAI. The primary treatment of thyroid cancer is surgery. More extensive surgery is associated with better survival rates. Excellent control rates in the neck have been found using 200 cGy/fraction, five times a week, for 5 weeks, and doxorubicin 10mg/m<sup>2</sup> IV, 90 minutes before the first RT treatment and weekly thereafter. The optimal regimen is probably the combination of cisplatin (40 mg/m<sup>2</sup>) and doxorubicin (60 mg/m<sup>2</sup>) given every 3 weeks; in a randomized trial involving 84 evaluable patients, this combination yielded a somewhat higher response rate (26%) than doxorubicin alone (17%) and, perhaps more significantly, produced a number of patients with complete responses (12%) several of whom survived for more than 2 years.</p>
Adrenocortical tumors and pheochromocytoma	<p>The initial treatment of choice for adrenocortical tumors is surgical excision. Patients with Cushing's syndrome form an adrenal tumor should be assumed to have a suppressed pituitary-adrenal axis and</p>

s	<p>patients will need long-term glucorticoid replacement. Perioperative coverage is provided by hydrocortisone, 100 mg IV every 8 hours, on the day of operation. The daily dose is tapered gradually over the next 5 days to maintenance levels of cortisone acetate, 25 mg orally every morning and 12.5 orally every night. Patients with residual functional disease after surgery or who have recurrent or metastatic disease not amenable to surgical resection should be treated with mitotane (o,p'-DDD). The usual starting dose is 8 g to 10 g daily, although many patients discontinue to the side-effects. About 70% respond with decreased steroid secretion and in about 30% to 40% tumor size is reduced significantly. Nonresponders can be treated with teyrapone (750 mg orally every 4 hours) or aminoglutethamide (250 mg orally every 6 hours initially, with stepwise dose increase to a total of 2g/day or until dose-limiting side-effects occur). The cornerstone of treatment of pheochromocytoma is surgical resection. Seven to ten days before operation phenoxybenzamine, 10 mg to 20 mg three or four times a day, or prazosin, 2 mg to 5 mg orally twice a day, is instituted to induce alpha-adrenergic blockade. Beta blockade may also be required if arrhythmias are present during surgery. Metyrosin, 0.25 g to 1 g orally four times a day, can block catecholamine biosynthesis and is a useful adjunct. The combination of cyclophosphamide, 750 mg/m<sup>2</sup> IV on day 1; vincristine, 1.4 mg/m<sup>2</sup> IV on day 1; and dacarbazine, 600 mg/m<sup>2</sup> IV on days 1 and 2, given in 3 to 4 week treatment cycles has produced impressive anti-tumor effects in both tumor shrinkage and blood pressure control.</p>
Pancreatic endocrine tumors (Insulinomas, vipomas)	<p>Eighty percent of insulinomas are benign and are cured by surgical resection. Surgical resection is curative of vipomas. In acute severe Zollinger-Ellison syndrome, that arises from gastrinomas, continuous nasogastric suction should be started, fluid and electrolyte status should be monitored and replaced, as needed. IV H-2 blockers (e.g. cimetidine or ranitidine) should be started promptly, supplemented with anticholinergics. If acid secretion is kept at less than 20 mEq/hour, ulcer disease can usually be controlled. Ranitidine, 50 mg three to four times daily, will control most patients with Zollinger-Ellison syndrome. Some patients may require 50 mg IV four times daily. Once the patient is stabilized surgery can be performed. Resection of all functional tumor, defined as return of gastrin levels to normal with negative stimulatory tests, is possible in approximately 20% of patients. Long term therapy options for patients with Zollinger-Ellison syndrome include continued management with cimetidine or ranitidine and anticholinergics; elective total gastrectomy, and resection of the primary tumor. The majority of glucagon-producing tumors are malignant and most patients will have metastases at the time of diagnosis. Single agent chemotherapy activity, major tumor shrinkage, has been seen in 15% of those treated with doxorubicin, streptozocin, 5-fluourouracil (5-FU), etoposide (VP-16), and cyclophosphamide. In addition alpha-interferon has been shown to cause reduction in hormone production and in fewer patients, tumor masses. In general combination chemotherapy regimens have been based on streptozocin. In carcinoid</p>

	tumors no advantage was seen in combination therapy. In islet cell tumors response improved from 36% from streptozocin alone to 63% for 5-FU and streptozocin. If is reasonable to treat symptomatic patients and/or those with clearly progressing tumor with streptozocin, 500 mg/m <sup>2</sup> IV and 5-FU, 400 mg/m <sup>2</sup> IV, daily for 5 days, each cycle repeated in 5 weeks.
Carcinoid	Medical management of the carcinoid syndrome includes use of alpha- or beta adrenergic blockers (propranolol, phenoxybenzamine), antiserotonin agents (cyproheptadine), phenothiazines (chlorpromazine) and corticosteroids. Propranolol, a beta-blocking agent, has been reported to decrease the frequency and intensity of carcinoid-related flushing. The doses usually used are 10 mg, three times a day, given orally. Phenoxybenzamine, 20 mg/daily, has also been reported to decrease the frequency and severity of flushing and diarrhea. Cyproheptadine (Perictin), 4 mg to 8 mg four times daily, is useful in select patients. In patients with bronchial carcinoid, prednisone, 10 mg to 20 mg per day, has been of benefit. Diphenoxylate hydrochloride (Iomotil) one to two tablets two to four times per day, is useful in controlling diarrhea. If the tumor is malignant and has metastasized beyond the possibility of a surgical cure, medical management includes dietary changes such a smaller more frequent meals or increased carbohydrates, IV if needed, if 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 benzothiadiazine diuretic should be given with diazoxide. Propranolol and glucocorticoids have also been used.
Solid Tumors	Docetaxel and Capecitabine (DC). Docetaxel and Carboplatin (AUC=6)(DC). Docetaxel and Cisplatin (DP). Gemcitabine and Capecitabine. Irinotecan and Cisplatin (IP). Pemetrexed and Carboplatin (PC).
Tumors of Unknown Origin	Docetaxel and Cisplatin (DP)

Source: FDA, Hamilton '90: Table 39-1; Pg. 333, Solimando & Waddell '12, NCI '20

In theory even a single cancer cell remaining in the body after surgery may be sufficient for the cancer to start growing again. It is therefore very common to follow surgical treatment of cancer with some other type of treatment that is designed to kill any remaining cancer cells. The two most widely used **nonsurgical treatments** involve the use of X-rays and chemicals to kill cancer cells. The problem faced by nonsurgical treatment of cancer is to find a way to selectively kill cancer cells that kills cancer cells effectively and never kills or harms normal cells. A very effective way of interfering with the ability of cancer cells to divide is to damage their DNA. Another way of interfering with DNA is to actually block the copying process. In order to damage DNA molecules and stop cancer cells from proliferating patients with cancer are exposed to agents that are known to damage DNA, such as X-rays or chemicals, or sometimes both. The treatment of cancer with X-rays is called radiation therapy and the treatment of cancer with chemicals is called chemotherapy. For those with cancer, with immediate survival at stake, the benefits of cancer treatment far outweigh the slightly increased risk of another type of cancer in ten or twenty years.

**Chemotherapy** has been shown to greatly increase the cure of certain types of cancers. The most striking chemotherapeutic advances – drugs such as cisplatin, bleomycin and etoposide (and methotrexate) – have made testicular cancer, the most common malignancy in young men, also the most treatable. Today's anti-cancer drugs can produce cures even of the far advanced testicular cancer, remissions for prostate cancer and prolonged remissions and cures for bladder cancer patients. In 1941 hormone therapy was introduced for advanced prostate cancer. In the 1960s actinomycin D became a standard. Some 40 percent to 50 percent of patients responded while 10 percent achieved complete remission. By the mid-1970s the vinblastine and bleomycin were combined, increasing the proportion of patients who experienced response and remission. Clinical trials of cisplatin began in the early 1970s. In 1977 it was reported that a combination of cisplatin, vinblastine and bleomycin together with surgery after chemotherapy could achieve complete remissions in up to 85 percent of patients. For patients with a durable complete remission, doctors could eventually "cure" 70 to 80 percent of testicular cancer patients. In the 1970s and 1980s researchers developed a combination – methotrexate, vinblastine, adriamycin and cisplatin (MVAC) that would result in two-thirds of bladder cancer patients achieving remission. However, it produced only short term results and only 10 percent of bladder cancer patients were disease-free after five years. During the 1980s and 90s, less-toxic but equally effective drugs were studied. For testicular cancer, etoposide, replaced vinblastine and the regimen most often prescribed for testicular cancer today is etoposide and cisplatin with or without bleomycin. For bladder cancer, emcitabine + cisplatin was shown to be as effective as MVAC. Androgen-blocking Casodex and flutamide are now keystones in treating metastatic prostate cancer and chemotherapeutic combinations are showing early promise in hormone-resistant disease. In children drugs have boosted the cure rate of pediatric Wilm's tumor to 80 percent (Mooney '07: 41-44).

The immediate **side-effect** of these chemotherapeutic and radioactive agents on normal cells of the body that are also dividing is a far more serious problem. Cells are continually being replaced as they are lost from the surface of the skin and from the intestine and lungs and uterus and other places. Cells in the bone marrow are constantly dividing in order to make new red and white blood cells that have a very short life span in the bloodstream and must be continually replaced. When a person is treated for cancer with radiation therapy or chemotherapy these dividing bone marrow cells get into the same difficulty that cancer cells do, and many of them die. As a result fewer new red cells are made and that is why treatment for cancer often makes people feel very weak and tired. Similarly, the depletion of white cells compromises the immune system, and patients on chemotherapy or radiation therapy are much more prone to all sorts of infections. Although injury to the bone marrow is one of the more serious complications of cancer treatment any cells that are usually dividing are at risk. For example, the normal process of replacing cells in the intestines is interfered with and intestinal problems like nausea, vomiting, and diarrhea are common complications of chemotherapy. Another common complication is that the growth of cells in the hair follicles is affected resulting in a loss of hair. Chemicals used in cancer chemotherapy damage DNA or interfere with making new DNA. Those that damage DNA are alkylating agents, nitrosoureas, Cisplatin, bleomycin, Adriamycin, danorubicin, dactinomycin, plicamycin and mitomycin. Those that interfere with making new DNA are arabinosylcytosine (AraC), Hydroxyurea, 9-thioguanine, 6-mercaptopurine, 5-fluorouracil, and methotrexate (Friedberg '92: 115, 116).

**Hydrocortisone crème** cures coronavirus, aspergillosis and many precancerous conditions.

**Hormone therapy** is often used to treat hormone-sensitive cancer. Hormone therapy for cancer is also called endocrine therapy. Hormone therapies associated with menopause and aging seek

to increase the amount of certain hormones to compensate for age or disease related hormonal declines, or surgical removal of a cancerous endocrine gland. Hormone therapy, as a cancer treatment, either reduces the level of specific hormones in the body or alters the cancer's ability to use these hormones to grow and spread. Cancers that are most likely to be hormone-receptive include breast cancer, prostate cancer, ovarian cancer and endometrial cancer. Various drugs can alter the body's production of estrogen and testosterone. **Anti-hormone drugs**, such as tamoxifen (Nolvadex) and toremifene (Fareston) for breast cancer, and the anti-androgens flutamide (Eulexin) and bicalutamide (Cadodex) for prostate cancer, block cancer cell's ability to interact with the hormones that propel cancer growth without reducing the body's production of hormones. **Aromatase inhibitors** (AIs), such as letrozole (Femara), anastrozole (Arimidex) and exemestane (Aromasin), target enzymes that produce estrogen in postmenopausal women, thus reducing the amount of estrogen available to fuel tumors. Luteinizing hormone-releasing hormone (LH-RH) agonists and antagonists reduce the level of hormones in the body by altering the mechanisms in the brain that tell the body to produce hormones. LH-RH agonists include Leuprolide (Lupron, Viadure, Eligard) for prostate cancer, Goserelin (Zoladex) for breast and prostate cancers and Triptorelin (Trelstar) for ovarian and prostate cancers. One LH-RH antagonist currently approved for men with prostate cancer is abarelix (Plenaxis) that is also under investigation for use in women with breast cancer. Many women who've had surgery for breast cancer take tamoxifen only for five years because taking it for a longer period doesn't offer any further benefit and may actually increase the risk that cancer will recur (Mooney '07: 56-62).

A number of natural substances have been identified that block the proliferation of new blood vessels. One of the most potent **antiangiogenic** chemicals is thalidomide. Compounds like thalidomide operate by interfering with particular chemical signals – one called  $TGF\alpha$ , in particular, and these molecules are not only important for blood vessel formation but for other vital functions including the immune response. 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). In general, a gene cannot be directly inserted into a person's cell. It must be delivered to the cell using a carrier, or "vector" known as a **monoclonal antibody**. The vectors most commonly used in **gene therapy** are viruses. Viruses have a unique ability to recognize certain cells and insert their DNA into the cells. In some gene therapy clinical trials, cells from the patient's blood or bone marrow are removed and grown in the laboratory. The cells are exposed to the virus that is carrying the desired gene. The virus enters the cells and inserts the desired genes into the cells' DNA. The cells grow in the laboratory and are then returned to the patient by injection into vein. This type of gene therapy is called *ex vivo* because the cells are grown outside the body. The gene is transferred into the patient's cells while the cells are outside the patient's body. In other studies, vectors (often viruses) or liposomes (fatty particles) are used to deliver the desired gene to cells in the patient's body. This form of gene therapy is called *in vivo*, because the gene is transferred to cells inside the patient's body. Many gene therapy clinical trials rely on retroviruses to deliver the desired gene. Other viruses used as vectors include adenoviruses, adeno-associated viruses, lentiviruses, poxviruses and herpes viruses (Mooney '07: 50-55).

**Cancer vaccines** are the new cutting-edge treatment that trains the immune system to attack cancer cells. Although cancer vaccines are still being tested, and are not yet FDA approved, early studies show promise that cancer vaccines can be a viable treatment for certain types of cancer. Cancer is a term for more than 100 diseases characterized by the uncontrolled, abnormal growth of cells. The immune doesn't recognize cancer cells as foreign. Cancer vaccines try to

get the immune system to overcome its tolerance of cancer cells so that it can recognize them and attack them. In 1991 the first human cancer antigen was found in cells of a person with melanoma. The two main approaches for cancer vaccines are whole-cell vaccines and antigen vaccines. Whole-cell vaccines may take whole cancer cells from a patient or sometimes several patients, or use human tumor cell lines derived in a laboratory. Antigen vaccines try to trigger an immune response by using only certain antigens from cancer cells. One major strategy involves combining vaccines with additional substances called adjuvants, which act as chemical messengers that help T cells work better. An example of one type of adjuvant, called cytokine, is interleukin-2, a protein made by the body's immune system that can also be made in a lab. Cancer vaccines have shown promise in clinical trials with many types of cancer – skin cancer (melanoma, kidney cancer (renal cell), lymphoma, myeloma and solid tumors such as lung cancer. Less than 3 percent of U.S. adults with cancer participate in clinical trials (Mooney '07" 63-70). A number of natural substances have been identified that block the proliferation of new blood vessels. One of the most potent anti-angiogenic chemicals is thalidomide. Compounds like thalidomide operate by interfering with with particular chemical signals – one called TGF $\alpha$ , in particular, and these molecules are not only important for blood vessel formation but for other vital functions including the immune response. 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). NSAIDS however are known to irritate the intestine and quitting chronic consumption of them might reduce colon cancer risk. Stop consuming rat poison, it causes rectal bleeding first sensed as a slimy anus, and is the lead suspect in colon and rectal cancer.

A small percentage (around 1-5%) of patients with leukemia, Hodgkin's disease, ovarian and other cancers have developed so-called **secondary leukemias** or, less often, other cancers, that can be attributed to their prior therapeutic exposures. e.g oral Methotrexate is readily available online and may cause myelosuppression of the bone marrow. One of the most tragic examples of this is the very high accumulated or overall risk of breast cancer in women who received broad-field chest X-rays of Hodgkin's disease when they were aged between 13 and 16 years. The figure is around 40 percent, or 4 out of 10 exposed. Most of these women will have developed breast cancer 20 to 30 years after the initial mutational event. Marie Curie and her daughter Irene both died of radiation induced bone marrow failure. Marie Curie herself was so hot that her letters are radioactive to this day. By 1902, just seven years after Röntgens discovery of X-rays, it became clear that exposure caused not only painful erythema and dermatitis, but, in some individuals, malignant skin cancer. The widespread vogue for therapeutic and diagnostic use of radiation during the 1930s and 1950s did not appear to have appreciated the risk involved. Another tragic example of therapy begetting cancer is the relatively high frequency of lymphomas, some skin cancers, and cervical carcinomas in patients receiving immunosuppressive therapy – either as kidney or heart transplant recipients or for autoimmune diseases. In these instances, the greatly increased risk arises primarily as the consequence of common herpes or papilloma viruses. Skin cancer has been known to develop as an unintentional consequence of treating psoriasis with UV light plus photo-activated compounds (psaloran). The acute or single dose of gamma radiation received by those who developed leukemia as estimated, in units called Grays, to be from 1 to 4. This is approximately the same as some therapeutic doses in medicine but around 1000 times our natural environmental exposure level per year. A total body exposure to 5 Grays is usually lethal (Greaves '00: 206-208). Patients whose cancer was caused by radiation must not be treated with invariably lethal dose of radiation treatment.

Medicines are available to help deal with the complications of depletion of bone marrow cells and with other complications if they arise. In recent years an innovative approach to the problem of bone marrow damage during radiation therapy or chemotherapy has led to a new form of cancer treatment called **bone marrow transplantation**. In this treatment a person with cancer is given very high doses of chemicals – enough to kill more cancer cells than is possible with conventional radiation therapy. These high doses cause so much damage to the bone marrow that without some other treatment the marrow simply could not recover and the patient would be left with absolutely no blood cells. This problem is overcome by giving the patient a transfusion (transplant) of perfectly normal bone marrow. Ideally, the patient is given their own bone marrow cells back (autologous bone marrow transplant) by removing and storing marrow cells before the treatment. But sometimes this is not possible because the patient's marrow may already be seriously depleted of cells from radiation therapy or chemotherapy, and bone marrow cells are taken from someone else, a healthy donor (heterologous bone marrow transplant). Cells from the donor's marrow are able to seed in the patient and replenish bone marrow very effectively. The marrow of identical twins is exactly the same and are not rejected at all, and cells from a brother or sister are not as foreign as cells from an unrelated individual. So donors must be closely matched to the recipient. Bone marrow transplantation is especially well suited for cancer which affects cells in the marrow itself, such as leukemia. Massive destruction of the bone marrow by chemical treatment can effectively kill all the cancer cells and the person can then receive "new" marrow and be totally cured. The treatment of cancer by bone marrow transplantation is however very expensive. Some insurance carriers may consider bone marrow transplantation experimental and may not reimburse health care facilities the considerable cost of the treatment (Friedberg '92: 117, 118).

#### **Trends in the Five-Year Survival Rates of Certain Cancers 1960-2015**

Site	1960-63	1970-73	1975-77	1987-89	2009-2015
All types	39%	43%	49%	55%	69%
Brain and Nervous system			23	29	34
Breast	63	68	75	84	91
Colon	43	49	50	60	66
Rectum	38	45	48	58	69
Esophagus			5	9	21
Hodgkin lymphoma			72	79	89
Kidney and renal pelvis			50	57	76
Larynx			66	66	62
Leukemia	14	22	34	43	66
Liver and bile duct			3	5	20
Lung and bronchus	8	10	12	13	21
Melanoma	60	68	82	88	94
Myeloma			25	27	54
Non-Hodgkin			47	51	75

lymphoma					
Oral cavity and pharynx			53	54	68
Ovary			36	38	48
Pancreas			3	4	10
Prostate	50	63	68	83	99
Stomach			15	20	32
Testis	63	72	83	95	97
Thyroid			92	94	99
Urinary Bladder	53	61	72	79	78
Uterine cervix	58	64	69	70	69
Uterine corpus	73	81	87	82	83

Source: Friedberg '92: 141 In general survival rates for African-Americans are 5-10 percent lower. American Cancer Society Fact and Figures 2020. pg. 18

There are some types of cancer that can be completely cured in a high percentage of case. This includes cancers of the mouth, testicles and certain leukemias and lymphomas. It is not unusual for people to be apparently well for varying periods after treatment, a time called remission, only to relapse with the disease. It is possible to predict with a high degree of certainty that if one survives longer than the generally expected time for that type of cancer in the absence of further treatment, one can be considered to be cured, meaning that it is unlikely the cancer will ever return. There has been steady improvement in the five year relative survival rate for some of the commoner types of cancers that were diagnosed in the United States during five periods from 1960 to 1985. Between 1985 and 1988 the three-year survival rate for cases of lung cancer that were localized and treated by surgery was close to 70 percent. Stage 1 cancer of the breast has a five-year survival rate of about 80 percent. But this survival drops to 65 percent with stage 2 breast cancer, to 40 percent for stage 3 and to 10 percent with stage 4. Similarly cancer of the colon that is strictly localized, as in stages A and B, has a 74 percent three year survival rate. This drops to about 56 percent for stage C and to 15 percent with stage D. Similarly encouraging results have emerged for childhood cancer diagnosed before the age of 15 (Friedberg '92: 140, 141).

A major problem that affects the chances for a cure with cancer treatment is that cancer cells can become **resistant** to agents that are designed to kill them. New cancer cells do not always look or behave exactly as their parents do. One of the consequences of this instability is that cancer cells are able to change in ways that allow them to outwit efforts to kill them. When a chemical designed to kill cancer cells by damaging its DNA is injected or swallowed, it eventually passes into the bloodstream, as do all chemicals that are taken into the body. In order for the chemical to find the DNA in cells, the chemical must be transported to the interior of the cells. This requires work by protein machines in the cell, and once they have successfully transported the chemical into their interior, cells must do more work to actively prevent the chemical from leaking out and from being destroyed before it has had an opportunity to wreck the DNA. If only one such cell develops out of billions of cancer cells, that cell will now be resistant to the particular anticancer drug in use. It will continue to grow and divide and pretty soon will give rise to millions of new cancer cells that are unaffected by the anticancer drug being used. Some cancer treatment use two or even three different anticancer drugs in succession, or even at the

same time. And in some cases this strategy will result in a cure when a single drug did not (Friedberg '92: 149, 150).

The following strategies have been outlined for **improving cancer care**: Supportive decision-making. The cancer care system needs to support patients in making informed medical decisions that match their needs, values and preferences. Cancer care teams should provide patients and their families with understandable information about cancer prognosis and the benefits, harms and costs of treatments. Team-based cancer care. This requires a workforce that is adequately staffed, trained and coordinated. Evidence-based cancer care. Researchers should investigate the benefits and harms of various treatment options so doctors, patients and patients' families can be more informed when making treatment decisions. This information needs to include the impact of treatments on quality of life, symptoms and patients' overall experience with the disease. A "learning" information technology system. This is a system that can "learn" by enabling real-time analysis of data from cancer patients in a variety of care settings to improve knowledge and help guide medical decisions. Such a system should be developed by the federal government and professional medical groups. Accessible and affordable cancer care. Currently, access to cancer care can be difficult for the poor, racial and ethnic minorities, seniors, and those without health insurance. The federal government should develop a national strategy to provide accessible and affordable cancer care (Preidt '13).

**Precancerous conditions** should be swiftly treated. Treat coronavirus, *Aspergillus niger*, other mold allergy or mite infested area with hydrocortisone, eucalyptus, lavender or peppermint (HELP). The literature wants for rat poison to be as suspect as non-steroidal anti-inflammatory drugs (NSAIDs) for rectal bleeding. Metronidazole treats antibiotic resistant *Clostridium difficile* and *Helicobacter pylori*. Ampicillin (Principen) treats pneumonia, otitis, sinusitis and meningitis. Epsom salt, saline or chlorine pool or ocean bath treat methicillin resistant *Staphylococcus aureus* (MRSA) and painful, exercise debilitating and potentially genetically damaging, toxic shock syndrome with *Streptococcus spp.* Pneumovax is effective at preventing *S. pyogenes* and many pneumonias. **45, XO** occurs in 1:10,000 live-births, occurring frequently in first-trimester (Turner syndrome) is the leading cause of spontaneous abortions; associated primarily with unique somatic features; they have an enlarged clitoris and vestigial male gonads that are best surgically removed in adolescence to prevent cancer. 47, XYY; 47, XXY (**Klinefelter syndrome**) occurs in 1:900 live-births causing minimal somatic abnormalities; individuals with Klinefelter syndrome are characterized by a tall, eunuchoid habitus, sterility and small testes. 47, XXX and 47, XYY individuals do not usually exhibit somatic abnormalities but 47, XYY individuals may be tall and are often employed as soldiers and law enforcement officers, in dire need of a Bachelor degree, of unknown sexuality, or need for surgery, other than General George Washington was tall, married, childless, loved to execute deserters, and was the first President of the United States before he died. XXX individuals may carry two sets of female reproductive organs. XXY individuals may have vestigial gonads growing internally. XXX and XXY like to consider themselves women (Wright et al '03). An estimated 10% of the population consider themselves gay, lesbian, bisexual or transgender. Medicaid must stop paying for harmful cosmetic transgender hormone and surgical male-to female sex change operations. Medicaid and military health system must pay for the detection and removal of any precancerous vestigial internal gonads of 47, XYY, 47, XXY, 47, XXX and 45, XO pursuant to Sec. 1927 of the Social Security Act under 42USC§1396r-8 and 24USC§34.

The best approach to preventing and treating heart disease and cancer is the **tried-and-true combination** of exercise, eating a healthy (vegan) diet, weight control, not smoking and

undergoing appropriate cardiovascular health and cancer screenings (Mooney '07: 76). 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. 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).

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 **vegan diet** 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, multivitamins may be helpful. 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 cream-less) and probiotic yoghurt (Gerson '90: 139). When sustaining a vegan diet it is necessary to ensure excreted calcium is replaced with green leafy and cruciferous vegetables and there is enough phosphorus from mushrooms, soy and mung beans on a daily basis. Plain white rice is antidiarrheal, anti-emetic and nutritious, making complete proteins with beans should be avoided or minimized with an extra helping of fresh, steamed and boiled vegetables.

### **C. Carcinogens**

More than **900 chemicals** have been determined to be capable of inducing cancer in humans or animals after prolonged or excessive exposure by numerous agencies involved in the identification of carcinogens such as the International Agency for Research on Cancer (IARC), National Toxicology Program (NTP), Environmental Protection Agency (EPA) monitored by the American Cancer Society list of Known and Probable Human Carcinogens. There are many well-known examples of chemicals that can cause cancer in humans. The fumes of the metals cadmium, nickel, and chromium are known to cause lung cancer. Vinyl chloride causes liver sarcomas. Exposure to arsenic increases the risk of skin and lung cancer and Hodgkin's lymphoma. Leukemia can result from chemically induced changes in bone marrow from exposure to benzene and cyclophosphamide, among other toxicants. Other chemicals, including benzo[a]pyrene and ethylene dibromide, are considered by authoritative scientific organizations to be probably carcinogenic in humans because they are potent carcinogens in animals. Chemically-induced cancer generally develops many years after exposure to a toxic agent. A latency period of as much as thirty years has been observed between exposure to asbestos, for example, and incidence of lung cancer. New research continues to find additional human

carcinogens. During the decades ending in 1980, 1990, 2000, and 2010, respectively, there were 23, 27, 24, and 25 agents classified as carcinogenic to humans for the first time, and 11 more were so classified in Volume 100. Some designations of new carcinogens were not based on conclusions found first in the Monographs but reflected the expansion of the IARC program to include additional types of agent already known to be carcinogenic. For example, tobacco smoking and alcoholic beverages were evaluated for the first time during 1986–1988, biological agents during 1994–1997, and ionizing radiation during 2000–2001, many decades after these agents had been recognized as human carcinogens. The diversity of carcinogenic agents that have been identified more recently puts these “bursts” of new classifications in perspective. New carcinogenic agents from Volumes 90–99 have included 10 additional human papillomavirus types, estrogen–progestogen menopausal therapy, benzo[*a*]pyrene, indoor coal emissions, ethanol in alcoholic beverages, 1,3-butadiene, dyes metabolized to benzidine, 4,4'-methylenebis(2-chloroaniline), and *ortho*-toluidine. Except for indoor coal emissions and ethanol, which had not been evaluated before, these agents had been classified as probably carcinogenic or possibly carcinogenic, indicating that continued research on suspected carcinogens can lead to a more definitive classification (Cogliano et al '11).

### Cancer sites by carcinogen

Cancer site	Probable Carcinogen	Possible Carcinogen
Lip, oral cavity and pharynx		
Lip		Hydrochlorothiazide, Solar radiation
Oral cavity	Alcoholic beverages, Betel quid with tobacco, Betel quid without tobacco, Human papillomavirus type 16, tobacco smokeless, tobacco smoking	Human papillomavirus type 18
Salivary gland	X-radiation, gamma-radiation	Radioiodines, including iodine-131
Tonsil	Human papillomavirus type 16	
Pharynx	Alcoholic beverages, Betel quid with tobacco, Human papillomavirus type 16, Tobacco smoking	Asbestos (all forms), Opium (consumption of), Printing processes, Tobacco smoke, secondhand
Nasopharynx	Epstein-Barr virus, Formaldehyde, Salted fish, Chinese-style, Tobacco smoking, Wood dust	
Digestive tract, upper	Acetaldehyde associated with consumption of alcoholic beverages	
Digestive organs		
Esophagus	Acetaldehyde associated with consumption of alcoholic beverages, Alcoholic beverages, Betel quid with tobacco, Tobacco, smokeless, Tobacco smoking, X-	Dry cleaning, Mate drinking, hot, Opium (consumption of), Pickled vegetables (traditional Asian), Rubber production industry, Very hot beverages (squamous cell carcinoma)

	radiation, gamma-radiation	
Stomach	<i>Helicobacter pylori</i> , Rubber production industry, Tobacco smoking, X-radiation, gamma-radiation	Asbestos (all forms), Epstein-Barr virus, Lead compounds, inorganic, Nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation, Opium (consumption of), Pickled vegetables (traditioanal Asian), Processed meat (consumption of), Salted fish, Chinese-style
Colon and rectum	Alcoholic beverages, Processed meat (consumption of), Tobacco smoking, X-radiation, gamma-radiation	Asbestos (all forms), Night shift work, Red meat (consumption of), <i>Schistosoma japonicum</i>
Anus	Human immunodeficiency virus type 1, Human papillomavirus type 16	Human papillomavirus types 18, 33
Liver and bile duct	Aflatoxins, Alcoholic beverages, <i>Clonorchis sinensis</i> , 1,2-Dichloropropane, Estrogen-progestogen contraceptives, Hepatitis B virus, Hepatitis C virus, <i>Opisthorchis viverrini</i> , Plutonium, Thorium-232 and its decay products, Tobacco smoking (in smokers and in smokers' children), Vinyl Chloride	Androgenic (anabolic) steroids, Arsenic and inorganic arsenic compounds, Betel quid without tobacco, DDT, Dichloromethane ethylene chkoride), Human immunodeficiency virus type 1, <i>Schistosoma japonicum</i> , Trichloroethylene, X-radiation, gamma-radiation
Gall bladder	Thorium-232 and its decay products	
Pancreas	Tobacco, smokeless, Tobacco smoking	Alcoholic beverages, Opium (consumption of), Red meat (consumption of), Thorium-232 and its decay products
Digestive tract, unspecified		Radio-iodines, including Iodine-131
Respiratory organs		
Nasal cavity and paranasal sinus	Isopropyl alcohol production, Leather dust, Nickel compounds, Radium-226 and its decay products, Radium-228 and its decay products, Tobacco smoking, Wood dust	Carpentry and joinery, Chromium (VI) compounds, Formaldehyde, Textile manufacturing
Larynx	Acid mists, strong inorganic, Alcoholic beverages, Asbestos (all forms), Opium (consumption of), Tobacco smoking	Human papillomavirus type 16, Rubber production industry, Sulfur mustard, Tobacco smoke, secondhand
Lung	Acheson process, occupational	Acid mists, strong inorganic, Art

	<p>exposures associated, with, Aluminum production, Arsenic and inorganic arsenic compounds, Asbestos (all forms), Beryllium and beryllium compounds, Bis (chloromethyl) ether; chloromethyl methyl ether (technical grade), Cadmium and cadmium compounds, Chromium (VI) compounds, Coal, indoor emissions from household combustion, Coal gassification, Coal-tar pitch, Coke production, Engine exhaust, diesel, Haematite mining (underground), Iron and steel founding, MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture), Nickel compounds, Opium (consumption of), Outdoor air pollution, Painting, Particulate matter in outdoor air pollution, Plutonium, Radon-222 and its decay products, Rubber production industry, Silica dust, crystalline, Soot, Sulfur mustard, Tobacco smoke, secondhand, Tobacco smoking, Welding fumes, X-radiation, gamma-radiation</p>	<p>glass, glass containers and pressed ware (manufacture of), Benzene, Biomass fuel primarily wood), indoor emissions from household combustion of, Bitumens occupational exposure to oxidized bitumens and their emissions during roofing, Carbon electrode manufacture, alpha-Chlorinated toluenes and benzoyl chloride (combined exposures), Cobalt metal with tungsten carbide, Creosotes, Diazinon, Fibrous silicon carbide, Frying, emissions from high temperature, Hydrazine, Insecticides, non-arsenical, occupational exposures in spraying and application, Printing processes, 2,3,7,8-Tetrachlorodibenzo-para-dioxin</p>
Bone, skin and mesothelium, endothelium and soft tissue		
Bone	Plutonium, Radium-224 and its decay products, Radium-226 and its decay products, Radium-228 and its decay products, X-radiation, gamma-radiation	Radioiodines, including iodine-131
Skin (melanoma)	Solar radiation, Ultraviolet-emitting tanning devices, Polychlorinated biphenyls	
Skin (other malignant neoplasms)	Arsenic and inorganic arsenic compounds, Azathioprine, Coal-tar distillation, Coal-tar pitch, Cyclosporine, Methoxsalen plus ultraviolet A, Mineral oils, untreated or mildly treated, Shale oils, Solar radiation, Soot, X-	Creosotes, Human immunodeficiency virus type 1, Human papillomavirus types 5 and 8 (in patients with <i>epidermodysplasia verruciformis</i> ), Hydrochlorothiazide, Merkel cell polyomavirus (MCV), Nitrogen mustard, Petroleum refining,

	radiation, gamma-radiation	occupational exposures, Ultraviolet-emitting tanning devices
Mesothelium (pleura and peritoneum)	Asbestos (all forms) Erionite, Fluoro-edenite, Painting	
Endothelium (Kaposi sarcoma)	Human immunodeficiency virus type 1, Kaposi sarcoma herpes virus	
Soft tissue		Polychlorophenols or their sodium salts (combined exposures), Radioiodines, including iodine-131, 2,3,7,8-Tetrachlorodibenzo-paradioxin
Breast and female genital organs		
Breast	Alcoholic beverages, Diethylstilbestrol, Estrogen-progestogen contraceptives, estrogen-progestogen menopausal therapy, X-radiation gamma-radiation	Dieldrin, Digoxin, Estrogen menopausal therapy, Ethylene oxide, Night shift work, Polychlorinated biphenyls, Tobacco smoking
Vulva	Human papillomavirus type 16	Human immunodeficiency virus type 1, Human papillomavirus types 18, 33
Vagina	Diethylstilbestrol (exposure in utero), Human papillomavirus type 16	Human immunodeficiency virus type 1
Uterine cervix	Diethylstilbestrol (exposure in utero), Estrogen-progestogen contraceptives, Human-immunodeficiency virus type 1, Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Human papillomavirus types 26, 53, 66, 67, 68, 70, 73, 82
Endometrium	Estrogen menopausal therapy, Estrogen-progestogen menopausal therapy, Tamoxifen	Diethylstilbestrol
Ovary	Asbestos (all forms), Estrogen menopausal therapy, Tobacco smoking	Talc-based body powder (perineal use), X-radiation, gamma-radiation
Male Genital Organs		
Penis	Human papillomavirus type 16	Human immunodeficiency virus type 1, Human papillomavirus type 18
Prostate		Androgenic (anabolic) steroids,

		Arsenic and inorganic arsenic compounds, Cadmium and cadmium compounds, Firefighters, occupational exposure, Malathion, Night shift work, Red meat (consumption of), Rubber production industry, Thorium-232 and its decay products, X-radiation, gamma-radiation
Testis		DDT, Diethylstilbestrol (exposure in utero), <i>N-N</i> -Dimethylformamide, Firefighters, occupational exposure, Perfluorooctanoic acid
Urinary Tract		
Kidney	Tobacco smoking, Trichloroethylene, X-radiation, gamma-radiation	Arsenic and inorganic arsenic compounds, Cadmium and cadmium compounds, Perfluorooctanoic acid, Printing processes, Welding fumes
Renal pelvis and ureter	Aristolochic acid, plants containing, Phenacetin, Phenacetin, analgesic mixtures containing, Tobacco smoking	Aristolochic acid
Urinary bladder	Aluminum production, 4-Aminobiphenyl, Arsenic and inorganic arsenic compounds, Auramine production, Benzidine, Chlornaphazine, Cyclophosphamide, Magenta production, 2-Naphthylamine, Opium (consumption of), Painting, Rubber production industry, <i>Schistosoma haematobium</i> , Tobacco smoking, ortho-Toluidine, X-radiation, gamma-radiation	4-Chloro-ortho-toluidine, Coal-tar pitch, Dry cleaning, Engine exhaust, diesel, Hairdressers and barbers, occupational exposure, 2-Mercaptobenzothiazole, Pioglitazone, Printing processes, Soot, Tetrachloroethylene, Textile manufacturing
Central Nervous System		
Eye	Human immunodeficiency virus type 1, Ultraviolet emissions from welding, Ultraviolet-emitting tanning devices	Solar radiation
Brain and central nervous system	X-radiation, gamma-radiation, Vinyl chloride	Radio-frequency electromagnetic fields (including from wireless phones)
Endocrine glands		

Thyroid	Radio-iodines, including Iodine-131, X-radiation, gamma-radiation	
Lymphoid, hematopoietic, and related tissue		
Leukemia and/or lymphoma	Azathioprine, Benzene, Busulfan, 1,3-Butadiene, Chlorambucil, Cyclophosphamide, Cyclosporine, Epstein-Barr virus, Etoposide with cisplatin and bleomycin, Fission products, including Strontium-90, Formaldehyde, <i>Helicobacter pylori</i> , Hepatitis C virus, Human immunodeficiency virus type 1, Human T-cell lymphotropic virus type 1, Kaposi sarcoma herpes virus, Lindane, Melphalan, MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture), Pentachlorophenol, Phosphorus-32, Rubber production industry, Semustine (methyl-CCNU), Thiotepa, Thorium-232 and its decay products, Tobacco smoking, Treosulfan, X-radiation, gamma-radiation	Benzene, Bishloroethyl nitrosourea (BCNU), Chloramphenicol, DDT, Diazinon, Dichloromethane (Methylene-chloride), Ethylene oxide, Etoposide, Firefighters, occupational exposure, Glyphosate, Hepatitis B virus, Magnetic fields, extremely low frequency (childhood leukemia), Malaria (caused by infection <i>Plasmodium falciparum</i> in holoendemic areas), Malathion, Mitoxantrone, Nitrogen mustard, Painting (childhood leukemia from maternal exposure), Petroleum refining, occupational exposures, Polychlorinated biphenyls, Polychlorophenols or their sodium salts (combined exposures), Radio-iodines, including Iodine-131, Radon-222 and its decay products, Styrene, Teniposide, 2,3,7,8-Tetrachlorodibenzo-para-dioxin, Tobacco smoking (childhood leukemia in smokers' children), Trichloroethylene,
Multiple or unspecified sites		
Multiple sites (unspecified)	Cyclosporine, Fission products, including strontium-90, X-radiation, gamma-radiation (exposure in utero)	Chlorophenoxy herbicides, Plutonium
All cancer sites (combined)	2,3,7,8-Tetrachlorodibenzo-para-dioxin	

Source: International Agency for Research on Cancer. 9 October 2020

An exhaustive epidemiologic study on cancer submitted to the Congressional Office of Technology Assistance in 1981 estimated that tobacco was responsible for about 30 percent of all American cancers, diet was responsible for another 35 percent, infection perhaps 10 percent, reproductive and sexual behavior about 7 percent, occupational hazards about 5 percent, geophysical factors such as sunlight 3 percent, alcohol 3 percent, pollution 2 percent, medicine and medical practices 1 percent and food additives and industrial products less than 1 percent each (Lichter & Rothman '99: 61, 62). The American Cancer Society stresses, at least 42% of

newly diagnosed cancers in the US – about 750,000 cases in 2020 – are **potentially avoidable behavioral causes**, including the 19% of all cancers that are caused by **smoking** and the 18% of cancers are caused by a combination of excess body weight, alcohol consumption, poor nutrition, and **physical inactivity**. Certain cancers caused by infectious agents, such as human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Helicobacter pylori* (*H. pylori*), could be prevented through behavioral changes or vaccination to avoid the infection, or treatment of the infection. Many of the more than 5 million skin cancer cases that are diagnosed annually could be prevented by protecting skin from excessive sun exposure and not using indoor tanning devices (ACS '20). It is estimated: Around 15 percent of the total cancer burden worldwide can be linked to persistent infection with common **viruses** such as HPV, HBV, HCV, EBV, HHV8 and HTLV-1 (Greaves '00: 171-173, 168). **Dioxin**, from red meat, fish, and dairy products, may be responsible for 12 percent of human cancers in industrialized societies (Robbins '01: 42 143, 144). Adding all of this comes to 69 percent. 31 percent **other potentially treatable** occupational and accidental overexposure to carcinogens including the sun (6%), radiation, bacterial and fungal infections. Persons whose cancer was caused by **radiation exposure**, such as from the laser of a defective CD ROM or DVD drive, must not be treated with invariably lethal dose radiation treatment. Radiation treatment is also known to cause secondary cancers years later, that should probably not be treated with more radiation. Some sort of radiation test must be devised to determine whether a person is radioactive or their cancer was caused by radiation, to make radiation therapy safer.

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 (Robbins '01: 42 143, 144). 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. In light of the VA’s presumption for herbicide exposure underlying the Blue Water Navy Vietnam Veterans Act of 2019 Monsanto has sold Roundup to DuPont, and will hopefully stop its overuse and contractual abuse.

There is little question that exposure to high doses of cancer-causing agents (called **carcinogens**) increases cancer risk. One of the most dramatic examples was the discovery of a profound increase in the incidence of various types of cancer in people who were exposed to **radiation** from the atomic bomb explosions in Japan in World War II. Another dramatic example of the relationship between environmental carcinogens and cancer comes from detailed studies on **cigarette smokers**. The increased risk of lung cancer in smokers is anywhere from ten to fifty times higher than that of a nonsmoker. In the year 1990, more than 30 percent of the cancer related deaths in men, and more than 20 percent of the cancer related death in women in the

United States were from lung cancer. In Scotland during the period 1984 to 1986 more than 39 percent of the total cancer-related deaths in men were from lung cancer. Passive smoking, the inhalation of second hand cigarette smoke also increases lung cancer risk. Lung cancer has also been associated with exposure to **asbestos** in people who handle asbestos occupationally and numerous other examples of what we call occupational cancer – cancer for which there is a high risk due to particular kinds of exposure during work. Since 1930 lung cancer is the only common cancer for which the death rate has increased progressively, almost certainly because of cigarette smoking, but not all cigarette smokers get lung cancer, in fact nine out of ten don't and many people who never smoked a cigarette get lung cancer. **Mesothelioma** deaths from the asbestos fiasco are estimated to peak in 2020 (Friedberg '92: 50-55).

Known risk factors of **oropharyngeal cancer** include any form of tobacco use and alcohol consumption, with a synergistic relationship conferring a 30-fold increased risk for individuals who both smoke and drink heavily. HPV infection of the mouth and throat, believed to be transmitted through sexual contact, also increases risk. HPV vaccines have primarily been evaluated against genital diseases but will likely prevent most HPV-associated oral cancers as well. Unfortunately, immunization rates are much lower than for other disease-preventing vaccines, with only 51% of adolescents ages 13 to 17 years (49% of boys and 54% of girls) up to date with HPV vaccination in 2018 (ACS '20: 20). Native American women suffer high rates of **nasal cancer**, probably initiating in epithelia burned and contaminated by hot ashes blown back from a cooking fire. In 1761 in London, John Hill – doctor, botanist, and playwright – published a one-shilling pamphlet cautioning against the immoderate use of tobacco snuff. He described several cases of fatal polypuses of the nose or nasal carcinoma in men who were heavy, long-term users of snuff, and he proffered the following advice, "no man should venture upon snuff, who is not sure that he is not so far liable to cancer: and no man can be sure of that". At the beginning of the 20<sup>th</sup> century, an American clinician, Dr. R. Abe, provided compelling evidence that oral cancer was linked to tobacco exposure. The **oral cavity** is also the hot spot for cancers associated with some of the more exotic smoking styles developed in India and other parts of South East Asia. It is estimated that over 200 million people currently chew betel quid which is a mixture of betel leaf, areca nut, slaked lime, and usually, tobacco. Lethal lesions of the oral cavity are described in Indian medical texts from around 600 B.C. For **pipe smokers**, the lower lip appears to be more at risk than the upper, and it may be that the damage elicited by heat exacerbates the impact of tobacco carcinogens. For the traditional high tar **cigarette**, and particularly with inhalation, the major bronchial tracts incur the highest insult and consequent cancer rate (squamous bronchial carcinoma).

Tobacco use is a major contributor to the global burden of disease, responsible for about 25% of cancer deaths worldwide and more than half of all deaths among long-term tobacco users. Tobacco was responsible for more than 8 million deaths in 2017, including 1.2 million deaths from secondhand smoke exposure among nonsmokers. The Framework Convention on Tobacco Control (WHO FCTC), was unanimously adopted by the World Health Assembly in 2003 and subsequently became a legally binding accord for all ratifying states in 2005. Several major tobacco-producing nations, including Argentina, Indonesia, Malawi, and the United States, are among the few nations that have not yet ratified the treaty. Numerous federal, state, and local tobacco control policies have been enacted since the 1964 Surgeon General's Report on Smoking and Health, including laws to increase cigarette prices; improve cessation treatment; enforce worksite, bar, and restaurant smoking restrictions; improve health warnings; and restrict advertising. The prevalence of current cigarette smoking among US adults ages 18 and older declined from 42% in 1965 to 14% (more than 34 million adults) in 2018. From 1999 to 2018,

current cigarette smoking (past month) among US high school students decreased from 29% to 8%. Despite decades of declines in cigarette smoking prevalence, about 30% of all cancer deaths, and as much as 40% of those among men in some Southern states, are still caused by smoking cigarettes. This is partly because smoking rates remain high in many segments of the population. Tobacco use remains the leading preventable cause of death in the US. Cigarette smoking increases the risk of several cancers, including those of the oral cavity and pharynx, larynx, lung, esophagus, pancreas, uterine cervix, kidney, bladder, stomach, colorectum, liver; and acute myeloid leukemia. Smoking may also increase risk of fatal prostate cancer and a rare type of ovarian cancer. Health consequences increase with both duration and intensity of smoking. Smoking cessation reduces the risk of developing cancer and other smoking-related diseases, and also improves outcomes for cancer survivors. In 2018, 62% (55.0 million) of the 89.1 million Americans who had ever smoked at least 100 cigarettes were former smokers (ACS '20: 56, 42-47).

Almost 1 in 5 cancers is caused by excess body fat, alcohol consumption, poor nutrition, and a sedentary lifestyle. Aside from avoiding tobacco use that is attributed with causing 19% of cancers, maintaining a healthy weight and limiting alcohol consumption are the most effective strategies for reducing the risk of cancer. An estimated 18% of cancer cases are attributable to the combined effects of excess body weight, alcohol consumption, unhealthy diet, and physical inactivity, in addition tobacco use. An estimated 5% of cancers in men and 11% in women can be attributed to **excess body weight**. Excess body weight (i.e., being overweight or obese) is associated with an increased risk of developing several types of cancer: uterine corpus (endometrium), esophagus (adenocarcinoma), liver, stomach (gastric cardia), kidney (renal cell), brain (meningioma), multiple myeloma, pancreas, colorectum, gallbladder, ovary, female breast (postmenopausal), and thyroid. Excess body weight may also increase the risk of non-Hodgkin lymphoma (diffuse large B-cell lymphoma), male breast cancer, and fatal prostate cancer. Limited evidence suggests that excess body weight negatively impacts breast cancer survival. Evidence is growing about the adverse health consequences of cumulative exposure to excess body fat over the life course as a result of excessive weight gain that begins during childhood. Overweight prevalence among men (about 40%) and women (about 25%-30%) has remained relatively stable since the early 1960s. However, obesity prevalence has markedly increased; in 1960-1962, 11% of men and 16% of women were obese, and by 2015-2016, approximately 38% of men and 41% of women were obese. In 2015-2016, excess body fatness was prevalent in 26% of children ages 2-5 years; 34% of children ages 6-11 years; and 40% of adolescents ages 12-19 years (ACS '20: 50).

An estimated 6% of cancer cases can be attributed to **alcohol** consumption. Alcohol consumption increases risk for cancers of the mouth, pharynx, larynx, esophagus, liver, colorectum, female breast, and stomach. Cancer risk increases with alcohol volume, and even a few drinks per week may increase risk for some cancers. Alcohol consumption combined with tobacco use synergistically increases the risk of cancers of the mouth, pharynx, larynx, and esophagus far more than the additive effect of these exposures separately. Approximately 4% to 5% of all cancer cases and deaths can be attributed to **dietary factors**. Diet patterns high in red and processed meat, starchy foods, refined carbohydrates, and sugary drinks are associated with a higher risk of developing cancer (predominantly colon), whereas those with an emphasis on a variety of fruits and vegetables, whole grains, legumes, and fish or poultry and fewer red and processed meats are associated with lower risk. One study found that individuals who have the healthiest diet have an 11%-24% lower risk of cancer death than those with the least healthy diet. In addition, improving diet quality over time is associated with an overall reduced risk of death.

Evidence suggests that **type 2 diabetes** independently increases risk for several cancers, including liver, endometrium, pancreas, colorectum, kidney, bladder, breast, and perhaps ovary (ACS '20: 50, 51)..

An estimated 3% of cancer cases can be attributed to **physical inactivity**. Greater time spent in sedentary behavior may increase risk of other cancer types. **Physical activity** decreases the risk of colon (but not rectal), female breast, and endometrial cancers, as well as kidney, bladder, esophageal (adenocarcinoma), and stomach (cardia). These cancers are however describe those cancers which are most disabling. Cancer patients who are physically active are less likely to have adverse effects and to die from their cancer than those who are inactive. Even low amounts of physical activity appear to reduce cancer mortality. Extended leisure-time sitting has been associated with increased risk of cancer death, although 60-75 minutes per day of moderate-intensity activity may offset this excess risk (ACS '20: 51). Emphasis on maintaining an athletic level of physical exercise is necessary to encourage smokers, who are physically inactive by nature of their addiction, to perform cardiovascular exercise to redress lung cancer risk from the dangerous combination of cigarette smoking and physical inactivity. While exercise does not necessarily cure all precancerous conditions and carcinogenic exposures, it makes up for a lot of abuse. Where there is a way to pulmonary health, smokers are more likely to find the will-power it takes to stop smoking, if only while the clear their respiratory system by jogging.

A little over 200 years ago a British surgeon by the name of Percival Pott made the observation that many men with cancer of the skin or of the scrotum were chimney sweeps. The soot that accumulates in chimneys and in other places where coal is burnt contains very potent carcinogens. Some of the same carcinogens produced when tobacco is burned or automobile exhaust emissions. Shortly after Dr. Pott described his findings to a scientific organization in England the Danish chimney sweepers' guild heard about his study and urged its members to take frequent baths and within about twenty years a large drop in the incidence of scrotal cancer was noted in chimney sweeps in northern Europe compared to the incidence in England where they continued to bathe infrequently. The observations of Sir Percival Pott, the English surgeon who first noted the correlation between chimney sweeping and cancer of the scrotum nearly two hundred years ago, marked the beginning of the formal science of occupational carcinogenesis, the study of the relationship between cancer risk and the type of work one does. Occupational exposure to many chemicals and mixtures of chemicals such as benzene, chromium, tar, and nickel to mention a few, and to physical agents such as ionizing radiation (X-rays) and asbestos fibers, that come under the regulation of Occupational Safety and Health Administration (OSHA). Agents that pose a cancer hazard in the workplace are generally quite easily identified because many employees are likely to be affected. Identifying carcinogens in the home and lifestyle can be more of a problem because there are so many different variables to check out. Sometimes media reports of cancer clusters indicate an entire region is exposed to a peculiar carcinogen (Friedberg '92: 50-55, 100, 101).

Carcinogenic chemicals in the environment are thought to act by damaging the DNA in cells, resulting in permanent changes or mutations in the genes. Geographic incidence of cancer varies widely due to environmental exposures found in different locations and cultural lifestyles. During the three-year period 1984 to 1986 in Switzerland slightly more than 33 men per 100,000 died of prostatic cancer, compared with about 23 men per 100,000 in the United States. However, in Japan only about 5 men per 100,000 died of this disease. But when Japanese men immigrate to the United States their incidence of prostatic cancer rises. Cancer of the skin is two hundred times more common in Queensland, Australia than in Bombay, India due to different

levels of ultraviolet radiation from the sun that penetrate through the ozone layer in these two parts of the world, and the protection of having dark skin affords against skin cancer caused by sunlight. Cancer of the esophagus is three hundred times more common in northeast Iran than in Nigeria. Genetic factors may be partly responsible for this, but radioactive material in the soil is extremely high in northwest Iran. Even within a single country, such as the United States, the cancer death rates differ from one state to another. The total death rate for all types of cancer is highest in New York, Connecticut, Rhode Island and Massachusetts, and is lowest in Idaho, Wyoming and Utah (Friedberg '92: 103, 101, 102). In current Aborigine or hunter-gatherer societies, some individuals do live to be 70 to 90 years of age and estimates of age-associated cancer mortality in these groups are generally quite low or less than 10 percent. Migrant populations tend to acquire the differential cancer risk of the host country. 90 percent of cancers may have definable causes and be, in principle, preventable. These causes have been labeled as 'environmental', loosely translated to include pesticides, pollutant byproducts or petrochemical and nuclear industries (Greaves '00: 116, 117).

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 – chlorpyrifos, coumaphos, fonofos, phorate, permethrin and butylate. Risks were two to four times higher than among men who were 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).

The documented association of certain cancers with particular environmental situations is now a formal discipline in the study of cancer and is called **cancer epidemiology**. Although the industrial byproducts of man are highly suspect in the causation of cancer, the great majority of chemicals in the world (including carcinogens) do not come from factories, they exist naturally. Many of these chemicals evolved in plants precisely because they are poisonous to normal cellular processes. That's how a potato plant, (among many other plants and vegetables) protects itself from being eaten by insect predators. Natural pesticides present in vegetables are not only powerful carcinogens, but are present in far higher amounts than could possibly be achieved by the spraying of crops. In a typical diet 99.9 percent of the pesticides are natural and come from the fruit and vegetables eaten. 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. As life-forms that depend on oxygen humans have evolved a particular type of metabolism that produces waste products that are capable of causing cancer. The second important consideration about cancer is that in many instances there is no identifiable cause of

the disease. Cancer is extremely common, occurs in animals and did so before the evolution of humans (Friedberg '92: 55-57).

**Industrial dermatoses** are common. Sixty-five percent of all the industrial diseases are dermatoses. The patient with an average case of occupational dermatitis is compensated for 10 weeks, resulting in a total cost of over \$100 million a year in the United States. The most common cause of these skin problems is contact irritants, of which cutting oils are the worst offenders. Lack of adequate cleansing is a big contributing factor. **Atopic eczemas**, or atopic dermatitis, is a rather common, markedly pruritic, chronic skin condition that occurs in two clinical forms: infantile and adult. The clinical lesions in the infantile are form are blisters, oozing and crusting, with excoriation. Adolescent and adult forms marked dryness, thickening (lichenification), excoriation and even scarring. The course varies from a mild single episode to severe chronic, recurrent episodes. The family history is usually positive for one or more of the triad of allergic diseases: asthma, hay fever or atopic eczema. Wool and lanolin (wool fat) commonly irritate the skin of these patients. **Contact dermatitis**, or dermatitis venenata, is a very common inflammation of the skin caused by the exposure of the skin either to primary irritant substances, such as soaps, or to allergenic substances, such as poison ivy resin. The lesion can be of any stage, from mild redness, eczema, or vesicles to large bullae (blisters) with oozing. Crusting from secondary bacterial infection, excoriations, and lichenifications occur. Any agent can affect any area of the body, however, certain agents commonly affect certain skin areas. **Drug eruptions** are a common cause of dermatoses, and any patient with a rather generalized skin eruption should be questioned concerning the use of oral or parenteral drugs. Any drug systemically administered is capable of causing a skin eruption (Sauer '85: 69, 73, 75, 76) the list is too long to quote.

People who have an occupation involving a lot of washing, or an outdoor hobby such as car maintenance, gardening or fishing, often develop very uncomfortable dry hands with hacks on the fingertips known as **irritant dermatitis**. Regular use of hand cream will quickly restore the hands to normal, and will make dry, red, wrinkled hands feel more comfortable and also look much more attractive. Allergic dermatitis is much less common than irritant dermatitis, and often first appears in the twenties. In allergic contact dermatitis the body develops a specific allergic reaction against a substance that most people can handle with no problem. A good example is nickel, which is found in many of the materials handled all the time in the course of the working day. Cutlery contains nickel, even if it is labeled stainless steel, and it is in coins, spectacle frames, bicycle handlebars, front door keys, and most jewelry. However, about 10% of the population develop a sore, itchy rash when they handle nickel. Other common allergens are chrome, material used in curing or coloring leather, rubber and related chemicals, plants, e.g. *Primula obconica*, fragrances and preservatives used in creams and ointments. Patch tests involve putting a very small quantity of the material or materials most likely to cause allergic dermatitis on the back, in a specially designed type of dressing. This is removed after 48 hours, the area is examined, and is then inspected again 48 hours later (Mackie '92: 59-63).

**Hypersensitivity pneumonitis** or extrinsic allergic alveolitis, is often associated with specific professions. In these instances, animal, vegetable or bacterial enzyme material may induce the disease. For example, inhalation of *Thermoactinomyces vulgaris* or fungal spores of *Microsporium faeni*, which can contaminate hay, moldy sugar cane, or mushroom compost, have been causally related to farmer's (thresher's) lung, bagassosis, and mushroom-worker's lung. In a similar way, *Cryptostroma corticale* has been associated with maple bark disease of woodworkers, *Penicillium caseii* to cheeseworker's disease, *Aspergillus clavatus* and *A.*

*fumigatus* to brewer's lung disease. A regimen of environmental control and hyposensitization is normally prescribed for pollinosis. Currently, three basic drugs have preempted ephedrine for use in the control of asthmatic attacks: epinephrine (adrenalin) and its congeners administered by aerosol, the methylxanthines administered intravenously for acute attacks and orally for chronic asthma, and the steroids (cortisone), corticosteroids, for severe and intractable states, in combination with other drugs mentioned (Elvin-Lewis '77: 76, 77).

The Occupational Safety and Health Administration estimates that 11 million workers are exposed to some **200 substances** associated with occupational asthma, and about 15 percent of "disabling" cases of asthma are related to the workplace. The Americans with Disabilities Act (ADA) covers asthma and requires employers to take reasonable measures to accommodate employees with special health issues and disabilities (Berger '04: 228, 229). In 1985 as a direct result of the AIDS epidemic, health authorities implemented the use of universal health precautions to protect against transmission of HIV and hepatitis C. All health care and emergency workers began wearing protective gear, including surgical gloves, which are typically made from natural rubber, or latex. Today, it's estimated that more than 5.6 million American health care workers use more than 7 billion pairs of gloves each year. That has resulted in a significant increase in latex allergies, with an estimated 1 to 6 percent of the general population affected, and 5 to 10 percent of health care workers (Berger & Gordon '04: 260).

### **Work Related Causes of Pneumonitis and Asthma**

Farm workers	Organic phosphorus insecticides
Bakers, farmers, flour mill workers, and grain elevator workers	Flour and grain dust
Silk-processing workers, research laboratory workers, and insect-raising facility workers	Insects
Prawn, snow-crab and fish processors	Seafood and other marine organisms
Laboratory workers and animal handlers	Animal dander
Detergent producers, food industry workers, and blood-processing lab workers	Various enzymes
Carpet manufacturing workers, pharmaceutical industry workers, latex glove manufacturing workers, and health care workers	Latex and gums
Plastic, rubber or foam manufacturing workers; spray painters; foam insulation installers	Diisocyanates such as toluene, diphenylmethane, and hexamethylene
Solderers and electronics industry workers	Abietic acid, soldering fluxes
Woodworkers, foresters and artisans	Plicatic acid in Western red cedar wood dust

Refinery workers	Metals such as chromium, platinum and nickel
Textile workers	Dyes
Plastic and epoxy resin workers	Anhydrides, such as trimellitic and phthalic anhydride
Adhesive handlers	Acrylates
Health care workers	Glutaraldehyde and formaldehyde
Pharmaceutical industry workers	Certain pharmaceuticals
Toluene 2, 2-diisocyanate	Polyurethane synthesis

Source: Berger '04: 64, Bethel '89: 163

The **chronic form of hypersensitivity pneumonitis** may be extremely difficult to diagnose. Cough and dyspnea develop insidiously and are not directly related to specific episodes of antigenic challenge. Physical examination may show hyperexpansion, diminished breath sounds, hyper-resonance and rhonchi of COPD or the "Velcro" sounding rales of diffuse interstitial fibrosis. The chest radiograph usually demonstrates hyper-expansion with a generalized increase in interstitial markings, but may be easily mistaken for the picture of simple COPD. Pulmonary function testing in individuals with chronic forms of hypersensitivity pneumonitis is variable, with degrees of both restrictive and obstructive diseases. Lung volumes are usually diminished, although ratio of residual volume to total lung capacity may be elevated. The diffusion capacity for carbon monoxide (DLCO) is depressed). Lung biopsy of patients who have more acute forms of hypersensitivity pneumonitis demonstrate marked interstitial infiltration consisting of plasma cells, lymphocytes, and clumps of epithelial cells with scattered granulomas. Many foamy macrophages are seen within alveoli and terminal airways, and a terminal bronchiolitis may be present. In the chronic form of the disease there is nonspecific peribronchial fibrosis with some degree of centrilobular emphysema.

A suspected diagnosis of **hypersensitivity pneumonitis** may be confirmed by three immunologic procedures (1) an inhalation challenge with suspected antigens, however, it is rarely necessary and should be performed only by personnel familiar with the disease and capable of treating the potential severe pulmonary reactions that may ensue, (2) agar gel precipitation tests may be performed because more than 70% of patient sera contains precipitating antibodies. Generally, standard Ouchterlony double diffusion test is sufficient and (3) skin testing with the suspected antigen may elicit either a type III (Arthus) response or a dual response consisting of a type I response followed by the Arthus reaction in several hours. Delayed hypersensitivity skin reactions are not seen in these patients. In patients whose diagnosis remains uncertain an open lung biopsy is recommended. The only effective treatment hypersensitivity pneumonitis is complete avoidance of the offending antigen. Corticosteroids may dramatically abort the acute attack, with improvement seen as early as 1 or 2 hours following their administration. Treatment of the chronic forms of the disease is less successful and patients whose lungs have progressed to a state of centrilobular emphysema with interstitial fibrosis, even if further antigenic exposure is avoided, rarely improve even with corticosteroid therapy (Dreisin '89: 232-236).

**Tumor promoters** or initiators are certain chemicals that can increase the likelihood that a particular carcinogen will cause a cell to become cancerous, even though by itself that chemical is not a carcinogen. Essentially, they can turn a weak cancer-causing chemical into a much stronger one. Lifestyle factors in cancer, such as diet and alcohol consumption, act as tumor promoters rather than as carcinogens. Although pure ethanol does not cause damage to the DNA, or mutations, or cancer, the consumption of ethanol has been linked to liver cancer and breast cancer with studies showing that women who had between three and nine drinks a week had a 30 percent increased risk of breast cancer, and those who consumed more than nine drinks a week had a 60 percent increased risk of breast cancer. In general to reduce cancer risk, don't smoke, avoid a lot of sun, don't drink excessively, avoid eating or drinking synthetic chemicals whenever possible, eat a balanced diet, and get plenty of exercise and stay as fit as possible. Above and beyond do everything in moderation and avoid all excesses, particularly of **protein**.

The metabolic machinery is made up of **protein**. Every cell in the body has the ability to make every type of protein. However, although liver cells know how to make muscle cell proteins and bone cell proteins, they normally don't. Cells also manufacture different protein machines at different times in order to certain jobs that are only needed at a particular time. If one of these proteins is defective, the machine may become faulty or completely nonfunctional and when this happens to certain types of protein machines, cells can become cancerous. Cells follow strict instructions that specify the manufacture of individual proteins that are stored in the DNA. The DNA of every cell contains about fifty-thousand instructional units called genes. Each gene provides the instructions required to manufacture one protein in the cell. Every cell in the body has exactly the same amount of DNA and the same fifty thousand genes. Different types of cells use only the instructions in the particular set of genes for the particular set of proteins that they need. Protein machines determine when a cell should divide in two and when it should not. They specify that when a cell is surrounded by other cells it should respect their territory and should not invade their space. If for any reason these protein machines for normal cell growth do not function exactly the way they are supposed to, the growth of cells can become severely deranged. Such cells may now divide and increase in number and may start invading the territory of their neighbors. In normal cells DNA contains genes, and genes provide the instructions for making protein machines which in turn control the normal growth of cells (Friedberg '92: 108, 109, 60-63). Protein is the primary cancer growth factor and most cancer and heart patients, without access to 95% effective medicine, must exclude all intentional consumption of protein, including gluten (wheat protein), keeping protein consumption to the 5% of diet minimum, due to the accidental combination of vegetable amino acids the body uses to synthesize complete proteins.

Cancer **may or may not be contagious** and immunocompromised people should not take chances. In the early part of the nineteenth century, doctors and students at the Hospital St. Louis in Paris inoculated themselves with the discharges of ulcerating cancers without any dramatic consequences. In experiments that would today be regarded as unethical, US research, Chester Southam, showed in the 1960s that cancer cells are indeed rejected or rendered innocuous when deliberately injected into healthy volunteer. To quote: for this knowledge we are greatly indebted to the prisoners Ohio State Penitentiary who freely volunteered, without payment or special consideration of any kind, to serve as healthy recipients in this research. Southam also showed however, that transplanted cancer cells would grow, at least as nodules, if the recipient was a cancer patient himself and in an advanced state of illness (and presumably immunosuppressed). A similar cavalier experiment in the early 1960s did result in the propagation of cancer cells from one individuals to another. A melanoma sample from a

terminally ill 50 year-old woman was transplanted into the buttock of her 80 year old mother in, an attempt to understand cancer immunity. The mother was informed that the tumor from her daughter might grow and metastasize in her body but the investigators considered the risk of this occurrence very remote. The implanted melanoma biopsy was surgically removed after 24 days but too late to stop its spread, fifteen months later, the mother died of disseminated melanoma. Melanoma cells are particularly adept at metastasizing. The Cincinnati Transplant Tumor Registry, as of 1991, recorded some 72 patients, mostly kidney recipients, who developed either localized or metastatic cancer soon after transplantation or within three years of transplant (Greaves '00: 96, 97).

The great majority of cancers are not caused by any sort of **infectious agent**, so they are not contagious. However, in recent years it has become appreciated that certain cancers are clearly related to certain viruses. For instance, although HIV (human immunodeficiency virus) is not cancer itself, infected people have a significantly increased risk of getting cancer. There is also evidence that many cases of cancer of the cervix in women are caused by the papillomavirus, which can be transmitted by heterosexual activity. The virus also causes benign warts of the genitals of both men and women, but does not seem to be associated with genital cancer in men. Long before cells in the cervix become cancerous they undergo a premalignant change that can be detected by a Pap smear and when identified the abnormal cells can be removed by simple treatments (Friedberg '92: 82, 83). Around 15 percent of the total cancer burden worldwide can be linked to persistent infection with common viruses or other microbial invaders that are transmitted person to person. The links include; liver cancer (or hepatocarcinoma) with hepatitis B and C (HBV and HCV) Individuals with persistent HBV infection are some 200 times more likely to develop liver cancer than uninfected persons. Nasopharyngeal cancer (which is common in South East Asia and in smokers), and African Burkitt's lymphoma with Epstein Barr virus (EBV). Kaposi's sarcoma with a new human herpes virus (HHV8); and finally, a form of adult leukemia (common in southern Japan and the Caribbean basin) that is associated with an RNA virus or retrovirus called HTLV-1. In recent years, suspicion has been focused on the papilloma viruses. There are more than 100 types of human papilloma viruses (HPVs), several of which are linked to tumor or cancer development. HPV1 and 2 are associated with the common skin wart; HPV6, 10 and 11 with genital warts; and HPV5 and 8 with squamous cell carcinoma of the skin. Papilloma viruses 16 and 18 are now strongly implicated in cervical cancer, as well as cancers of the vulva, vagina, perianal region and penis. Over 95 percent and possibly all of the typical cervical squamous cell carcinomas are infected with HPV16 or 18, although in other parts of the world other papilloma viruses may be involved. These cancers may be preventable with prophylactic vaccination (Greaves '00: 171-173, 168).

It is now known that sexually transmitted diseases (STDs) such as the **Human Papilloma virus** (HPV) are present in most types of cervical and other reproductive organ cancers, STDs also contribute to other types of cancer. Since the late 1800s researchers have suspected that cervical cancer was sexually transmitted. Today, 15-20 types of HPV have been classified as oncogenic and the DHHS has added HPV to the list of cancer-causing agents. Large studies have found that HPV is present in more than 99 percent of cervical cancer tumors. HPV 16 and 18 are responsible for about 70 percent of cervical cancers. Other HPV types are associated with the remaining 30 percent of cases. Only one out of 1,000 women with HPV develops invasive cervical cancer. HPV appears to be necessary, but not sufficient, to the development of cervical cancer. Other cofactors are alcohol, smoking, diet, familial history, HIV infection, hormonal factors (multiple pregnancies and the use of both oral contraceptives and DES, low socioeconomic status, the presence of other sexually transmitted infections, such as chlamydia

and/or herpes simplex virus 2 and having an uncircumcised male partner. Certain high risk HPV types are also now considered to be a cause of many cancers of the vagina, vulva, anus and penis, which taken together outnumber cases of cervical cancer. The average age for diagnosis of these cancers is significantly later than for cervical cancer. The median age of diagnosis for vaginal cancer is 68 years and 69 years for vulvar cancer. Anal cancer is typically diagnosed at 63 years for women and 58 years for men, and the average age of diagnosis for cancer of the penis is 68 years. HPV 16 and 18 are the most often associated with vaginal, vulvar, anal and penile cancer. HPV is also associated with 20 percent (other studies go as high 100%) of oropharyngeal (primarily the tongue and tonsils) cancers and 90 percent of skin cancers in immunocompromised patients. Further research needs to be done to establish a causal relationship between HPV and other oral, head and neck cancers.(Mooney '07: 35, 36, 37). HPV is hypothesized to cause 100% of oropharyngeal cancers, but this theory almost certainly overlooks the Epstein-Barr virus, and common oral fungus *Candida*.

**Viruses** are not the only infectious microbes associated with cancer; animal parasites and bacteria are clearly implicated also. A very rare form of cancer seen in China that arises in the bile ducts has been associated with infection with the fluke parasite *Clonorchis sinensis*. Bladder cancer, in Egypt and some parts of Africa, has been linked with persistent exposure to schistosome (or *Bilharzia*) parasites in contaminated drinking water. A common stomach bacteria, *Helicobacter pylori*, is indicted for gastric lymphoma and stomach carcinomas. Remissions can be induced by antibiotics that kill the bacteria (Greaves '00: 171-173, 168). *E. coli* toxin is likely to be carcinogenic is best treated with metronidazole (Flagyl ER) and bottled water. **Fungus** is an obvious infectious cause of cancer, although it is typically left out of the literature and failure to diagnose and treat invasive pulmonary and extrapulmonary aspergillosis may be the reason for high death rates from lung cancer and other cancers of soft tissue and bone. The common infectious yeast *Candida albicans* sometimes, in severe infections, transmits its genetic code to human tissue forming human tissue tumors with antigen markers, that are usually benign after the *Candida* infection is treated with over-the-counter anticandidal remedies or prescription antifungals, but can flare up with every reinfection with *Candida* in that location and become malignant, usually squamous cell carcinomas. **Aspergillosis** is the most common and powerful carcinogenic agent, *Aspergillus* spp. mold produces carcinogenic aflatoxin B, best treated with topical hydrocortisone crème. Furthermore, methicillin resistant *Staphylococcus aureus* (MRSA) requires curative saline solution with a Epsom salt, ocean, chlorine or saline pool or jacuzzi, bath to prevent painful **toxic shock syndrome** in conjunction with common *Streptococcus* spp. treated with antibiotics. Penicillin, Ampicillin (Principen) to treat pneumonia, sinusitis and meningitis. Metronidazole (Flagyl ER) to treat gastrointestinal infections by antibiotic resistant *Clostridium difficile* and *Helicobacter pylori*.

Sunlight is essential for human well-being. The sun produces heat and illumination, and through plant photosynthesis, the food necessary for survival. The sun is also the primary source of vitamin D. Vitamin D is formed when UV light converts 7-dehydrocholesterol in the skin into vitamin D<sub>3</sub>. A protein in the skin then transports it to the blood and the liver for use. Sunlight contains radiation of many different wavelengths, from invisible low-frequency infrared heat radiation, through the visible light spectrum, to invisible ultraviolet rays. Shorter wavelength X-rays also form part of sunlight. The light rays of ultraviolet (UV) radiation are categorized into three different wavebands called A, B and C. The sun is the principal source of UV radiation. Outdoor workers have up to four times the total UV exposure of indoor workers. Reflection of UV rays is increased 25 percent by sand, and 5 percent by water. Reflection is lessened by cloud cover (20-90 percent) and the passage of light through water. It is unaffected by heat, cold, wind

and visible light. For the last few decades, scientists have been monitoring changes in the ozone layer – the protective layer of the stratosphere. The reduction of ozone levels has led to an increase in the levels of UVB rays reaching the earth. There are three forms of skin cancer related to sun exposure. Malignant melanoma is linked to sporadic but intense sun exposure, particularly sunburn in childhood. Squamous cell carcinoma and basal cell carcinoma are more treatable and are thought to be linked to more life-long low-grade exposure to UV radiation. Sunscreens contain organic chemical compounds that absorb UV radiation, and sunblocks contain finely ground particles that reflect UV rays away from the skin. All sunscreens are leveled with a sun protection factor (SPF) number that tells how long one can stay in the sun before burning. If burning would normally occur in 30 minutes, a 15 SPF will enable exposure to be prolonged 15 x 30 minutes. An SPF of less than 15 is not worth using. It is never a good idea to be on a beach during the peak sun hours of noon and 3 pm. The American Academy of Dermatology recommends never deliberately sunbathing. If spending more than 20 minutes in the sun sunscreen should be used (Davenport et al '03: 74-76). People over age 40 need to treat sun damaged skin with moisturizer.

**Ionizing radiation** is hazardous. Approximately one-half of all ionizing radiation currently received by individuals in the United States comes from natural background sources. These include: (a) cosmic rays; (b) naturally occurring elements in the earth such as uranium, thorium and radium, and (c) emission within the body from such isotopes as potassium-40 and carbon-14. These sources deliver about 80 millirems or ionizing radiation per year to a person living at sea level. Background does received may be approximately doubled at high altitudes, or where concentrations of radium in the ground are unusually high. Approximately 43% of all ionizing radiation is currently received from medical sources, largely from diagnostic X-rays. These result in an annual exposure of about 92/millirems/year (0.092 cGy; 1 millirem = 0.001 cGy) for the average United States citizen. Most other exposure is from mining and processing radioactive ores (2% to 3%), fallout from nuclear weapons (2% to 4%) and such consumer products as television sets, smoke detectors and relatively high levels of radiation are emitted by laser products such as DVD players and CD-ROM drives for computers (1% to 4%). The average person living at sea level in the United States thus receives about 180 millirems (0.18 cGy) of ionizing radiation per year. This is roughly equivalent to that received during an upper or lower gastrointestinal series. Mammography results in up to 3 times this amount of radiation to the breast, whereas only about 10 millirems (0.01 cGy) are received from a chest X-ray. It has been estimated that approximately 1% of all cancers in the United States may be attributable to irradiation from other than background sources (Thomas '86: 14, 15). As the safety limit, the National Academy of Sciences has recommended, that the average person receive not more than ten roentgens (8.696 cGy) of man-made radiation to the reproductive organs from conception to the age of 30. In recent years there has been an increasing awareness in the medical profession of the potential danger of radiation from X-ray treatments, and steps have been instituted to limit the radiation dose (Gerson '90: 87, 88).

### **Radiation Exposure Due to Medical Tests**

<b>Medical Tests</b>	<b>Effective Dose cGy</b>	<b>Medical Tests</b>	<b>Effective Dose cGy</b>
Television	0.005 per hour at 5 cm	CD-ROM Writer (laser disc writer)	0.05 – 0.5 per hour (if sabotaged)
Radiographs X-rays	0.0004 (dental bitewing) – 0.083 (pelvis, hips)	Coronary angiogram	0.46 – 1.58

Intravenous pyelogram 6 films of kidneys	0.25	Mammogram	0.013
Barium	swallow 0.15, meal 0.3, follow-up 0.3, enema 0.7	Nuclear Medicine scan	0.15 – 1.70
Computed tomography (CT) scan	Head 0.2, chest 0.8, abdomen 1, pelvis 1, head and chest 1.1	Annual dose allowed radiation workers	5
Thallium cardiac stress test	0.75 – 5.7	Detectable health effect on annual basis, vomiting if exposed in one dose.	10

Source: 1 milliSievert = 0.1 cGy

A small percentage (around 1-5%) of patients with leukemia, Hodgkin's disease, ovarian and other cancers have developed so-called secondary leukemias or, less often, other cancers, that can be attributed to their prior therapeutic exposures. One of the most tragic examples of this is the very high accumulated or overall risk of breast cancer in women who received broad-field chest X-rays when they were aged between 13 and 16 years. The figure is around 40 percent, or 4 out of 10 exposed. Most of these women will have developed breast cancer 20 to 30 years after the initial mutational event. Marie Curie and her daughter Irene both died of radiation induced bone marrow failure. Marie Curie herself was so hot that her letters are radioactive to this day. By 1902, just seven years after Röntgen's discovery of X-rays, it became clear that exposure caused not only painful erythema and dermatitis, but, in some individuals, malignant skin cancer. The widespread vogue for therapeutic and diagnostic use of radiation during the 1930s and 1950s did not appear to have appreciated the risk involved. Skin cancer has been known to develop as an unintentional consequence of treating psoriasis with UV light plus photoactivated compounds (psoralen). The acute or single dose of gamma radiation received by those who developed leukemia as estimated, in units called Grays, to be from 1 to 4. This is approximately the same as some therapeutic doses in medicine but around 1000 times our natural environmental exposure level per year. A total body exposure to 5 Grays is usually lethal (Greaves '00: 206-208).

As the safety limit, the National Academy of Sciences has recommended, that the average person receive not more than ten roentgens (equivalent to 8.77 cGy (centiGray) or 0.087 Gray), of man-made radiation to the reproductive organs from conception to the age of 30. The roentgen is a unit measurement of radiation dose. One roentgen of air kerma deposits 0.00877 gray (0.877 rad = 0.877 centiGray cGy commonly used to describe radiation therapy) of absorbed dose in dry air, or 0.0096 gray (0.96 rad) in soft tissue. One roentgen (air kerma) of X-rays may deposit anywhere from 0.01 to more than 0.04 gray (1 to 4 cGy) in bone depending on the beam energy (Gerson '90: 87, 88). The primary worry about radiation therapy is that concealed in the confusing radiation metrics is the fact that the normal therapeutic dose of about 5,000 cGy in 500 cGy fractions delivered to a specific area is ten times higher than the 500 cGy lethal whole body dose. Patients whose cancer is likely to have been caused by radiation poisoning, including probable occupational exposures, such as due to defective lasers in DVD players and CD-ROM drives on computers, are highly discouraged from exposing themselves to yet another potentially lethal dose of radiation in attempt to treat their radiation caused cancer.

Acute **radiodermatitis** is divided into three degrees of severity. The first degree is manifested by the slow development of erythema, hyperpigmentation and usually hair loss. A single dose of x-rays necessary to produce these changes is called an "erythema dose". All of the changes in the first degree are reversible. The second degree is characterized by vesicle formation, erosions, hair loss, secondary infection and delayed healing. Atrophic and telangiectasis are the end results. The third degree of radio-dermatitis includes ulceration, infection and greatly delayed healing. Epitheliomatous changes are very common in the chronic ulcer or scar. Chronic radiation dermatitis can follow acute radiation injury or develop slowly, following repeated small radiation exposures. The dosage of ionizing radiation on the skin is cumulative; the effects of previous radiation therapy is never erased by the passage of time. When a complete course of radiation therapy has been given to a particular body area, no further radiation should be administered to this area at any future time. Acute cases of radio-dermatitis can be treated symptomatically with bland local measures (Sauer '85: 279-282).

The effects on the mucosal membranes in the oral cavity, esophagus and gastrointestinal tract are similar to that of the skin but occur in half the time and the mucosa is rapidly covered with a whitish membrane. High-dose irradiation of the salivary glands may cause decreased salivation, and the saliva thickens, the resulting xerostomia can cause dental caries and periodontal problems years after treatment. Dysphagia and odynophagia are frequently noticed in patients who receive irradiation of the mediastinum due to epithelitis of the esophagus, that may occasionally lead to necrosis and stenosis. The mucosa of the small bowel is very radiosensitive and very early changes occur in the basal cells of the crypts of Liberkun between the villi. Overproduction of mucus, hyperemia and edema may lead to diarrhea with malnutrition and cachexia. Sometimes progressive obstruction and ulceration may result. If a surgical procedure precedes abdominal or pelvic irradiation, it may increase the risk of complication. The liver and kidneys are relatively radiosensitive organs. The whole liver may tolerate a dose of 2500 cGy in standard fractionation. Radiation hepatitis appears a few months following the irradiation, and include hepatomegaly, ascites, pain, jaundice and weight gain. The tolerance dose of the kidney is 2000 cGy. Irradiation of the testis can diminish their size. The spermatozoa completely disappear between 4 and 8 weeks after radiation. Sterilization may be temporary or permanent, depending on the total dose. Irradiation of ovaries in younger women may cause arrest of menstruation and development of menopausal symptoms, including hot flashes, sweating and anxiety.

Acute radiation pneumonitis usually begins 4 to 6 weeks following treatment and is limited to the area of the treatment field. Symptoms may present as fever, cough, bloody sputum, chills and malaise. Late irradiation fibrosis of the lungs may occur 3 months to a year after treatment and is often asymptomatic. Irradiation of the eye often results in conjunctivitis, with or without ulceration or permanent opacity, depending on the dose. Interstitial keratitis can also occur. There is a 50% incidence of cataract formation with doses of 750 to 1000 cGy delivered in 3 weeks to 3 months. Most of these cataracts can be avoided by adequately blocking the lens out of the field of treatment. Radiation cataracts can easily be removed surgically, but often no treatment is necessary. One of the most serious complications of irradiation is spinal cord injury. The tolerance of the spinal cord is often quoted as 4500 cGy delivered over 4 ½ to 5 weeks. At lower doses, a transient myelopathy may develop with a resultant feeling of electric current or "pins and needles" down the spine into the lower extremities. This usually subsides by may herald transverse myelitis, which is irreversible. Many medications, including "over the counter" preparations will potentiate or mask radiation reactions, wherefore during the course of radiation

therapy incidental medication should be prescribed by the radiation oncologist on call (Ahuja '86: 266-268).

#### **D. Cost**

Another major issue is the cost of cancer care, which increased from \$72 billion in 2004 to \$125 billion in 2010. At the current rate, it will increase another 39 percent to \$173 billion by 2020 (Preidt '13). The Agency for Healthcare Research and Quality estimates that cancer-related direct medical costs in the US in 2015 were \$80.2 billion, with 52% of those costs resulting from hospital outpatient or office-based provider visits and 38% from inpatient hospital stays (ACS '20). A number of studies demonstrate that individuals with cancer are at higher risk of experiencing financial difficulty than are individuals without cancer (Guy et al '15). Cancer is one of the most costly medical conditions to treat in the United States (Soni et al '16). Cancer patients can receive multiple types of treatment, including surgery, radiation therapy, and systemic treatment. Historically, inpatient hospitalizations have been the major drivers of the costs of cancer care. Compared to a decade ago, cancer patients are receiving increasingly expensive chemotherapy and biologics, both alone and in combination (Shih et al '15). The list price of newly introduced systemic therapies and supportive drug-based treatments is growing (Conti et al '15), and prices of both infusion and oral drugs continue to increase after product launch. Prices higher than \$10,000 a month for individual drugs and biologic agents are common (Shi et al '17)(Gordon et al '18).

A number of terms have been used to describe the financial impact of cancer, its treatment, and the lasting effects of treatment, including financial distress, financial stress, financial hardship, financial toxicity, financial burden, economic burden, and economic hardship (Tucker-Seeley et al '16). In a nationally representative sample, recently diagnosed cancer survivors aged 18 to 64 years reported \$1,107 annual in out-of-pocket spending, compared with \$747 annually for previously diagnosed cancer survivors and \$617 annually for those without a cancer history (all in 2010 dollars) (Guy et al '13). In a study of long-term breast cancer survivors, 18% paid \$2,100 to less than \$5,000 in out-of-pocket expenses, and 17% paid more than \$5,000 (Jagsi et al '14). In a study conducted using the nationally representative Medical Expenditure Panel Survey (MEPS), 4.3% of cancer survivors aged 18 to 64 years reported high out-of-pocket burden compared with 3.4% of those without a cancer history (Guy et al '15). In a study using the nationally representative Medicare Current Beneficiary Survey, 28% of cancer survivors reported high out-of-pocket burden compared with 16% of those without a cancer history. Approximately 84% of the Medicare beneficiaries were aged 65 years and older (Davidoff et al '13).

Material financial hardship (defined as bankruptcy, loans, debt, inability to pay for care, or making other financial sacrifices) was more common among cancer survivors younger than 65 years compared with those 65 years and older (28.4% vs. 13.8% (Yabroff et al '16). In a study of 4,719 adult cancer survivors aged 18 to 64 years who completed the 2012 Livestrong survey, debt and bankruptcy were higher among survivors aged 45 to 54 years and aged 18 to 44 years compared with survivors aged 55 to 64 years (Banages et al '16). Research from the Childhood Cancer Survivor Study found that adult survivors of childhood cancers were more likely to spend at least 10% of their annual incomes on out-of-pocket medical costs than their siblings (10.2% vs. 2.9% (Nipp et al '17). Financial hardship among younger patients, however, may not solely result from higher out-of-pocket spending for cancer care. In a study using data from the 2001–2008 MEPS, a higher proportion of individuals aged 55 to 64 years reported spending 20% or

more of their incomes on health care and premiums relative to younger individuals aged 18 to 39 years (10.1% vs. 7.1%)

In one study of non-elderly cancer patients (ages 18–64 years) identified from the 2012 Livestrong survey, income between \$41,000 and \$80,000 and income of \$40,000 or below were both associated with increased risk of borrowing money or going into debt compared with income of \$81,000 and higher. Other studies have shown increased risk of financial hardship among individuals with household incomes below thresholds of \$50,000 or \$20,000 (Chino et al '14). Several studies have shown that working age cancer patients experience loss of work, difficulty in returning to work, declines in income, and general loss of productivity as a result of cancer diagnoses (Dowling et al ;13). Change in employment after diagnosis (switching to part-time work and taking extended leave) was associated with a substantially increased risk of material financial hardship compared with no change (49.1% vs. 20.2%; In the Medicare population, access to supplemental insurance and Medicare Part D plans has helped shield patients from some of the out-of-pocket cost burden. In an analysis of data from MEPS 2002–2010, outpatient prescription costs for adults older than 65 years decreased by 43% after the introduction of Medicare Part D, while younger patients (not yet Medicare-eligible) did not experience a similar decline in out-of-pocket expenditures for prescription drugs over the same period (Kircher et al '14). The influence of type of insurance plan on the risk of financial hardship among younger patients (i.e., younger than 65 years) has not been thoroughly explored. One study found that patients with public insurance (Medicaid or Medicare) have an increased risk of financial hardship compared with patients who have private insurance (Banegas et al '16). However, having public health insurance may also be associated with fewer savings and assets and, therefore, increased financial vulnerability

To cope with expenses, cancer survivors have reported decreasing spending on leisure activities, food, clothing, and utilities; selling stocks, investments, possessions, or property; and changing housing. Studies of cancer survivors have suggested that between 33% and 80% of the survivors have used savings to finance medical expenses, and between 2% and 34% have borrowed money to pay for their care or have medical debt (Zafar et al '13). In a study of women with breast cancer, self-reported debt varied by race and ethnicity, with 27.1% of white, 58.9% of black, 33.5% of Latina, and 28.8% of Asian women reporting treatment-related debt (Jagsi et al '18). In a study of colon cancer survivors in Washington state, the mean debt among the survivors with debt was \$26,860 (in 2009 dollars) (Shankaran et al '12). In a longitudinal survey of 281 terminally ill cancer patients, 29% reported using most or all of their household's financial savings because of illness (Tucker -Seeley et al '15).

A study of 2,108 patients from the 2010 National Health Interview Survey (NHIS) found that individuals who responded a lot (8.6%) to the survey question: To what degree cancer causes financial problems for you and your family? were more likely to report the following when compared with those who reported no financial burden: Poor physical health 18.6% vs. 4.3%. Poor mental health 8.3% vs. 1.8%. Poor satisfaction with social activities and relationships 11.8% vs. 3.6% (Fenn et al '14). One cross-sectional study, using the Livestrong 2012 survey data of 4,719 cancer survivors, reported that 63.8% of the survivors had worried about paying large bills related to cancer, 33.6% had gone into debt, 3.1% had filed for bankruptcy, and 39.7% had to make other kinds of financial sacrifices because of their cancer, its treatment, or the lasting effects of treatment. Of those who reported going into debt, 9.1% had filed for bankruptcy, 55% incurred debt that totaled \$10,000 or more, and 68% had to make other kinds of financial sacrifices because of the costs associated with their cancer care. Furthermore, this

study found that an increased likelihood of filing for bankruptcy was associated with the following characteristics of cancer patients: Younger age (adjusted OR, 18–44 years, 1.81; adjusted OR, 45–54 years, 1.86; vs. 55–64 years). Lower household income (adjusted OR, ≤\$40,000, 4.50; adjusted OR, \$41,000–\$80,000, 2.80; vs. ≥\$80,000). Public health insurance (adjusted OR, 1.82; vs. private health insurance) (Banegas et al '16).

An estimated 1.7% of cancer survivors filed for bankruptcy in the 5 years after diagnosis. Cancer survivors were 2.7 times more likely to file for bankruptcy than individuals without a cancer history (Ramsey et al '13). Others have reported a prevalence of bankruptcy ranging from 1.2% to 3% of the study populations of cancer survivors (Yabroff et al '16). Younger individuals may be particularly vulnerable to financial hardships because of a lack of savings and assets, as well as competing financial obligations (e.g., children). Moreover, younger survivors lack the protection of Medicare coverage, placing some without insurance or with high-deductible health plans at risk of financial toxicity. In a study of bankruptcy rates among western Washington residents with and without cancer, bankruptcy rates were highest among both cancer survivors and non-cancer controls aged 20 to 34 years (10.06 and 3.15 per 1,000 person-years, respectively) and lowest among survivors and controls aged 80 to 90 years (0.94 and 0.57 per 1,000 person-years, respectively) (Ramsey et al '13). In one retrospective cohort study of cancer patients who filed for bankruptcy compared with those who did not according to data in the western Washington SEER Cancer Registry, filing for bankruptcy was associated with an increased risk of mortality adjusted HR, 1.79. Prostate cancer (adjusted HR, 2.07) and colorectal cancer adjusted HR, 2.47 patients had the highest hazard ratios (Ramsey et al '18).

The probability of being employed among persons reporting a cancer diagnosis decreased 9 percentage points 3 years from the date of diagnosis, with no recovery for those alive in years 4 and 5. During this time, survivors' labor market earnings dropped by up to 40%. Family income dropped by 20% during this time but recovered by year 4 (Zajacova et al '15). Another analysis reported that, among the employed, those receiving cancer care missed 22.3 more workdays per year than individuals without any cancer treatment (Finkelstein et al '15). An estimated productivity loss for adult survivors of adolescent and young adult cancers was \$4,564 compared with \$2,314 for adults without a cancer history (in 2011 dollars) (Guy et al '14). Employed cancer survivors reported cancer interfered with physical tasks (25%) and mental tasks (14%) required by their jobs (Ekwueme et al '14).

Commercial insurers in the United States are shifting more direct medical care costs to patients through higher premiums, deductibles, and coinsurance and copayment rates. The 2016 Commonwealth Fund Biennial Health Insurance Survey indicated that 33% of insured adults aged 19 to 64 years had medical bill problems or accrued medical debt. Oral cancer drug-based treatments are frequently covered under patient pharmacy benefits' specialty tier, requiring high coinsurance that patients pay out of pocket. High cost-sharing plans, including tiered outpatient prescription formularies (i.e., copays that escalate depending on whether the drug is generic or branded, and by price) may be particularly troublesome for patients with cancer who are prescribed expensive oral chemotherapeutics. The proportion of health care plans with multitiered (>3) prescription formularies, in which expensive oral specialty drugs are associated with the highest cost sharing, is reported to have increased from 3% in 2004 to nearly 88% in 2017 by the 2017 Employee Health Benefits Survey. When compared with individuals without a cancer history, cancer survivors have higher out-of-pocket costs, even many years after initial diagnosis, reflecting ongoing cancer care and care for any late or lasting treatment effects. In addition, cancer survivors are more likely to report being unable to work because of their health,

including more missed work days or additional days spent in bed because of poor health (Guy et al '15).

Adult cancer survivors were significantly more likely to have chronic conditions, including heart disease, diabetes, asthma, and arthritis, than were adults without a cancer history. They were also more likely to have multiple chronic conditions. Cancer survivors who had multiple chronic conditions were more likely to be limited in their ability to work compared with cancer survivors without these other conditions. Among cancer survivors, those with four or more chronic conditions had annual productivity loss of \$9,099, \$7,224–\$10,973) compared with those without any additional chronic conditions (in 2013 dollars) Guy et al '17). Receipt of cancer-directed treatment and the presence of other comorbidities were also found to be associated with higher out-of-pocket spending in the Medicare population. In a study using data from the Medicare Current Beneficiary Survey linked to Medicare claims (1997–2007), 2-year mean out-of-pocket spending was higher by \$1,526 among patients receiving chemotherapy and \$1,470 among patients receiving radiation therapy compared with patients who did not receive treatment (Davidoff et al '13).

A cross-sectional study using data from the 2011 to 2014 National Health Interview Survey found that nonelderly individuals with a recent or previous cancer diagnosis were more likely to report changing their prescription drug use (e.g., not filling prescriptions or skipping doses) for financial reasons than those individuals without a history of cancer (Zheng et al '17). Another study examined the association between imatinib copayment and medication adherence among patients with chronic myeloid leukemia, from 2002 to 2011, using MarketScan health plan claims. Over the study period, monthly copayments for imatinib ranged from \$0 to \$4,792, with a mean and median of \$108 and \$30, respectively. Patients in the highest quantile of monthly copayments for imatinib (mean, \$53) compared with those patients in the lowest quantile (mean = \$17) had a statistically significant adjusted risk ratio (RR) of 1.70 for discontinuing imatinib during the first 180 days of treatment (Dusetzina et al '14). Other studies examined the association between copayment amounts for adjuvant endocrine therapy, aromatase inhibitors (AIs), and tamoxifen and noncompliance in women with breast cancer. Studies have been relatively consistent in showing that at the highest levels of copayment, cancer patients become less likely to take cancer-related medications on a daily basis (nonadherence), or they discontinue their medications over the long term (nonpersistence of use). Reduced adherence to cancer medications may be worse when the total out-of-pocket cost of all prescription drugs taken by the patient is considered (Kim et al '18). A cross-sectional cohort study of 10,508 patients for whom oral chemotherapy was initiated between 2007 and 2009 examined the association between prescription abandonment rates and cost sharing. Abandonment was defined as a paid prescription claim gap of more than 90 days. An adjusted analysis found that claims with cost sharing of \$251 to \$350 had 2.3 times the likelihood of abandonment; \$351 to \$500 had 3.28 times the likelihood of abandonment; and more than \$500 had 4.46 times the likelihood of abandonment, when compared with cost sharing of \$100 or less (Streeter et al '11).

Although many individual risk factors for financial hardship have been identified, the evidence that demonstrates the degree to which these factors contribute to the risk of later financial hardship is insufficient, as is information about the interplay between these factors and clinical factors at the time of diagnosis. Specific areas in need of further study to address their influence on the risk of financial distress after a cancer diagnosis include: Preexisting debt. Prediagnosis conditions (i.e., overall comorbidity burden and the presence of specific illnesses). Types of employment (e.g., hourly vs. salaried). Asset levels. Because ample evidence exists that

financial distress occurs even among patients with health insurance, the role that forms of insurance play in protecting individuals from financial distress requires further study. Medicare may at least partially protect older persons from financial harm; however, in addition to this universal benefit for persons older than 65 years, other factors that are associated with older age might also reduce the risk of financial distress, namely, retired adults typically have higher levels of assets (e.g., owning a home outright), pensions or retirement accounts as sources of income, and Social Security. Another factor is that physicians may treat older patients less intensively and thus less expensively. For adults of working age, characteristics of work-sponsored or individually purchased commercial insurance that vary from plan to plan—specifically, deductibles, copay levels, and coverage exclusions—may influence the risk of financial distress. These factors also warrant further study. After patients are diagnosed with cancer and miss work during treatment, their ability to continue to work or return to work greatly influences their future risk of financial hardship. Studies are needed that relate particular treatments, modalities of treatment (e.g., infusional therapy vs. oral therapy), and toxicities of treatments with work absenteeism, loss of productivity, and likelihood of returning to the workforce (PDQ '20).

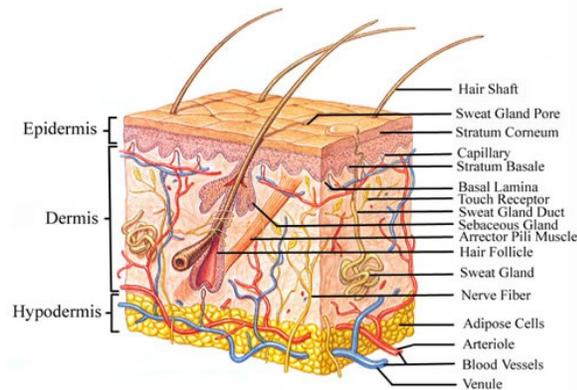
Implementation of the U.S. Affordable Care Act in 2008 provided a *natural experiment* to determine whether expanding access to health insurance for millions of Americans had an impact on rates of financial distress or insolvency for persons with cancer. Proposed pilots for different Medicare payment systems may also offer opportunities for quasi-experimental approaches that compare implementation with nonimplementation (CMS '16). The United States has the highest level of health spending in the world, between 16-18% of GDP. The ACA cost more than the ignored American Health Insurance Program (AHIP) proposal, did not provide Medicare for All, nor Medicaid Prices for All. Hyperinflation in the unacceptably high cost of the Affordable Care Act is not affordable to either Treasury or consumer. The hyperinflation in premiums is unacceptable. The Treasury cannot afford the subsidies. The 2020 Annual Report of the Federal Old Age Survivor Insurance Trust Fund and Federal Disability Insurance Trust Fund at pg. 87 reports that the under age 65 death rate after steadily declined from 750 per 100,00 in 1940 to 248.5 per 100,000 in 2010 when the ACA was passed. Subsequently, although the sky-high over age 65 death rate continued to steadily decline to an estimated 4,432 per 100,000 in 2018, the under age 65 death rate began to increase. In 2011 the under age 65 death rate increased to 249.2 per 100,000. In 2012 it decreased to 248.8 per 100,000, still more than in 2010, before the ACA. Subsequently, the under age 65 death rate increased to 249.6 per 100,000 in 2013, 251.7 in 2014, 255.2 in 2015, 260.8 in 2016, 261.5 in 2017. In 2018, after the tax penalty was reduced to zero, the death rate declined to 255.8 and in 2019 to 255.3. The estimated reduction to 254.3 in 2020 is overruled pending release of COVID-19 fatalities. The under age 65 death rate of 255.3 per 100,000 in 2019 is 2.7 percent higher than 2010. This is an unacceptable outcome for the ACA. The increase in working age death rate under the ACA justifies the the exercise of the grave power of annulling an Act of Congress pursuant to *United States v. Gainey*, 380 U.S. 63, 65 (1965).

Financial navigators are being used in community and academic settings to help cancer patients avoid adverse financial consequences after a cancer diagnosis (Conti et al '14). Looking at price transparency and provider behavior, one controlled study found that providing clinicians with information about test costs in electronic medical record order-entry forms reduced the number of tests ordered compared with not providing this information (Newcomer et al '14). By providing millions of previously uninsured Americans with health insurance, the Massachusetts health insurance plan and the U.S. Affordable Care Act have presented an opportunity for natural pre-post experiments for health care policies that are aimed at reducing the financial exposure of

an individual during severe illness. Because insurance appears to mitigate rather than eliminate the risk of financial distress from a cancer diagnosis and treatment, other interventions aimed at improving financial outcomes for insured persons are likely needed. Reducing and/or eliminating patient copayment/coinsurance for *pathway*-adherent cancer care in the fee-for-service Medicare program and/or commercial plans would also likely act to reduce patient and family burden across multiple treatment modalities—radiation, drugs, inpatient and outpatient coinsurance, and copayments (Kline et al '15). Another set of policies would eliminate the ban on pharmaceutical manufacturer-provided couponing and other patient-assistance programs to Medicare beneficiaries (Howard '14).

## I. Histology

### 1. Skin



The **skin is the largest organ** in the body, and it fulfills many vital functions. It forms a protective barrier between the body and the environment and plays an important role in the immune system by detecting infections. It helps regulate the body's temperature, preventing overheating by sweating and it protect against damage from ultraviolet (UV) radiation. As a sensory organ, the skin helps discern conditions in the outside world – temperature, texture, vibrations – and is a medium for social and sexual communication (Davenport et al '03: 8).

Skin is composed of three layers: the epidermis, the dermis, and the subcutaneous tissue (hypodermis) (Greaves '00: 175). The skin is composed of tissue that grows, differentiates and renews itself constantly. Since the skin is a barrier between the internal organs and the external environment, it is uniquely subjected to noxious external agents and is also a sensitive reflection of internal disease. The skin is divided into three rather distinct layers. From inside out, they are the subcutaneous tissue, the dermis and the epidermis. The **epidermis** is nonvascular and varies in thickness from 0.04 mm on the eyelid to 1.6 mm on the palms. In decreasing number, the four types of cells in the epidermis are: keratinocytes, melanocytes, Langerhans cells, and Merkel cells. Beneath the epidermis is the **dermis** (Corium), which has two layers. Anatomically, the corium can be divided into papillary (upper) and reticular (lower) layers. The papillary layer is superficial, and the reticular layer is deeper. Collagen constitutes approximately 70% of the dry weight of the dermis. Elastic fibers which give skin its elastic properties, constitute approximately 1%. The reticular layer merges with the subcutaneous fascia at its deepest aspect (Tran, Turk & Baldwin '04: 355). The dermis has a rich blood and nerve supply. The sebaceous glands and the shorter hair follicles originate in the dermis. The **subcutaneous tissue**, is a layer that serves as a receptacle for the formation and the storage of fat, is a locus of highly dynamic lipid metabolism, and supports the blood vessels and the nerves that pass for the tissues beneath to the dermis above. The deeper hair follicles and the sweat glands originate in this layer.

The skin, hair and nails develop early in the life of the embryo: the **basal layer** of the epidermis begins to develop just four weeks after conception. By seven weeks, flat cells overlying the basal layer form the **periderm**, which is cast off at about 24 weeks and replaced by more complicated

double-layered structure of the epidermis and dermis. The function of the periderm is not wholly understood, but it is probably concerned with the absorption of nutrients. Nails start to take shape 10 weeks after conception. The dermis (**mesoderm**) develops at 11 weeks and by 12 weeks, indented basal buds of the epidermis form the hair bulbs, with dermal papillae supplying vessels and nerves to the epidermal structures. By 17 weeks, fingerprint ridges are determined and sebaceous glands are becoming active under the influence of maternal hormones that cross the placenta. This sebaceous activity continues until a baby is about six months old, then it tapers off until puberty (Davenport et al '03: 9).

The **connective tissue** consists of collagen fibers, elastic fibers, and reticular fibers. All of these, but most importantly the collagen fibers, contribute to the support and the elasticity of the skin. The collagenous fibers are made up of eosinophilic acellular proteins responsible for nearly a fourth of overall protein mass. These fibrils are composed of covalently cross-linked and overlapping units called tropocollagen molecules. When tannic acid or the salts of heavy metals, such as dichromates, are combined with collagen, the result is leather. Elastic fibers are thinner than most collagen fibers and are entwined among them. They are composed of the protein elastin. Elastic fibers do not readily take up acid or basic stains such as hematoxylin and eosin, but they can be stained with Verhoeff's stain. Reticular fibers are thought to be immature collagen fibers, since their physical and chemical properties similar. They can be stained with silver (Foots stain). Reticulum fibers are sparse in normal skin but are abundant in certain pathological conditions of the skin such as the granulomas of tuberculosis, syphilis, and sarcoidosis, and in the mesodermal tumors such as histiocytomas, sarcomas and lymphomas (Sauer '85: 2).

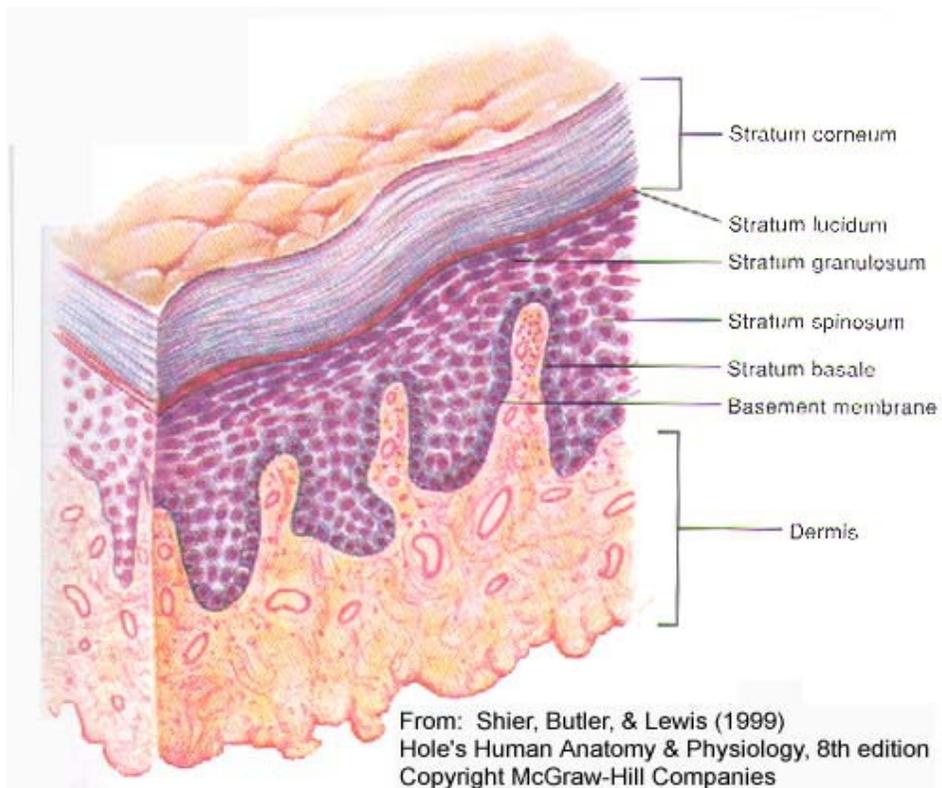
The **epidermis** is the most superficial of the three layers of the skin and average skin thickness about the width of the mark of a sharp pencil, or less than 1 mm. There are two distinct types of cells in the epidermis, the keratinocytes and the dendritic cells, or clear cells. The **keratinocytes**, or keratin-forming cells, are found in the basal layer and give rise to all other the other cells of the stratified epidermis. The **dendritic cells** are of three types: (1) melanocytes (melanin-forming cells), (2) Langerhans cells, and (3) indeterminate dendritic cells. The epidermis is divided into five layers. From inside out, they include the following: the living layers (1) basal layer, (2) prickle layer, (3) granular layer, (4) lucid layer, and (5) horny layer – the dead end product.

The **basal layer** of cells lies next to the corium and contains both keratin-forming and melanin forming cells. The basal layer cells are shaped like upturned bricks. They are anchored to a basement membrane from which threads extend down to anchor the membrane to the upper dermis. The keratin-forming cells can be thought of as stem cells, which are capable of progressive differentiation into the cell forms higher up in the epidermis. It normally requires 3 or 4 weeks for the epidermis to replicate itself by the process of division and differentiation. This cell turnover is greatly accelerated in such diseases as *psoriasis* and *ichthyosiform erythroderma*. The melanin-forming cells, or melanocytes, are sandwiched between the more numerous keratin-forming cells in the basal layer. Melanin pigmentation in the skin, whether increased or decreased, is influenced by many local and systemic factors. The melanocyte-stimulating hormone from the pituitary is the most potent melanizing agent.

The **prickle layer**, or stratum malpighii, is made up of several layers of epidermal cells, chiefly of polyhedral shape. The prickle cell layer is composed mainly of keratinocytes packed closely together. This layer gets its name from the existence of a network of cytoplasmic threads called

prickles, or intercellular bridges, that extend between the cells. These prickles are most readily visible in this layer, but, to a lesser extent are present between all the cells of the epidermis. The third layer is the **granular layer**. Here the cells are flatter and contain protein granules called keratohyaline granules. The granular layer is made up of flattened keratinocytes that contain not only granules of the protein keratohyaline but also lamellar granules that produce a "cement" that binds the cells together. The **lucid layer** is next and appears as a translucent line of flat cells. This layer of the skin is present only on the palms and the soles. The granular and the lucid layers make up the transitional layer of the epidermis and act as a barrier to the inward transfer of noxious substances and outward loss of water. The outermost layer of the epidermis is the horny layer. The **horny layer** (stratum corneum) sits above the granular layer. By now the cells are flattened, with no nuclei or granules. The cells of the horny layer overlap each other like tiles, with the edges stuck together with a fatty "cement" ideal for waterproofing purposes. The horny layer varies in thickness according to the region of the body, it is thickest on the soles of the feet. It is made up of stratified layers of dead keratinized cells that are constantly shedding. The chemical protein in these cells - keratin – is capable of absorbing vast amounts of water. This is readily seen during bathing, when the skin of the palms and the soles becomes white and swollen. The normal **oral mucous membrane** does not have any granular layer of horny layer (Sauer '85: 3, 4).

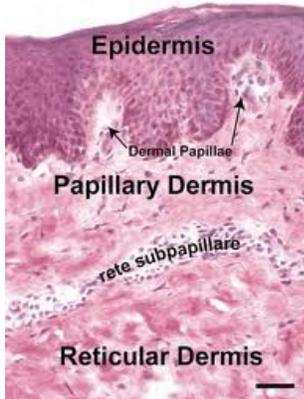
### Epidermis



The **epidermis** renews itself constantly by cell division in its deepest layer, the basal layer. Keratinocyte cells produced by division of the basal player are pushed toward the surface to become, in turn, the prickly cell layer, the granular level, and the horny layer, also called the stratum corneum, where they die. As the cells ascend toward the surface, they alter in structure and function. The time it takes for cells to pass from the basal cell layer to the horny layer is about 14 days. It takes another 14 days or so for cells in the horny layer to die and be rubbed off

by daily wear and tear. The epidermis varies in depth from 5 cells to 30 cells, depending on the part of the body. The thickness of the skin at any one part of the body always remains constant – the cells lost at the skin surface are balanced by the new skin cells produced in the basal layer. Complex systems of cell growth regulation come into action to speed up to slow down cell division and maturation in the epidermis. Approximately 30,000 dead skin cells are shed from the epidermis every minute (Davenport '03: 18, 19).

The epidermis is largely made up of **keratin** – a protein that in effect provides the body with a protective coating. It is keratin that keeps too much moisture from evaporating from the surface of the skin. Keratin is virtually impenetrable by harmful substance and also has anti-bacterial properties. Keratin is also a major constituent of the epidermal appendages, the hair and nails. Ninety-five percent of all cells in the epidermis are **keratinocytes** – these are the cells that slowly move upward from the basal layer to the skin's surface. They contain keratin – the main structural protein of the epidermis. Threads of keratin within keratinocytes in the basal and prickle cell layers gradually combine to form bundles that interweave and then become stuck together by a "cement" produced by granules in the granular layer. By the time they reach the horny layer, they form a mat that is an almost impenetrable barrier that stops substances from passing into and out of the body. Interspersed among the basal cells are the **melanocytes**, adapted nerve tissue cells that send out projections called dendrites between the epidermal cells. They produce the melanin that gives skin its color. **Merkel cells** (or disks) are concentrated in areas around hair follicles in the basal layer, and probably transmit the sensation of light touch to the brain. Other nerve ending in the skin are sensitive to deeper pressure and temperature changes. **Langerhans cells** are found in the prickle cell layer, and, like melanocytes, they are dendritic cells. The first line of defense against environmental hazards, they seize harmful microorganisms and deliver them to lymphocytes in the dermis so an immune response can be generated (Davenport et al '03: 19). In normal skin the entire process of keratinocytes dividing, moving from the basal layer area of the epidermis to the cornified outer layer of the skin, and being shed into the surrounding environment takes about 28 days (Mackie '92: 9).



The **dermis** is the layer of connective tissue that lies between the epidermis above and the subcutaneous fat below. Its function is to support the epidermis structurally and nutritionally. The dermis is composed of two layers the papillary layer, a bulbous connection with the basal layer on top and the reticular layer, a flat connection with the subcutaneous layer. The dermis is a network of interwoven fibers, composed principally of collagen and including a significant amount of elastin, which gives the skin its great strength and elasticity. These fibers are embedded in a strong ground substance of complex carbohydrates – mucopolysaccharides – that act as structural components in the connective tissue. Also within the dermis are several different types of cells – fibroblasts, mast cells, and macrophages – each with a different function. In addition, the dermis contains blood vessels, lymphatic vessels, nerves, and muscles. Nerve ending in the dermis act as receptors that pick up the sensations of light and heavy touch, pain, heat and cold. **Collagen** is the predominant fiber in the dermis. It is packed into bundles to give the skin strength and prevent tearing. Elastic fibers mingled with the collagen help the skin return to its original shape after movement or injury. Fibroblasts make up the majority of the cells in the dermis. They produce the connective tissue that "knits" the dermis together and tend to be located near collagen and elastin fibers.

**Blood vessels** in the skin help with temperature regulation. The network of vessels just above the subcutaneous fat also supplies the sweat glands and hair follicles. **Lymphocytes** are white blood cells involved in protecting the body from infection. They move between the lymphatic system and the bloodstream. Macrophages are a type of phagocyte. Their job is to consume cellular waste material and other debris, including bacteria. **Mast cells** are specialized cells that spring into action when challenged by external injury or foreign substances. Granules inside each cell release histamine and other chemicals that play an important role in the inflammatory response to infection. **Pacinian corpuscles** are one of several kinds of touch receptors found in the dermis. **Meissner's corpuscles** are a type of touch receptor. Joining the epidermis and dermis is a complex structure – the **basement membrane**. This membrane has many different layers and is responsible for holding the skin together. If individual layers in the basement membrane are faulty, the epidermis and the dermis become separated and body fluids move into the space created, causing a blister. This can happen either as an inborn problem – as a rare group of diseases in young babies called epidermolysis bullosa – or as a disease that develops in older patients later in life – bullous pemphigoid (Makcie '92: 5). A basement membrane separates the epidermis and dermis. The ground substance of the dermis is a semisolid gel in which fibers and cells are embedded. It holds water but allows nutrients, hormones and waste products to pass through. It lubricates the collagen and elastin fibers when the skin moves and also provides bulk, allowing the dermis to act a shock absorber.

The cellular elements of the dermis consist of three groups of **mesodermal cells**: (1) a reticulohistiocytic group, (2) a myeloid group, and (3) a lymphoid group. The **reticulohistiocytic group** consists of fibroblasts, histiocytes, and mast cells. Immature cells are known as reticulum cells. Fibroblasts form collagen fibers and may be the progenitors of all other connective tissue cells. Histiocytes normally are present in small numbers in blood vessels, but in pathological conditions can migrate in the epidermis as tissue monocytes. They can also form abundant reticulum fibers. When they phagocytize bacteria and particulate matter, they are known as macrophages. Histiocytes, under special pathologic conditions, can also change into epithelioid cells, which in turn can develop into so-called giant cells. Mast cells are also histiocytic cells. Mast cells have intracytoplasmic basophilic metachromatic granules containing heparin and histamine. The normal skin contains relatively few mast cells, but their number is increased in many different skin conditions particularly the itching dermatoses, such as atopic eczema, contact dermatitis, and lichen planus. In urticarial pigmentosa the mast cells occur in tumor-like masses. Plasma cells, rarely seen in normal skin sections, occur in small numbers in most chronic inflammatory diseases of the skin and in larger numbers in granulomas. The origin of plasma cells is unknown, but they are thought to arise from reticulum cells. In the **myeloid group** of cells, the polymorphonuclear leukocyte and the eosinophilic leukocyte occur quite commonly with various dermatoses, especially those with an allergic etiology. In the **lymphoid group**, the lymphocyte is commonly found in inflammatory lesions of the skin. The myeloid and the lymphoid group of cells are also found in their specific neoplasms of the skin. The ground substance of the dermis is a gel-like, amorphous matrix not easily seen histiologically, but it is of tremendous physiological importance since it contains proteins, mucopolysaccharides, soluble collagens, enzymes, immune bodies, metabolites and many other substances (Sauer '85: 2, 3).

The **subcutaneous fat layer** that sits below the dermis separates the skin from underlying bones and muscles. It is made up of loose connective tissue intermingled with fat cells. Its thickness varies depending on its location within the body. The boundary between the dermis and subcutaneous layer is generally indistinct; the one merges into the other (Davenport et al '03: 20,

21). A continuous arteriovenous meshwork perforates the subcutaneous tissues and extends into the dermis. **Blood vessels** of varying sizes are present in all levels and all planes of the skin tissue and appendages. The vascularization is so intensive that it has been postulated that its main function is to regulate heat and blood pressure of the body, with the nutrition of the skin as a secondary function. A special vascular body, the glomus, deserves mention. The **glomus body** is most commonly seen on the tips of the fingers and the toes and under the nails. Each one of these organs contains a vessel segment that has been called the Sucquet-Hoyer canal, that connects an arteriole with a venule directly, without intervening capillaries. The result is a marked increase in the blood flow through the skin. The **nerve supply** of the skin consists of sensory nerve and motor nerves. The **sensory nerves** mediate the sensations of touch, temperature, or pain. The millions of terminal nerve endings, or Merkel cell- neurite complexes, have more to do with the specificity of skin sensation than the better known highly specialized nerve endings, such as the Vater-Pacinian and the Wagner-Meissner tactile corpuscles. Itching, **pruritis**, is the most important presenting symptom of an unhappy patient. Itching apparently is a mild painful sensation that differs from pain in having a lower frequency of impulse stimuli. The release of proteinases (such as follows itch powder application may be responsible for the itch sensation). The pruritis may be of a pricking type or of a burning type and can vary greatly from one individual to another. Itching can occur without any clinical signs of skin disease or from circulating allergens or local superficial contactants. The **involuntary sympathetic motor nerves** control the sweat glands, the arterioles and the smooth muscles of the skin. Adrenergic fibers carry impulses to the arrectores pilorum muscles, which produce goose flesh when they are stimulated. This is due to the traction of the muscle on the hair follicles to which it is attached (Sauer '85: 4, 5).

The skin is packed with **sensory receptors** that give the body its sense of touch. This provides the brain with vital clues about the body in relation to its environment so it can act accordingly, such as withdrawing fingers from heat. Sensory receptors within the epidermis and dermis can pick up touch, pain, heat and cold. The skin has about a million nerve endings; most of these are in the skin on the face and hands, with relatively few on the back. Sensory nerves vary in complexity, but all react to physical sensations, converting them into nerve impulses that are transmitted along the central nervous system to the **thalamus inside the brain**. In the thalamus, these impulses are identified and relayed to the appropriate sensory regions of the brain. Every second, billions of signals are transmitted to the brain from stimuli all over the body and are processed to create a sensory image and warn of any danger. The sensory receptor cells that lie within the epidermis or the upper dermis tend to be very sensitive to touch and heat; others located deeper within the dermis specialize in detecting heavier pressure. Touch receptors are types of sensory receptors. They range from free nerve endings to more complex tactile receptors enclosed in capsules of connective tissue. There are touch receptors all over the body, but some areas of skin – notably the palms, soles and lips – have more than others and as a result are more sensitive to touch and pain. Touching the skin has great psychological importance. Stroking and cuddling promotes emotional development learning and growth in newborn infants and touching is known to enhance emotional well-being in people of all ages. Parts of the skin are also considered to be erogenous zones. **Merkel's cells** sense continuous light touch and pressure against the skin. Unlike other touch receptors they are not covered by a capsule of connective tissue. Free nerve endings are prevalent throughout the upper part of the dermis. They protrude into the epidermis. **Meissner's corpuscles** are especially sensitive touch receptors that are found in the upper dermis of the fingertips and palms, the lips, the soles of the feet, eyelids, nipples and external genitalia. **Ruffini's corpuscles** are touch receptors located deeper in the dermis; they pick up heavy prolonged touch and pressure. **Pacinian corpuscles**

detect the rapid movement (vibration) of tissues and change in pressure; they are found deep in the dermis, close to muscles and joints, and in the wall of the bladder (Davenport et al '03: 22, 23).

The **skin protects the body from the environment and from infection**. Various mechanisms come into play to ensure that this protection is effective. The skin's first line of defense is its robust, protective outer layer. Keratin, collagen and elastin combine to form a tough but flexible waterproof covering. Sebum helps keep the skin supple. Recognition of 'non-self' material entering through the epidermis is done by Langerhans' cells in the epidermis. Pigment in skin protects against ultraviolet radiation by absorbing and scattering the rays and by scavenging free radicals. In addition, the dryness and constant shedding of dead skin cells, the benign microorganisms (mostly bacteria) that normally live on the skin, the fatty acids of sebum, and the lactic acid of sweat, all combine to repel invading bacteria, viruses, fungi and parasites. Langerhans cells in the epidermis and lymphoid tissue also play an active role in monitoring the skin for foreign substances and particles, acting quickly to eliminate them. Despite these protective measures, infectious organisms can enter the skin in various ways. Natural openings abound: sweat pores, hair follicles, and sebaceous gland openings all allow bacteria, viruses and fungal infections to enter. Broken skin or insect bites can be the port of entry for diseases such as malaria. Warm, moist areas are prone to fungal infections such as athlete's foot.

**Sebaceous glands** are located on the skin wherever there are hair follicles. They are larger and more numerous on the scalp, face, chest and back. Most open into hair follicles; the only exceptions are the sebaceous glands on the eyelids, in the genital area and on the nipples. The sebum secreted by sebaceous glands is an oily compound containing various fatty substances. It enables the skin's outermost layer to retain water and controls water loss from the epidermis. The free fatty acids in sebum act as a disinfectant, helping to prevent bacteria and fungi from colonizing the skin. Sebum is produced at birth in response to maternal hormones, then disappears until puberty, when sebaceous glands develop, stimulated by androgens (the hormones produced by the testis, adrenal glands and to a lesser extent, the ovaries).

Without the **horny layer** of the skin, significant amounts of water would be lost to the environment and the body would become dehydrated. The lipid bilayer, a fine layer of fats on the outer surface of the horny layer, keeps water from evaporating from the skin and makes it very difficult for water to enter from outside. There are times when the skin's ability to keep out water can become slightly impaired. This may happen when the horny layer is excessively dry or soggy, warmer than usual, or damaged in some way, perhaps by detergent. If foreign organisms do penetrate the body's protective defense barriers, the **inflammatory response** prevents infection from becoming widespread. The damaged tissue releases chemicals that attract specialized scavenging cells, phagocyte-type white blood cells, to the infected area. Blood vessels inside the dermis dilate, increasing blood flow to the area. The walls of the tiny blood vessels become porous, allowing the phagocytes to move from the blood vessel into the area of tissue damage, where they engulf and destroy the invading microorganisms. The characteristic red, swollen, hot appearance of inflamed tissue is caused by the swollen blood vessels and the sharp increase in the number of cells in the tissue. The affected area becomes painful when the chemicals released during this process, such as serotonin and histamine, stimulate nerve endings in the dermis (Davenport et al '03: 24, 25)(Mackie '92: 9, 10).

Humans do not have a thick fur coat to provide warmth. A complex system of specialized blood vessels in the skin and the sweat glands to regulate **heat loss and conservation**. When the

temperature of the body increases and needs to be brought down again, the blood vessels near the surface of the skin **dilate**. This allows more blood to reach the skin so that heat is lost and the blood cools down. This brings a flushed appearance to the skin. How much the blood vessels dilate is controlled by nerves known as vasomotor fibers, which are controlled by the brain. At the same time, eccrine sweat glands produce increases amounts of sweat, which evaporates on the surface of the skin to cool the skin. When the air is dry, the sweating mechanism is a very effective way of maintaining a tolerable body temperature. In humid heat, however, sweat cannot evaporate as easily, to the sweating mechanism is not so helpful, and the body may overheat. A duct connects the coiled part of the sweat gland to a pore on the skin's surface through which the sweat reaches the surface of the skin. The coiled part in the dermis is where sweat first collects. The fluid that makes up sweat comes from the interstitial spaces between the cells. Fluid enters these spaces from the tiny blood vessels in the dermis (Davenport '03: 26).

There are two types of glandular appendage of the skin are the sebaceous glands and the sweat glands. The **sebaceous glands** form their secretion through disintegration of the whole glandular cell, whereas the sweat glands eliminate only a portion of the cell in the formation of secretion. The sebaceous glands are present everywhere in the skin except the palms and the soles. The secretion from these glands is evacuated through the sebaceous duct to a follicle that may or may not contain a hair. This secretion is not under any neurologic control but is a continuous outflowing of the material of cell breakdown. These glands produce sebum, which covers the skin with a thin lipoidal film that is mildly bacteriostatic and fungistatic and retards water evaporation. The scalp and the face may contain as many as 1000 sebaceous glands per square centimeter. The activity of the gland increases markedly at the age of puberty and, in certain individuals, becomes plugged with sebum, debris, and bacteria to form the blackheads and the pimples of acne.

The **sweat glands** are found everywhere in the human skin. They appear in greatest abundance on the palms and the soles and in the axillae. There are two main types of sweat glands: the eccrine, or small sweat glands, open directly onto the skin surface; the apocrine, or large sweat glands, like the sebaceous gland, usually open into a hair follicle. **Apocrine sweat glands** are mostly situated in the armpits and around the anus and genitals, with a few sometimes around the navel and nipples. They are larger than eccrine glands and become active at puberty, stimulated by production of the male sex hormone androgen. They have a secretory coil and duct, much like eccrine glands, but the duct opens into a hair follicle, in the same way as a sebaceous gland. Their secretions include protein, carbohydrate, ammonia, and fats, and have nothing to do with temperature regulation. Apocrine gland sweat does not smell in itself, but a strong odor can result from the action of bacteria on the sweat. The glands that produce wax in the ear canal and the mammary glands of the breasts are specialized apocrine glands. The apocrine sweat glands are found chiefly in the axillae and the genital region and do not develop until the time of puberty. These glands, in humans, have very little importance except for the production of odor (B.O.).

Any emotional stresses that cause adrenergic sympathetic discharge produce apocrine sweating. This sweat is sterile when excreted but undergoes decomposition when contaminated by bacteria from the skin surface, resulting in a strong and characteristic odor. The purpose of the many cosmetic underarm preparations is to remove these bacteria or block the gland excretion. The main disease of the apocrine gland is *hidradenitis suppurativa*, an uncommon, chronic infection of these glands caused by blockage of the duct, which usually occurs in patients with the acne-seborrhea complex. **Eccrine sweat glands** are distributed through almost all of the body, with

the greatest density being on the palms of the hands and the soles of the feet. These glands play a vital role in temperature regulation and are active from birth. The eccrine sweat glands and the cutaneous blood vessels are key factors in the maintenance of stable internal body temperatures, despite marked environmental temperature changes. Each gland has a coiled part deep in the dermis that secretes sweat and a duct that carries the sweat to the surface. The eccrine glands flood the skin surface with water for cooling, and the blood vessels dilate or constrict to dissipate or to conserve body heat. The eccrine sweat glands are distributed everywhere on the skin surface with the greatest concentration in the palms, the soles and the forehead. The sweat consists of water, salts, and other waste products that need to be removed for the body.

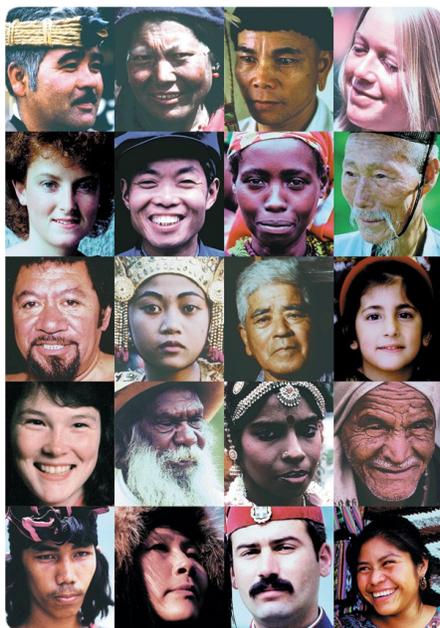
The prime stimulus for these small sweat glands is **heat**. When the temperature outside the body is very hot, an eccrine duct can reabsorb salt to help the body conserve it. If the body is too cold, the blood vessels close to the surface of the skin constrict to reduce the flow of blood. Warm blood is diverted into deeper blood vessels, and so heat is conserved (and the skin becomes paler). The layer of subcutaneous fat under the dermis provides extra insulation and, in addition, the arrector pili muscles, the tiny muscles attached to hair follicles, contract, lifting the hairs until they become erect. This has the effect of pulling on the skin to produce goose bumps. In mammals, with long, thick hair, the erect hairs trap a layer of warm air at the skin's surface; in humans this only has a small effect because human body hair is so short and fine. Fear and anger also make body hair stand on end. Their activity is under the control of the nervous system, usually through the hypothalamic thermostat. Both adrenergic and cholinergic fibers innervate the glands. Blockage of the sweat ducts results in the disease entity known as prickly heat (miliaria). When the sweat glands are congenitally absent, as in anhidrotic ectodermal dysplasia, a life-threatening hyperpyrexia may develop (Davenport '03: 27)(Sauer '85: 6, 7).

Compared with many creatures humans have a rather limited color palette when it comes to skin and hair, shades of yellow, brown, red and black that is caused by **melanin**, with the intensity of color varying from almost white (no melanin) to almost jet black (a large amount). The amount of melanin in the skin and hair is determined genetically. Melanin is a pigment produced by specialized cells called melanocytes. These are found in the basal layer of the epidermis. Each melanocyte contains melanosomes, in which melanin is synthesized. These melanosomes are engulfed by keratinocyte cells, and it is differences in their behavior that determine skin color. There are also melanocytes in the bulbs of hair follicles and in the retina of the eye. Melanocytes in a hair bulb are packaged into granules that pigment the hair shaft. Two forms of melanin color hair. Eumelanin is the dark pigment that predominates in black and brunette hair. Pheomelanin is lighter and found in red and blonde hair. Many people's hair contains a mixture of the two. The combination of pigments is determined genetically. The more pheomelanin, the lighter the hair. The age at which hair starts to turn gray is also genetically determined. This occurs as production of the melanin that colors the hair slowly decreases and the cells in the medulla at the center of each terminal hair shaft become filled instead with tiny air bubbles that reflect light. Hairs without melanin appear to be white because of the way they reflect light. (Davenport et al '03: 28, 29).

The skin cannot permanently change its color or the way that it reacts to **sunlight**. Many white-skinned people persist in trying to keep their skin permanently browner than nature intended, by sunbathing in summer, and by the use of sunbeds in winter. This will cause early aging of the skin and can, in time, make skin cancer more likely. In contrast, in countries where a white skin is more desirable, such as South Africa, bleaching creams may be used in an attempt to lighten the skin. These creams can be absorbed through the skin, where they may cause a very

disfiguring condition called ochronosis. This is a disfiguring slate-grey color that affects the soft bones or cartilage of the nose and cheeks due to deposition of dark pigments. While the skin is very good at repairing superficial epidermal damage with on residual scar, if the dermis is damaged a scar of some type is inevitable. With age the skin gradually becomes drier. The sebaceous glands which produce a lot, but not all, of the greasy or oily material that lubricates the skin, are very active in the teenage years but become less active with age. Oily or greasy material is also produced by the epidermal keratinocytes, and contributes to the protective waterproofing of the skin and to its suppleness. In addition, however, this oily or lipid material from the sebaceous glands and keratinocytes also helps the body retain water by preventing the evaporation of water form the sin surface. So both lipids and water, acting together, are important in preventing skin from drying out. Moisturizing creams can therefore be very light-acting, mainly by improving water retention, or much heavier, for example night creams, which mainly contain oils and heavy emollients. Moisturizers should be used regularly for dry skin after the age of 40 (Mackie '92: 12, 13).

The skin protects us from the ultraviolet (UV) light form the sun. **UV light** radiates from a part of the sun's electromagnetic spectrum that is invisible. UVA, B, and C represent different wavelengths. UVC is almost entirely filtered out by the Earth's ozone layer; UVB is absorbed by the skin and can directly interact with and mutate DNA (though it is relatively weak compared to UVC). UVA is absorbed differently, it does not damage DNA directly but acts indirectly via the generation of free radicals. The amount of UV exposure humans receive is dependent upon geography but varies with local climatic conditions and is most intense between the hours of noon and 3 pm. Melanin is manufactured by a minor population of cells in skin called melanocytes and then distributed in small packets, called melanosomes, to the majority cell type – the skin keratinocytes, as well as to hair follicles and the iris. When hair turns grey, it's because hair follicle melanocytes have become dormant. Albino traits have inherited mutations in the complex Cellular and biochemical pathways that lead to melanin synthesis.



Ethnic groups with black skin don't have more melanocytes but produce much more melanin per cell. In particular, they produce a form of brown/black melanin called eumelanin that is particularly good natural UVB filter. UV filtration efficiency is further enhanced in black skin by distributing melanosomes, diffusely within the keratinocytes. Caucasians make considerably less melanin and in the recipient keratinocyte, the melanosomes are grouped together reducing overall UV absorption capacity. Caucasians that are of very fair complexion make a higher proportion of their melanin as pheomelanin. This yellow and/or red pigment provides feeble UVB filter and its response to UV light (Greaves '00: 175, 176). Melanin helps protect the skin from damage caused by ultraviolet (UV) radiation from the sun by absorbing the UV rays before they penetrate to deeper layers of the epidermis and dermis. UV rays are, however, useful for helping to produce vitamin D – important for calcium metabolism and strong, healthy bones – and so moderate amount of UV

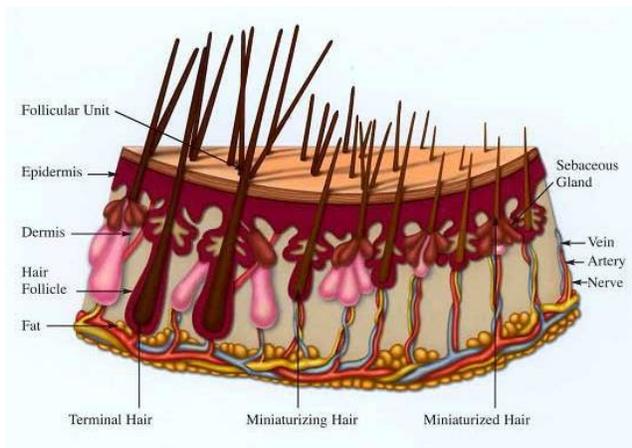
radiation on the skin is beneficial, especially for people whose diet is deficient in vitamin D. Sunbathing leads to a suntan through two processes. First, UV rays (mainly UVA) darken the skin by oxidizing melanin that already exists; UVB stimulates the melanocytes to produce more

melanin. The reason that some people tan more easily than others is because these people have more active melanocytes in their skin (Davenport et al '03: 28, 29).

## 2. Hair and nails

Parts of the epidermis have become specialized and form the so-called **epidermal appendages**, which project deep into the dermis. These are the hairs and nails, the sebaceous glands, and the sweat glands. Each strand of hair extends 0.16-0.20 inches into the skin. There are two types of hairs on the body, short, fine vellus hairs and longer, thicker terminal hairs. The nails protect the sensitive tips of the fingers and toes from damage, and they also serve as valuable tools for tasks involving prying or scratching. The dermis is the layer of connective tissue beneath the epidermis that forms the bulk of the skin. A sweat gland is a long, coiled, hollow tube that transports sweat to the skin's surface so it can evaporate. A sebaceous gland produces sebum, which lubricates, protects, and waterproofs the skin. Tiny blood vessels in the dermis not only nourish the skin and help fight infection by bringing in white blood cells; they also help the body cool off or warm up as required (Davenport '03: 16, 17).

**Hairs** are derived from the hair follicles of the epidermis. Since no new hair follicles are formed after birth, the different types of body hairs are manifestations of the effect of location and of external and internal stimuli. Hormones are the most important internal stimuli influencing various types of hair growth. This growth is cyclic, with a growing (anagen) phase and arresting (telogen) phase. The average period of scalp hair growth ranges from 2 to 6 years. However, systemic stresses, such as childbirth, may cause hairs to enter a resting stage prematurely. The adult has two main types of hairs: (1) the vellus hairs (Lanugo hairs of the fetus) and (2) the terminal hairs. The vellus hairs ("peach fuzz") are the fine short hairs of the body, whereas the terminal hairs are coarse, thick and pigmented. The latter hairs are developed most extensively on the scalp, the brows and the extremities.



The **hair follicle** is under the skin's surface. It is a specialized tubular construction of epidermal cells that grows down into the dermis at an angle and contains the hair root. The **dermal papilla** contains dividing cells and receives blood vessels and nerve endings that nourish the growing hair. It is from the dermal papilla that a new hair grows once the old hair has died. The **hair bulb** at the lower end of the follicle encloses the dermal papilla. Included within the hair bulb are melanocytes and keratinocytes, which give the hair its color and texture. An **arrector**

**pili muscle** is attached to each hair follicle. When this bundle of muscle fibers contracts, the hair is pulled upright, creating a "goose bump". There is a **sebaceous gland** associated with each hair follicle that helps lubricate the hair. The **cortex** consists of packed keratinocytes and contains the melanin pigment that gives the hair its color. In the medulla, at the center of a terminal hair, cells intermingle with air spaces. There is no medulla at all in vellus hairs. The **outer root sheath** penetrates the basement membrane of the epidermis. The **cuticle** of a hair, the exterior of the hair follicle, is made up of a thin layer of cells containing keratin. They overlap each other in a

way similar to roof tiles, with the free margins pointing toward the tip of the hair. A "split end" may result if this layer wears away (Davenport et al '03: 31).

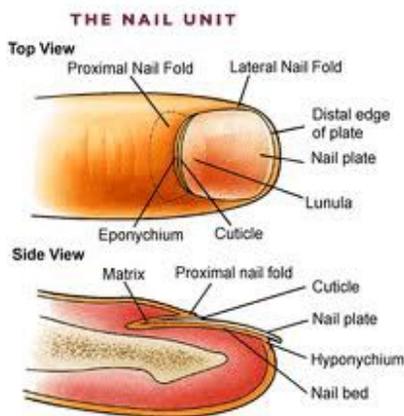
The hair follicle may be thought of as an invagination of the epidermis, with its different layers of cells. These cells make up the matrix of the hair follicle and produce the keratin of the mature hair. The protein-synthesizing capacity of this tissue is enormous, when one considers that at the rate of scalp hair growth of 0.35 mm/day, over 100 linear feet of scalp hair is produced daily. The density of hairs in the scalp varies from 175 to 300 hairs per square centimeter (Sauer '85: 5). There are about 100,000 hairs on the scalp of which about 70 are shed each day. Hairs on the scalp grow up to 0.015 inch every day, a half an inch a month. Hair is obviously most numerous on the scalp, but there are also fine hairs on other body sites. Scalp hair is referred to as terminal or coarse hair and fine body hair, found for example, on the forearm, as villous hair (Mackie '92: 6).

There are three stages in the **life cycle of a hair**. I **Active** (anagen) phase when the hair shaft grows from the dermal papilla that lasts from two to five years for hair on the scalp. II **Transitional** (catagen) phase is a short resting period after the hair has stopped growing, around the dermal papilla is a proliferation of epithelial cells forming a new hair bulb, on the scalp this phase usually lasts about two weeks. III **Resting** (telogen) phase the old hair is detached from the dermal papilla and ready to be shed, on the scalp this phase lasts for three or four months. The rounder the cross section of the shaft, the straighter the hair will be; the flatter the cross section, the more the hair will curl (Davenport et al '03: 30).

Hair is composed of modified **keratinocytes**. The very deepest part of the hair root – the papilla – is developed from the deepest part of the skin – the dermis – but most of the hair shaft develops from an ingrowth into the dermis of the epidermal keratinocytes before birth. These keratinocytes grow down and develop into the complicated structure that is the hair. As with the epidermis, the only part of the hair that is actually living is the deepest root area – all the hair seen above the skin surface is composed of dead, non-dividing cells. Hair follicles go through a slow, programmed pattern of growth and replacement. Over a period of about 2 years individual hair follicles (roots) go through a cycle of rapid growth, rest, then the hair is shed. This pattern of programmed replacement of hair is usually random over the scalp, and therefore at any one time no obvious areas of hair loss are seen on healthy scalps in children or women, although some men do experience permanent loss of scalp hair as they get older. Fewer hairs are lost during pregnancy, when the hair on the head can seem temporarily thicker. After delivery of the child, however, this advantage is lost and more hair goes into the resting and shedding phase. The scalp hair therefore becomes temporarily thinner returning to its regular cycle about 9 months after the birth (Mackie '92: 6, 7). The hair is made from the protein **keratin**, which also makes up the nails and is a major constituent in the epidermis.

Nails consist of **modified epidermal keratinocytes**, like the hair. Here again, before birth there is an ingrowth of the epidermis, in this case growing to form a nail plate on which the hard nail structure is formed. As with the hair, the outer cells composing the nail are dead. As human evolved we learned to use tools as a substitute for fingernails (Mackie '92: 8). As the principal instrument of touch, the fingertips and, toes, in constant use, are in need of extra protection. This is provided by the **nails**, which are also useful tools. The nail is the evolutionary remnant of a mammalian claw. It consists of a plate of hardened and densely packed keratin. In addition to protecting the finger ends, the nails have valuable prying and picking skills that were extremely useful in climbing trees, gathering food and for personal grooming.

The rate at which nails grow varies. Fingernails grow continuously and average between 0.02 and 0.05 inch per week. Toenails grow about a third more slowly. Nails grow faster in younger people and faster in summertime than in winter, possibly because blood circulates at a faster rate in summer, triggering more rapid cell division. It takes about six months for a fingernail to grow from the matrix to the free edge and up to 18 months for the nail on the big toe to do the same. Nails do not continue to grow for a short time after death, but the nail folds do shrink away from the nail plate, creating the illusion that the nail has grown (Davenport et al '03: 32). Like hair growth, which is periodic, nail growth is continuous. Nail growth proceeds at about one third of the rate of hair growth, or about 0.1 mm/day. It takes approximately 3 months to restore a removed fingernail and about three times that long for the regrowth of a new toenail. Nail growth can be inhibited during serious illnesses or in old age, increased through nail biting or occupational stress, and altered because of hand dermatitis or systemic disease. Topical treatment of nail disturbances is very unsatisfactory, owing to the inaccessibility of the growth-producing areas (Sauer '85: 6).



The nail consists of a **nail plate** and the tissue that surrounds it. This plate lies in a nail groove, which, like the hair follicle, is an invagination of the epidermis. The **matrix** or root of the nail runs from the proximal nail fold to the outer edge of the lunula. From this root, the nail plate grows over the nail bed, ending in a free edge at the fingertip. It is in the matrix that keratin is produced by cell division. Therefore, if the matrix is destroyed, the nail can't grow back. The **cuticle** is an extension of the horny layer of the skin of the nail fold. It acts a seal to protect the matrix from infection. The **lunula** is the only part of the matrix that can be seen. It looks like a pail "half-moon" at the base of the nail plate. The **lateral nail fold** is the bulge of skin on either side of the nail, at the boundary of the

epidermis and the nail. The **nail plate** is a hard transparent form of keratin that grows outward from the nail matrix. The **free edge** is the part of the nail that extends beyond the nail bed.



The skin on the fingertips is particularly well supplied with **nerve endings**. Each fingertip has more than 3000 touch receptors. On the fingertips, the outermost layer of skin form tiny ridges that make up unique patterns called **fingerprints**. The ridges follow the same patterns that are created below the skin's surface, where the dermis and epidermis join by means of interlocking projections down from the epidermis (called rete ridges) and up from the dermis (dermal papillae), these projections lock the dermis and epidermis together. Everyone has a unique pattern of

loops, whorls and arches, loops are the most common pattern, arches are the least common (Davenport et al '03: 32, 33). Fingerprints are characteristic features of human skin found on the palm side of the fingers and thumbs and on the soles of the feet. They are almost the only place on the body where the skin is not smooth. Biologists believe that fingerprints may have evolved to provide the hands and feet with rough surfaces that allow one to grasp and hold objects more easily. Fingerprints being to develop and are completely formed during the fetal stage of life. They have two fundamental characteristics that permit them to used to identify an individual.

First, fingerprint patterns are unique. No two humans have ever been found who have identical fingerprint patterns. Second, fingerprint patterns do not change during a person's lifetime. The skin in such locations is folded into hills and valleys known respectively as ridges and grooves. The ridges are frequently referred to as friction ridges, because they provide the friction needed to grip and hold an object. Scientists have identified more than 150 different ridge characteristics (also known as minutiae) by which two fingerprint patterns can be compared with each other (Newton '07: 2, 16, 17).

As far back as the eight century A.D., the practice of using fingerprints to identify and authenticate documents was introduced in China. **Fingerprints** may take on one of three forms: visible, plastic, or latent. **Visible prints** are left behind when a person transfers some type of colored material, such as blood, paint, grease, dirt or ink on his or her hand to a smooth surface by touching it. **Plastic prints** are produced when a person touches a soft material, such as clay, mud soap, or wax, in which the friction ridges produce a visible pattern. **Latent prints** are so called because they are invisible to the human eye. They are composed of eccrine secretions, produced by small sweat glands located just under the surface of friction ridges. Eccrine secretions are left behind after a person has touched an object. This residue typically consists almost entirely (98.5 percent) of water, in which are dissolved small amounts (1.5 percent) of a large variety of solids. About two-thirds of the solids are organic substances, while the remaining one-third is inorganic. The vast majority of fingerprints that law enforcement officials deal with are latent prints. A number of chemical techniques have been developed by which such prints can be made visible and therefore usable for purposes of identification. As early as the 1960s the FBI began to explore the process of automating this process and the final results was the Integrated Automated Fingerprint Identification System (IAFIS), in which computer programs scanned and compared two or more sets of fingerprints at high speed. The FBI is currently said to have more than 238 million fingerprints in its files (many of people long dead), about half of whom have been suspected or convicted of criminal activity. Law enforcement officers in the United Kingdom normally require two prints to match on 16 points in order for them to be considered identical. But that number is only 12 in Australia and New Zealand and 8 in India. Canada has no nationwide standard, and in the United States, each state sets its own standard, although the FBI uses a 12-point system (Newton '07: 2, 16-22, 20, 13-15).

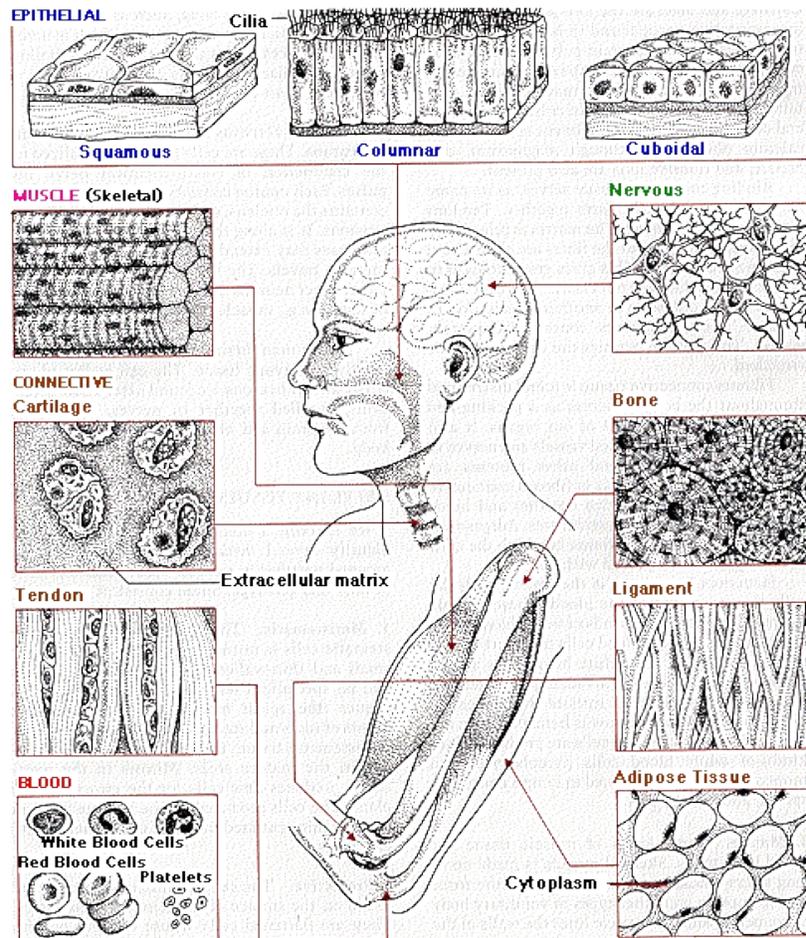
### 3. Histologic tissues

**Histology** is the study of the microscopic anatomy of cells and tissues of plants and animals. It is commonly performed by examining cells and tissues by sectioning and staining, followed by examination under a light microscope or electron microscope. Histopathology, the microscopic study of diseased tissue, is an important tool in anatomical pathology, since accurate diagnosis of cancer and other diseases usually requires histopathological examination of samples. Trained physicians, frequently board-certified as **pathologists**, are the personnel who perform histopathological examination and provide diagnostic information based on their observations. Scientists trained in *histotechnology* perform the preparation of histological sections and are employed as histology technicians (HT), histology technologists (HTL), medical scientists, medical laboratory technicians, or biomedical scientists. Although diverse in structure and function, all body parts are constructed of four basic soft tissue types: 1) epithelia, 2) connective, 3) muscle, and 4) nervous tissues (Mackie '92: 11).

**Epithelial tissues** act as protective linings and coverings. The layers of the skin are continuous with the linings of the inner cavities of the body – the mucous membranes. The margin between

skin and mucous membrane can easily be seen, for example, on the inner surface of the lip and on the lower eyelid and at the line of the eyelashes. Mucous membranes are equally susceptible to rashes as the skin. In some locales, absorption and secretion are important functions of these lining and covering cells. As secretory cells, epithelia form most glandular structures of the body. **Connective tissues** serve as connective and supportive tissues that bind and hold body structures together. Specialized fluid connective tissue types serve as liquid media important in transport, exchange, and body defense. **Muscle tissues** have the unique capability to contract or shorten. This enables muscle types to be involved in functions of support and movement. **Nervous tissue** cells are specialized for conduction of the complex telecommunications network of the body. These tissues act in a sensory capacity, to receive, disseminate, and store information collected from receptors. In a motor capacity, nervous tissues provide response potential by controlling effectors such as muscles or glands (Rubbelke '99).

## Tissues

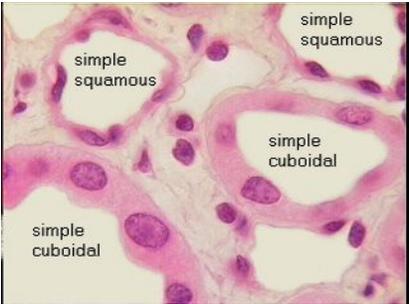
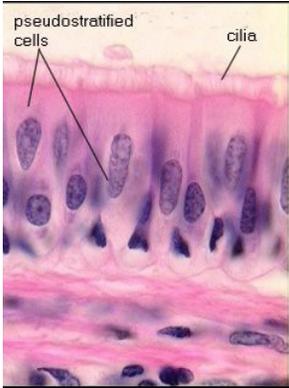
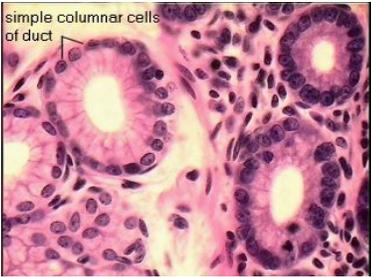


Credit: 14 October 2011 users.rcn.com

**Epithelia** possess tight intercellular junctions between cells. These junctions effectively cement cells together into single layered or multilayered sheets of cells. These tissue sheets drape body organs, line cavities, and cover external body surfaces providing protection from microbial invasion or friction. The epithelia of these sheets can also be secretory, producing lubricating, protective, or nutritive fluids of membrane. **Membranes** consist of a lining or covering epithelium with the loose connective tissues that anchor them to underlying tissues. For

example, the epidermis of the skin is an epithelium. Epithelia and loose connective tissue layers make up the various mucous membranes (lining respiratory, digestive, reproductive and other body tracts), serous membranes (lining the ventral body cavities), and synovial membranes (lining joint capsules). Serous membranes lining the ventral body cavities actually consist of two separate layers, a visceral layer and a parietal layer. The **visceral layer** is the component that closely wraps or invests organs in these cavities. The **parietal layer** lines the walls of the cavity. Epithelial cells of these membrane components secrete a small quantity of slippery serous fluid that accumulates in the space between them. This **serous fluid** acts as a lubricant to reduce friction between organs that shift and move as they perform bodily functions. Loose connective tissues of membranes are important sites of inflammation due to mast cells. Mast cells release histamine, heparin (an anticoagulant), and other vasoactive agents. Vascular effects of histamine are important initiators of inflammation. These include vasodilation in vessels and **increased permeability** in capillaries. The visible or "cardinal" signs of inflammation are explained by keeping histamine's vascular effects in mind. The **Four Cardinal Signs of Inflammation** are (1) redness caused by vasodilation of blood vessels; (2) edema caused by fluid loss from more permeable capillaries; (3) sensitivity to touch due to pressures and chemical shifts in interstitial fluids sensitizing receptors neurons and (4) elevated temperature due to heat carried to site from the body core by blood. Dermatitis, synovitis, peritonitis, pleuritis and pericarditis are all terms that describe inflammation. Notice the "itis" ending of these words. Any medical term with this ending implies inflammation in some tissue or location. All epithelia are named with descriptive terms that represent unique traits of the epithelia. The classification or naming system used to identify epithelia is based on **three key classification criteria**: (1) number of cell layers, simple or multiple (2) cell shapes, squamous, cuboidal and columnar and if stratified (3) surface modifications, cilia or microvilli. These criteria are used in combination with one another to name epithelia (Rubbelke '99).

### Slides of Epithelial Cells

Kidney Tubules	Epithelia of the Trachea	Ducts of Exocrine Glands
 <p>simple squamous</p> <p>simple cuboidal</p> <p>simple cuboidal</p>	 <p>pseudostratified cells</p> <p>cilia</p>	 <p>simple columnar cells of duct</p>

Credit: Rubbelke '99

**Glands** of the body are classified as either exocrine or endocrine types. Exocrine glands are glands that retain ducts to body surfaces. During development, endocrine glands lose their contacts to embryological surfaces (ducts) and become isolated as small blocks of tissues. Endocrine glands are therefore referred to as "ductless" glands. Endocrine and exocrine glands secrete various products. These include hormones, enzymes, metabolites, and other molecules.

In exocrine glands, products of these cells collect in the duct of the gland and flow toward the surface to which the duct is in contact. Since endocrine glands lack ducts, the product is released across the cell membrane into interstitial spaces around the cells. Diffusion of the product into capillaries follows. Most glands of the body are exocrine types with ducts connecting to anatomical surfaces. Contrast your salivary glands that open into the oral cavity with sweat glands that deposit their product on the body surface. Both types of glands are buried in deeper tissues but their products appear on a superficial surface. Connecting the glands to the surfaces are ducts! A great deal of variation can be found in the design of glands. They are classified into simple and compound types. Note there are tubular and alveolar types (Rubbelke '99).

**Secretory cells** of exocrine glands release their products into ducts in three different ways. The mode of secretion can be classified as merocrine, apocrine, or holocrine. Cells that secrete products via the **merocrine** method form membrane-bound secretory vesicles internal to the cell. These are moved to the apical surface where the vesicles coalesce with the membrane on the apical surface to release the product. In those glands that release product via the **apocrine** method, the apical portions of cells are pinched off and lost during the secretory process. This results in a secretory product that contains a variety of molecular components including those of the membrane. Mammary glands release their products in this manner. The third type of secretory release, **holocrine**, involves death of the cell. The secretory cell is released and as it breaks apart, the contents of the cell become the secretory product. This mode of secretion results in the most complex secretory product. Some sweat glands located in the axillae, pubic areas, and around the areoli of the breasts release their products in this manner. Sebaceous glands also are of this type. Regardless of gland type, structural complexity, or mode of secretion, epithelia are the secretory cells of all glands. Epithelia also form the ducts that connect the glands to the surface. Remember this as glandular structures found in tissues can be identified as clusters of tightly packed cells with very little intercellular space (an epithelial characteristic). When ducts are present and cut in longitudinal or cross-section, epithelial cells are also seen making up these structures. Simple cuboidal epithelia are the most typical type found in the body and ducts of exocrine glands. **Endocrine glands** are the hormone producing structures of the body. Some, like the thyroid are large and obvious. Others, for instance the islet cells of the pancreas, are small islands of endocrine cells embedded within the larger exocrine portion of this organ. In lacking ducts, endocrine cells release their secretory products into the interstitial spaces around the cells. The hormones diffuse into nearby capillaries and are then carried to all parts of the body. Only when the hormones encounter a "target organ" do they exert an effect (Rubbelke '99).

**Connective tissues** consist of dispersed cells that typically lack intercellular contact. Also, most connective tissues are vascularized with the single exception being cartilage. Extracellular spaces in connective tissues are therefore more abundant and contain vessels. In connective tissues, the extracellular space is termed the **extracellular matrix** because products of **specialized cells** accumulate here. These products include **protein fibers** and **ground substances** (mixes of various chemical substances). Connective tissues are broadly classified into three large groups: (1) Fluid connective tissues, blood and lymph; (2) Connective tissue proper, loose and dense connective tissues and (3) Supportive connective tissue, cartilage and bone. Some connective tissues of the body are **fluids**. Although it can be difficult to visualize fluids as "connective" components, an examination of their roles in body homeostasis provides insight into why they are considered tissues of this type. Blood and lymph are two extremely important fluids involved in transport and body defense. The fluid components of plasma that leak into interstitial spaces across capillary walls form interstitial fluids. Interstitial fluids are

important in a physiological sense in that solutes and respiratory gases (i.e. oxygen, glucose) of the blood diffuse across these fluids to body cells. The waste products that accumulate within active cells also diffuse in the opposite direction across these fluids, from cells to capillaries. Some of this formed interstitial fluid returns to the blood, leaking back across capillary walls from interstitial spaces. Remaining fluid drains off through nearby lymphatic vessels.

Subsequently, lymphatic capillaries and vessels are best described as a drainage/filtration system for tissue spaces. Under normal conditions, a balance exists with no excess fluid accumulating in tissues. Lymph draining from interstitial spaces eventually returns to the venous vascular flow. Inflammation disrupts the existing balance between these fluids, resulting in events that lead to abnormal plasma loss and its accumulation in interstitial spaces, a condition called **edema**. Although uncomfortable, one has to think of inflammation and edema from an immunological perspective to better understand why these events are supportive of body homeostasis. Increased blood flow brings more defensive leukocytes to an inflamed tissue. Enhanced capillary permeability allows the arriving defensive cells to move more easily from the blood into the interstitial spaces where they engage in phagocytosis and other activities. Phagocytosis is an important "first-step" in body defense.

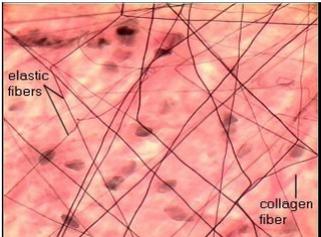
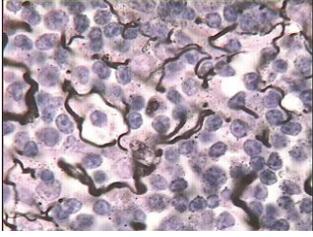
**Phagocytic cells** attracted to inflammatory events detect and attempt to destroy invading organisms or non-cellular agents that cause inflammation. Some of these phagocytic "veterans" then enter the lymphatic flow where they meet with lymphocytes in lymph nodes or other lymphatic tissues to "serve-up" or present antigens. These cells are called **antigen presenting cells or APC's**. These cells help stimulate immunological reactions involving B and T-lymphocytes. Highly specific T-lymphocytes, antibodies, or both are then produced and released into lymph returning to the venous blood flow. Eventually, these new "high tech" weapons find their way to sites of inflammation. The histamine-induced vascular effects induced there enable these "highly specific" defenses to arrive in larger numbers and move more efficiently into tissues to participate in the battle with the disease or foreign agent. In short, inflammation is important as part of a complex, positive-feedback mechanism of body defense that operates through blood and lymph fluids. Both initial and longer-term defenses involve cells of blood and lymph working together. Typically these defensive responses get progressively stronger until the initiating condition is removed and homeostasis returns.

**Connective tissue proper**, the second broad category of connective tissues, contains a variety of types. All possess visible protein fibers embedded in a fluid ground substance. Hydrophilic muco-polysacharrides and glycoproteins of this ground substance attract water to induce variation in its viscosity; it can be almost gel-like. Regardless, the ground substances of all connective tissue proper types flows around and makes intimate contact with cells. Therefore, these cells will not be seen occupying distinct spaces or lacunae within the matrix. Lacunae as we will see, are key features for identifying the supportive connective tissues, cartilage and bone, where ground substances are semisolid gels or crystals. Connective tissue proper contain three types of **protein fibers** and in some cases, a variety of cell types. Type, abundance, and orientation of protein fibers determine the kind of connective tissue proper.

The forming and mature cells of connective tissue proper are called fibroblasts and fibrocytes, respectively. A clear distinction between these two types is difficult. The **fibroblast** is the more active cell that forms fibers and ground substance. Therefore, in a young forming tissue these cells prevail. **Fibrocytes** on the other hand, are more abundant mature cells in a fully-formed tissue such as a tendon or ligament. However, tendons and ligaments can be strengthened or repaired. Fibroblasts, as resident or derived cells(differentiated from mesenchyme cells) within

the tendon or ligament form the fibers and ground substance required for this process. If fibers are smaller and arranged in loose, random arrays the connective tissue is properly classified as a **loose connective tissue** type. There are three loose types (1) loose connective or areolar tissue; (2) fat or adipose tissue and (3) reticular connective tissue. If fibers are large and occupy most of the extracellular spaces between cells you have a **dense connective tissue** type. The protein fibers of dense types can be arranged randomly within the matrix as irregular c.t. or in a common direction as regular c.t.. In dense regular types, fibers can be so abundant that fibrocytes and fibroblasts are squeezed into flattened rows between the fibers. Three types of dense connective tissue are recognized: (1) dense regular fibrous (collagenous); (2) dense irregular fibrous and (3) dense regular elastic (Rubbelke '99).

### Slides of Connective Tissues

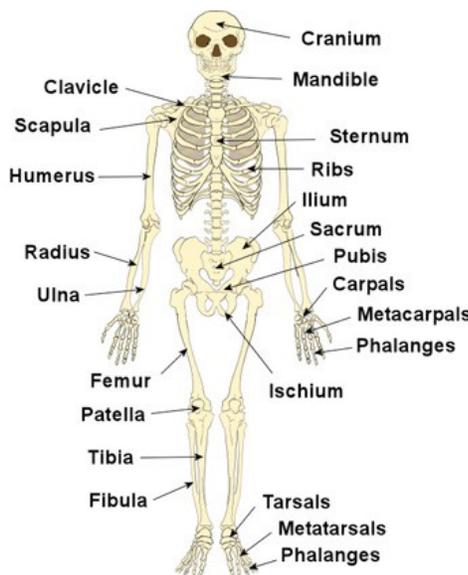
Fibers in loose c.t.	Reticular fibers in lymph node	Dense regular
 <p>elastic fibers</p> <p>collagen fiber</p>		

Credit: Rubbelke '99

**Supportive connective tissues** are strong and durable tissues that serve as supportive structures for other types - bone and cartilage. Most of the supportive elements of your body are bones. The **skeleton**, in serving as the anchoring points for muscles and tendons, enables not only support, but movement. In addition, bones are protective structures for critical organs like the brain, spinal cord, heart and lungs. **Cartilage** is the supportive tissue used where durability and flexibility are specific needs. Cartilage is also found covering the ends of long bones in the synovial joints as articular cartilages. Here, the smooth and slippery texture of cartilage helps minimize friction in joints. Supportive connective tissues then, include various types of cartilage and bone. All connective tissues contain protein fibers but in supportive connective tissues these fibers are usually hidden by the semisolid or solid ground substances within the matrix. Therefore, to identify cartilage and bone as connective tissue a criteria other than the presence of visible fibers is needed, and in cartilage and bone, one can see lacunae. **Lacunae** occur in cartilage and bone because gelatinous or solid ground substances do not flow around cells like fluids. After the extracellular matrix of cartilage and bone is formed, cells become less active metabolically and probably shrink in size. The spaces remaining around them become visible as the lacunae. In bone, lacunae are inter-connected via minute channels called canaliculi. Osteocytes link to one another via cytoplasmic extensions through canaliculi to provide an avenue for diffusion of nutrients and wastes. Canaliculi of **bone** are essential for osteocytes because diffusion cannot occur across crystalline solids (Rubbelke '99).

Every blood vessel inside the body is accompanied 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

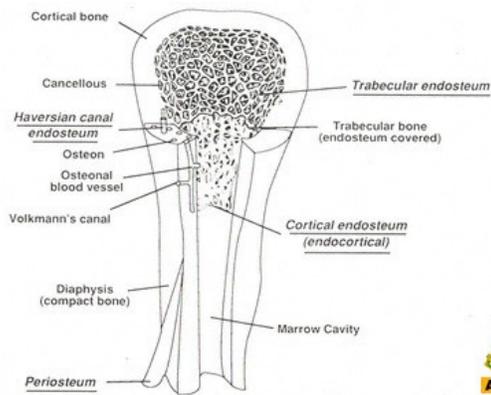
they do not have muscular walls like blood vessels, often working just by gravity. The reason lower legs do not fill up with fluid after a long day is that leg muscles squeeze the lymphatic vessels every step and that squeezes the fluid, known as lymph, upwards. All the body's lymph vessels converge in an impressively thick duct, known as the *ductus thoracicus*, where all the digested fat can 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 (Enders '15: 50-54). **Lymphatics** are collapsed, thin-walled, endothelium-lined channels devoid of blood cells, found in tissue sections. Although the major function of the lymphatic system is fat metabolism, and as a protective drainage system returning interstitial tissue fluid to the blood, they constitute an important pathway for disease dissemination through transport of bacteria and tumor cells to distant sites. Lymphocytes and monocytes not only circulate in the blood and lymph but also accumulate in discrete and organized masses, called the **lymphoreticular system**. Components of this system include lymph nodes thymus, spleen, tonsils, adenoids and Peyer's patches. Less discrete collections of lymphoid cells occur in the bone marrow, lungs, and gastrointestinal tract and other tissues (Saunders '94: 629, 630).



The **skeleton** serves many important functions; it provides the shape and form for our bodies in addition to supporting, protecting, allowing bodily movement, producing blood for the body, and storing minerals. The number of bones in the human skeletal system is a controversial topic. Humans are born with over 300 bones; however, many bones fuse together between birth and maturity. There are eight cranial bones and fourteen facial skeleton bones. An average adult skeleton consists of **206 bones**. The number of bones varies according to the method used to derive the count. Both men and women have 24 ribs, twelve on each side. The human skeleton is composed of both fused and individual bones supported by ligaments, tendons, muscles and cartilage. The Skeletal System serves as a framework for tissues and organs to attach themselves to. This system acts as a protective structure for vital

organs. Major examples of this are the brain being protected by the skull and the lungs being protected by the rib cage. Located in long bones are two distinctions of bone marrow (yellow and red). The yellow marrow has fatty connective tissue and is found in the marrow cavity. During starvation, the body uses the fat in yellow marrow for energy. The red marrow of some bones is an important site for blood cell production, approximately 2.6 million red blood cells per second in order to replace existing cells that have been destroyed by the liver. Here all erythrocytes, platelets, and most leukocytes form in adults. From the red marrow, erythrocytes, platelets, and leukocytes migrate to the blood to do their special tasks. Another function of bones is the storage of certain minerals, mainly, calcium and phosphorus, to regulate mineral balance in the bloodstream. Most anatomists agree there are 206 bones in the human body (Rondberg '96: 9-16).

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There are two types of bone tissue. **Cortical bone** makes up 80 percent. It is solid and dense, giving the skeleton most of its strength. The other 20 percent is **trabecular bone**, which is made up of fine lattice network that surrounds the bone marrow. Although this lattice network is very thin, it provides maximum support with minimum amount of material. Each bone consists of both types of bone tissue, with trabecular bone inside, next to the bone marrow, and cortical bone surrounding it. The amounts of cortical and trabecular bone differ from one

bone to another and even within the same bone. The vertebrae of the spine are composed mostly of trabecular bone surrounded by a thin cortical shell. At the other extreme, the long bones of the arms and legs are mostly made up of cortical bone, with trabecular bone concentrated only at the ends of the bones. Bone tissue is composed of tiny crystals of calcium and phosphorus embedded in a framework of interlocking protein fibers.

The main protein in the bone is collagen type 1. The calcium – phosphorus crystals give the bone strength, hardness and rigidity; the collagen fibers provide flexibility. Other minerals are also present in bone, including fluoride, sodium, potassium, citrate, and other trace minerals. These other minerals function as glue, holding the calcium and phosphorus crystals, that comprise 1 percent of body weight, together (Lane '99: 9). Although plentiful in meat and milk vegans must make a special effort to get plenty of calcium from green leafy and cruciferous vegetables, at every meal, and phosphorus from mushrooms, soy and mung beans.

Bones and teeth are made of the mineral **apatite**: Calcium combines with phosphate to form hydroxyapatite. Calcium is an important component of a healthy diet and a mineral necessary for life. Bone and teeth formation use 95 percent of metabolized dietary calcium. The rest of the calcium in the body has other important uses, such as some exocytosis, especially neurotransmitter release, and muscle contraction. In the electrical conduction system of the heart, calcium replaces sodium as the mineral that depolarizes the cell increasing the action potential. In cardiac muscles, sodium influx commences an action potential, but during potassium efflux, the cardiac myocyte experiences calcium influx, prolonging the action potential and creating a plateau phase of dynamic equilibrium. Long-term calcium deficiency can lead to rickets and poor blood clotting and in case of a menopausal woman, it can lead to osteoporosis, in which the bone deteriorates and there is an increased risk of fractures. While a longterm deficit can affect bone and tooth formation, over-retention can cause hypercalcemia (elevated levels of calcium in the urine and blood), impaired kidney function, prostate cancer and decreased absorption of other minerals. 1000 mg of **Calcium** per day, is the U.S. recommended daily allowance (RDA) for adults, equivalent to three glasses of milk per day, for people other than postmenopausal or pregnant women and patients using corticosteroids 1500 mg per day. **Vitamin D** metabolized by the skin from sunlight, is needed to absorb calcium. **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. The RDA is 1,000-1,250 mg/day of phosphorus (Muscarì '01: 301, 302)

Bone tissue is constantly replaced by removal of old tissue and replacement with new tissue. This process is known as the **bone remodeling cycle**. The cycle occurs when small amounts of bone are lost or broken down by cells known as **osteoclasts**. After this small amount of bone is

lost, or resorbed, a resorption pit is formed on the bone. Another type of cell, or **osteoblast**, moves into the area of bone that has been lost and replaced it with new bone. This process continues on small parts of all of our bones throughout life. Bone mass is maintained by the delicate balance of these two processes. The entire cycle can change in response to different needs of your body. The entire cycle usually takes 4 to 8 months but can range from as little as two months to as long as 2 years. Resorption is rapid, taking only 4 to 6 weeks, new bone formation is slow, taking up to 2 months for each remodeling cycle. Until age 30 the body makes more bone than is lost, but after 30 one tends to lose more bone than the body makes (Lane '99: 9, 10). A diet rich in calcium and phosphorus, usually meat and milk, is necessary to heal bones and teeth.

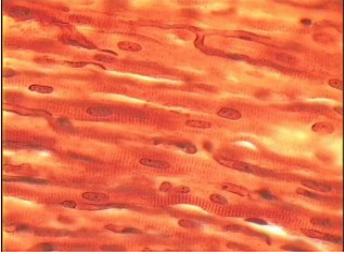
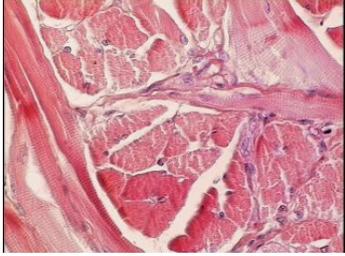
Connective tissues grow in two ways, by **interstitial** or **appositional growth**. The term interstitial implies growth takes place from within the tissue as cells divide by mitosis. Appositional growth on the other hand, implies a tissue grows by adding more cells or materials to its surface. Consider now how crystals enlarge, by deposition of solids on pre-formed crystal complexes. Bone is essentially a crystal so growth involves formation of new layers, called **lamellae**, over pre-existing layers. Bone enlargement then, is always a product of appositional growth. **Bone** always forms within one of two pre-existing connective tissues, mesenchyme or cartilage. **Mesenchyme** is the embryonic connective tissue most often viewed in slides of the umbilical cord. In the cranium and a few other locales flat bones form within mesenchyme tissues in a process called **intramembranous bone formation**. In most other locales where long bones develop, cartilage models of bone are the first structural elements to form. Thereafter, bone replaces this cartilage in a process called **endochondral bone formation**.

Epiphyseal (growth) plates of long bones persist as remnants of the original cartilage and these continue to expand via interstitial growth. However, bone replacement balances this cartilage growth nicely until puberty when hormonal changes occur. This results in a loss of the cartilage in these epiphyseal plates and this terminates longitudinal growth of bones at this time. Lengthening of long bones is really a product of interstitial growth of cartilage in epiphyseal plates and replacement of this cartilage by endochondral bone formation. After growth in height ceases, bones can still be strengthened or repaired because mesenchyme cells are found in the periosteal and endosteal membranes. When these mesenchyme cells are stimulated to form osteoblasts, new layers of bone are built on pre-existing layers via appositional growth. Since this bone growth is a product of mesenchyme, it is more accurately intramembranous bone formation (Rubbelke '99).

All **muscle tissues** are specialized for contraction, possessing the ability to shorten and therefore create a contractile force. Substantial metabolism is necessary to produce energy for these contractions and a useful by-product of chemical reactions is heat. Therefore, muscles contribute to thermoregulation, the maintenance of body temperature. Functions of muscles in our bodies include: support and movement, propulsion of blood through vessels, movement of food or body secretions through tracts, and thermoregulation. Muscle cells possess other attributes besides contractility. All muscles are excitable, able to respond to stimuli, an important capability also common to nervous tissues. Muscles are extensible in that they can be stretched and still maintain contractile ability, some muscles are better at this than others. Finally, muscle cells are associated with elastic connective tissues. These connective tissue elements enable muscles to contract or stretch and then return to their original length, an attribute called elasticity. Muscle types vary in their appearance histologically but one common attribute applies to all varieties, the cells of muscles are long and narrow. For this reason, the term fiber is common descriptive term

for muscle cells. Muscle cells, therefore are also muscle fibers or more specifically myofibers. There are three types of **myofibers**, (1) skeletal voluntary muscles attached to skeletal elements and cartilage; (2) cardiac involuntary muscles making up the myocardium of the heart and (3) smooth involuntary muscles in the walls of hollow organs, blood vessels, and all other body locales where muscles perform work (i.e. pupillary dilation or constriction of the eye).

### Slides of Muscle Cells

Smooth muscle around blood vessel	Longitudinal section of cardiac muscle	Skeletal muscle with both longitudinal and cross-section
		

Credit: Rubbelke '99

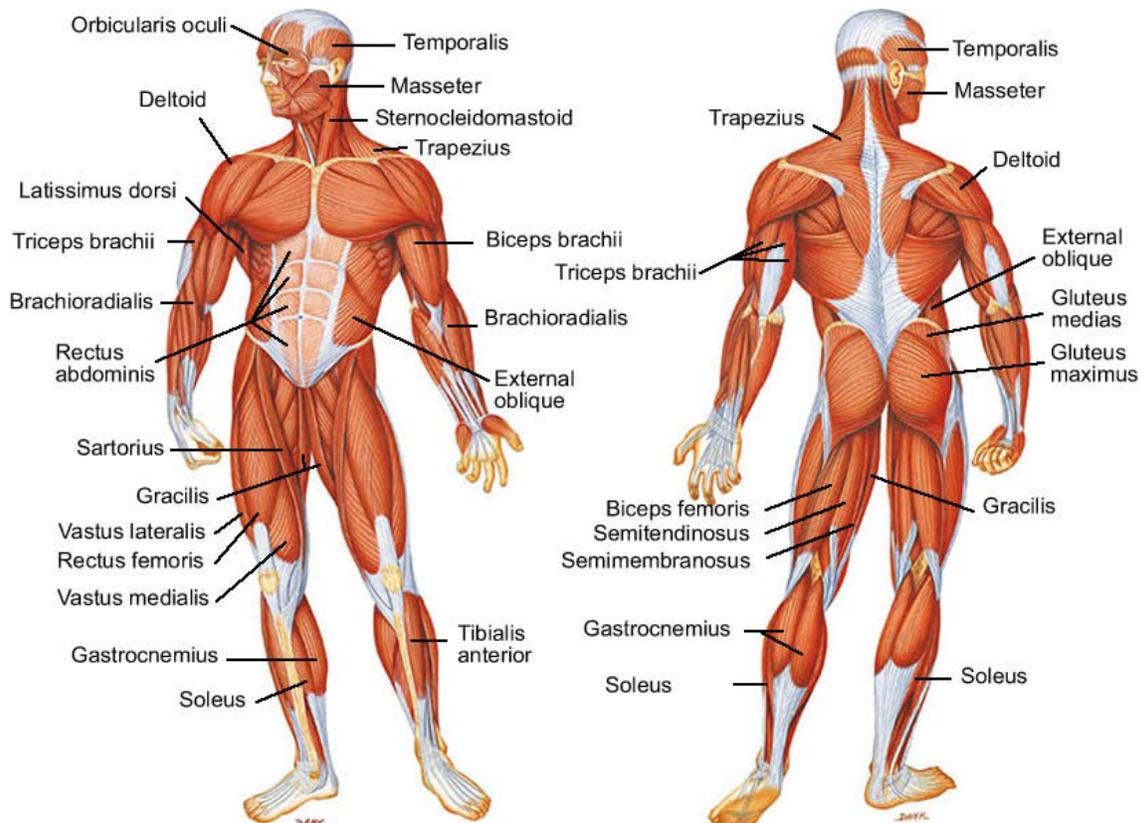
Skeletal and cardiac muscles are classified as striated types while smooth is a non-striated type. The term "**striated**" describes the repeating dark and light bands visible in longitudinal views of cardiac and skeletal muscle types. These bands are important in the identification of skeletal and cardiac muscle in longitudinal sections. **Smooth muscle** is found in walls of hollow organs and blood vessels where contractility and stretch are both specific needs. Smooth muscle cells are spindle-shaped. Smooth muscle also has contractile proteins but these are arranged randomly. In contrast to smooth muscle, cardiac and skeletal muscle types possess an internal ultrastructure of highly organized contractile myofilaments. Actin and myosin myofilaments are stacked and overlapped in regular repeating arrays to form **sarcomeres**. Dark A bands result where myofilaments overlap with light I bands present in areas of non-overlap. The A and I bands repeat along the length of the muscle fibers to create the striations visible under the light microscope. All muscles are invested with connective tissue elements. Delicate fibers wrap around individual muscle cells as **endomysium**. Heavier connective tissue with more collagen surrounds groups of muscle fibers as **perimysium**, dividing each muscle into fascicles. Dense irregular c.t. surrounding entire muscles is **epimysium**. This outer connective tissue covering is the anchor for attachment of surrounding fascia, tendons, ligaments, or aponeuroses (broad, flat tendons). **Collagen fibers** of these tissues intermingle to form tight connections between muscles and other body structures. Vascular elements pass through these connective tissues as they deliver blood to and from the muscles (Rubbelke '99).

**Muscle contraction** is stimulated by the motor neuron sending a message to the muscles from the somatic nervous system. Depolarization of the motor neuron results in neurotransmitters being released from the nerve terminal. The space between the nerve terminal and the muscle cell is called the neuromuscular junction. Neurotransmitters diffuse across the synapse and bind to specific receptor sites on the cell membrane of the muscle fiber. When enough receptors are stimulated, an action potential is generated and the permeability of the **sarcolemma** is altered. This process is known as **initiation** (Rondberg '96: 44, 45).

Step 1) Neuromuscular Control. The axons of the nerve cells of the spinal cord branch and attach to each muscle fiber forming a **neuromuscular junction**. i). An action potential passes down the nerve. ii). The nerve releases  $\text{Ca}^{++}$  that results in the release of Acetylcholine (ACh)

Step 2). ACh binds with the sarcolemma. Step 3). Muscle Fiber Action Potential i). ACh binds with receptors and opens  $\text{Na}^+$  channels.  $\text{Na}^+$  Channels open and there is a decrease in resting potential. ii).  $\text{Na}^+$  rushes in and the sarcolemma depolarizes. iii). The regional depolarization spreads rapidly. The positive patch in the membrane changes the adjacent patch of the membrane. Thus depolarization spreads. iv). The  $\text{K}^+$  channels open and the region repolarizes. Immediately after the action potential passes the membrane permeability changes again.  $\text{Na}^+$  channels close and  $\text{K}^+$  channels open.  $\text{K}^+$  rushes out of the cell. Step 4).  $\text{Ca}^{++}$  is released from the sarcoplasmic reticulum. i).  $\text{Ca}^{++}$  is stored in the sarcoplasmic reticulum. ii). Depolarization releases the  $\text{Ca}^{++}$ . iii). The  $\text{Ca}^{++}$  clears the actin binding sites. Step 5). Sliding Filament Theory of Contraction. During muscle contraction the thin actin filaments slide over the thick myosin filament. When Calcium is present the blocked active site of the actin clears. Step A: Myosin head attaches to actin. (High energy ADP + P configuration) Step B: Power stroke: myosin head pivots pulling the actin filament toward the center. Step C: The cross bridge detaches when a new ATP binds with the myosin. Step D: Cocking of the myosin head occurs when ATP  $\rightarrow$  ADP + P. Another cross bridge can form. The end result is the shortening of the sarcomere. The H zone disappears. The dark A band increases because the actin and the myosin overlap more. The light I band shortens. Step 6).  $\text{Ca}^{++}$  is removed from the cytoplasm. Step 7) Troponin blocks the actin site (Cummings '01).

### Muscles

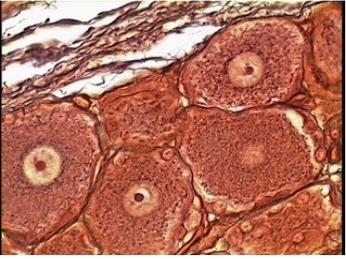
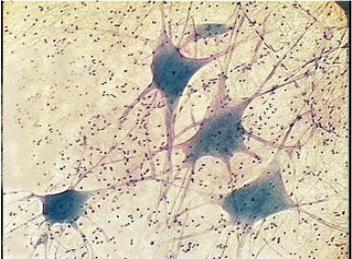
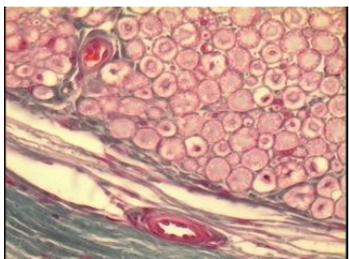


Credit: Pinterest

**Nervous tissue** includes all cells that provide communication between other tissue types surrounded by supportive cells called neuroglia are three types of nervous tissue (1) neurons, (2)

nerves and (3) receptors. Various receptors provide input to the brain which controls effectors such as muscles or glands. As the muscle cell stretches or contracts, the receptor provides information about its activity. Linking the receptor to the Central Nervous System(CNS) is the **sensory neuron**. A chain of two or three sensory neurons enable information to reach the brain. The brain processes incoming sensory information and when necessary sends output along motor pathways to the muscle. Motor pathways as you can see also consist of a chain of two or three neurons. The muscle, due to control exerted by the brain, functions normally. Most neuron cell bodies are located within the brain or spinal cord. Processes or extensions of these neuron cell bodies pass through nerves. Receptors are structures that monitor activity and conditions in various tissues. A variety of receptors can be found in tissue slides depending on location. Nerves link the nervous system to all peripheral tissues. Blood vessels and nerves often run together through tissues as they travel to body sites. Nerves are always present in structures that respond to nervous system control(i.e. muscles and glands).

### Slides of neurons and nerves

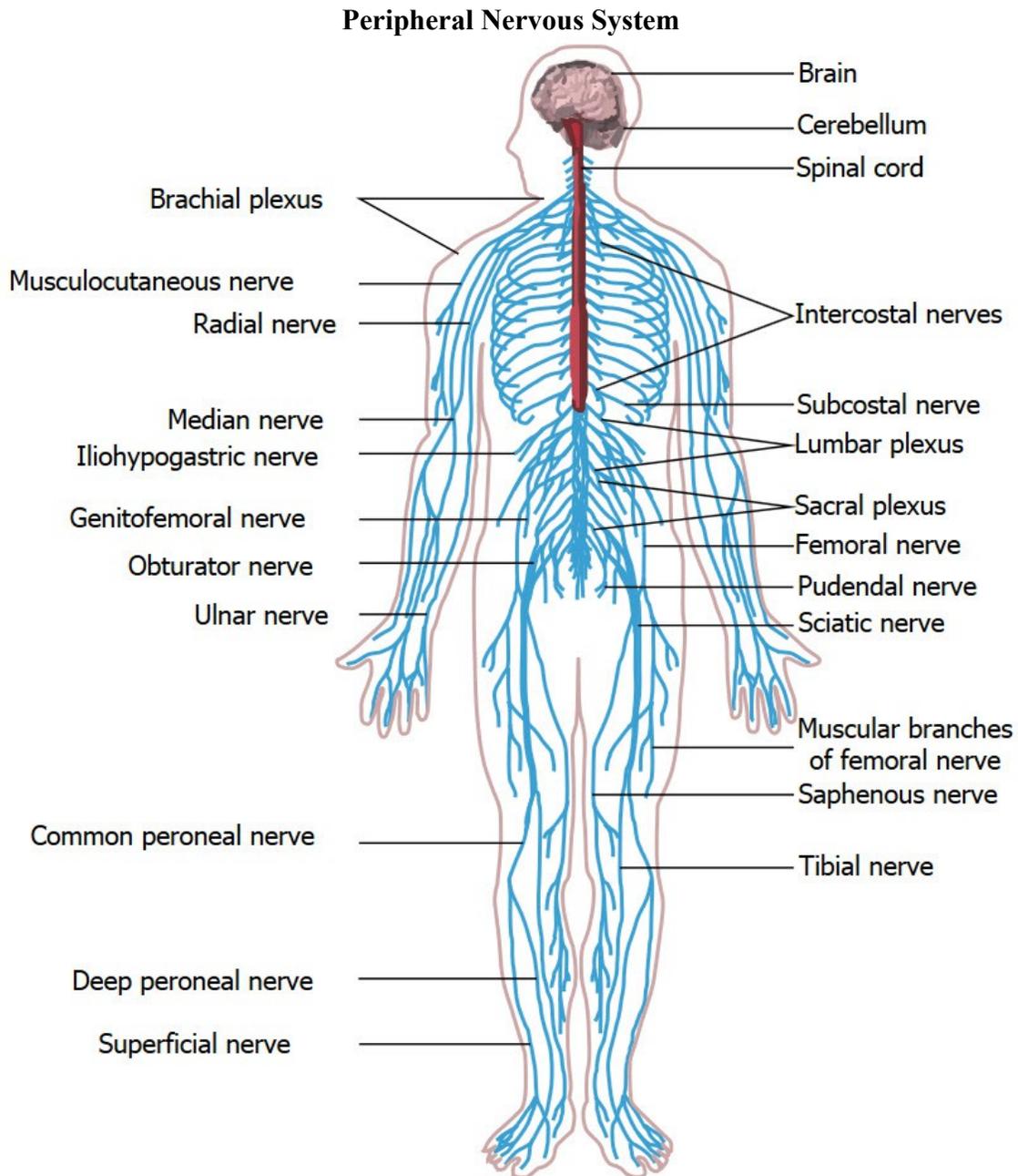
Unipolar sensory neurons of the dorsal root ganglion	Multipolar neurons in spinal cord smear	Cross-section of peripheral nerve
		

Credit: Rubbelke '99

Neurons occur in three varieties (1) **multipolar** types - the majority of neurons; (2) **bipolar** types-sensory neurons found in the special senses and (3) **unipolar** types-sensory neurons located in dorsal root ganglia. Key functional components of neurons shown are the **dendrites** and **axons**. Dendrites collect impulses from other neurons. These impulses summate on the **perikaryon** or nucleus and if sufficient in strength, generate output along the axon. Within the CNS axons terminate near dendrites of other neurons in **synapses**. If axons of CNS neurons carry output to muscles or glands, these pass through nerves of the PNS or peripheral nervous system. The cell body of the neuron is typically found in the CNS. **Nerves** are the wires or cables connecting the processing centers of the CNS to structures throughout the body. Some are called sensory nerves because they only carry sensory information into the CNS.

Most nerves are considered mixed nerves because they carry sensory input and motor output. Most tissues are held together via connective tissues and this is true for nerves also. **Dense connective tissues** surround entire nerves as **epineurium**. Inside the epineurium covering, groups of axons are isolated into cylindrical groups called **fascicles**. These are surrounded by a connective tissue component called **perineurium**. Extending inward from the perineurium are more delicate collagen and elastic fibers that form the **endoneurium**, connective tissue wrappings around and between axons. Axons are either myelinated or un-myelinated. In the PNS the myelin sheath is a product of a neuroglial cell called the **Schwann Cell**. At high magnification, these are visible as spiral wrappings around axons. From a functional standpoint,

myelin wrappings increase the speed and efficiency of impulse conduction along neurons. Impulses jump from one exposed site to another along the axon membrane in a saltatory or "jumping" conduction. These exposed membrane sites along axons are called **Nodes of Ranvier** and are visible in longitudinal views of nerves at higher magnification.



Credit: Kurzweil Accelerating Intelligence November 28, 2014

Receptors are structures that receive information. **Receptors** receive information about stimuli or physical changes in the internal or external environment. With receptors, our nervous system monitors various environmental conditions. When changes occur, these can warrant a response (motor output to effectors) to maintain homeostasis. Receptors are classified broadly as interoceptors (visceroreceptors) or exteroceptors. Interoceptors monitor internal body conditions whereas exteroceptors monitor changes in the external environment. All receptors are linked to sensory neurons. **Meissner's corpuscles** are fine-touch receptors. By moving the

object to the finger tips where Meissner's corpuscles are abundant, the brain gathers information about its shape, texture, and density, information the brain uses to identify the object. In the palm of the hand there are fewer fine-touch receptors. The **Pacinian Corpuscles** are pressure receptors located deeper in the skin enable the detection of an object due to its weight. Meissner's and Pacinian corpuscles are both encapsulated receptor types, surrounded by concentric layers of a specialized connective tissue (Rubbelke '99).

The **neurological exam** is the same for adults and children over the age of 2 years. Children tend to get different neurological problems than adults. The **fontanelles** of children under the age of 2 years should be inspected. Infantile **reflexes** should be assessed. **Sucking reflex** disappears at 3-4 months, touch infants lips with finger to elicit sucking response. **Rooting reflex** disappears at 3-4 months, stroke corner of mouth, observe infant moving head toward stimulation. **Moro reflex** decreased 3-4 months and disappears at 6 months, make loud noise or brace infant's head and back and simulate falling. Infants extend then flex arms and fingers. **Palmar grasp** strongest 1-2 months, disappears 3-4 months, place index fingers into infant's and infant will grasp them. **Tonic neck reflex** decreased 3-4 months and disappears at 6 months, with infant supine, turn head to one side. The upper and lower extremity on that side extend, the opposite extremities flex. **Stepping reflex** disappears before walking, hold infant under axilla in standing position, place feet on flat surface and infant will make stepping motions.

Test **biceps reflexes** (C5-C6) with the arm relaxed, palms down, depress biceps tendon and tap thumb, and see flexion of forearm. Test **triceps reflexes** (C6-C8) with the arm flexed at the elbow and palm toward the body, strike tendon above elbow and watch for contraction of triceps muscle and tension at elbow. Test **brachioradialis reflex** (C5-C6) with the forearms resting palms down, strike radius 1 to 2 inches above the wrist, observe flexion and supination of forearm. Test **patellar reflex** (L2-L4), sitting with feet off the ground, locate patellar tendon and tap it briskly just below patella, look for contraction of quadriceps with extension of knee. Test **ankle reflex** (L5-S2) with leg relaxed, dorsiflex ankle firmly, strike Achilles' tendon, feel and watch for plantar flexion. **Deep tendon reflexes** (DTRs) are grade 0 no response, 1+ low normal, diminished response, 2+ normal, 3+ more brisk than normal, and 4+ brisk, hyperactive (Muscari '01: 132-137).

## II. Dermatology

### 1. Eczema and Dermatitis

The first written work on dermatology describing diseases of the skin was credited to Girolamo Mercuriale in 1572 and was written in Latin. In 1714, Daniel Turner published the first textbook on the subject in the English language (*De morbis cutaneis: A treatise of diseases incident to the skin*), which was, in common with the Mercuriale book, a summary of the literature, it was translated into French and German, and separated leprosy and psoriasis into separate chapters. More than 60 years later in 1777, a massive text in Latin by the French dermatologist, Anne-Charles Lorry gave the first description of the skin as a living organ. It was a Viennese physician, Joseph Jacob Ritter von Plaenck who first attempted, in 1776, to classify skin diseases into categories on the basis of clinical appearance. In his book entitled *Doctrina de morbis cutaneis* (Teachings on the Diseases of the Skin), he arranged the 115 known types of skin diseases into 14 classes, and is regarded as the founder of the modern classification of skin diseases.

Robert Willan, born in 1757 to a Quaker family in Sedbergh, Yorkshire, was appointed in 1783 as physician to the newly established Carey Street Dispensary in London. Skin conditions became his life work which led to new classification system, based upon 10 (later 12) morphological types of skin lesions using terms such as scale, papula and pustule that we are familiar with today. From these lesion types, he divided skin diseases into eight Orders according to their clinical appearance. It was not until the beginning of the 19<sup>th</sup> century that psoriasis was recognized as being a specific clinical entity. The first four Orders were published in 1808 in a book entitled *On Cutaneous Diseases*. This was the first textbook of skin diseases to be systematically illustrated, containing 34 copper-engraved, hand colored plates showing the characteristics morphological appearances of the different skin conditions. Willan became ill and died in Madeira in April 1812 at the age of 55, before being able to complete the second volume that was to contain the remaining four of his Order. His pupil and friend, Thomas Bateman, who succeeded him as physician at the Carey Street Dispensary in 1804, took up the task of completing the classification of skin diseases. He bought the copyright of Willan's work and of the watercolour drawings that accompanied it and subsequently published his own work entitled *A Practical Synopsis on Cutaneous Diseases* in 1813. It was translated into five foreign languages and was so successful the Emperor of Russia ordered several copies and even presented Bateman with a ring worth 100 guineas (Baker '08: 2-4).

**Diagnosis** of a skin trouble localized to one part of the body generalization is the rule. In diagnosing a rather generalized skin eruption, the following three mimicking conditions must be considered (1) drug eruption, (2) contact dermatitis, and (3) secondary syphilis. By region: **Scalp:** Seborrheic dermatitis, contact dermatitis, psoriasis, folliculitis, pediculosis, and hair loss due to the following: male or female pattern, alopecia areata, tinea, chronic discoid lupus erythematosus, post pregnancy, or trichotillomania. **Ears:** Seborrheic dermatitis, psoriasis, infectious eczematoid dermatitis, senile keratosis, and rarely, fungal infection. **Face:** Acne, rosacea, impetigo, contact dermatitis, seborrheic dermatitis, folliculitis, herpes simplex, and less commonly, lupus erythematosus and actinic dermatitis. **Eyelids:** Contact dermatitis due to fingernail polish or hair sprays, seborrheic dermatitis or atopic eczema. **Posterior Neck:** Neurodermatitis, seborrheic dermatitis, psoriasis, or contact dermatitis. **Mouth:** Aphthae, herpes simplex, geographic tongue, contact dermatitis, and less frequently syphilis, lichen planus and pemphigus. **Axillae:** Contact dermatitis, seborrheic dermatitis, hidradenitis suppurativa, and less commonly, erythrasma, acanthosis nigricans, and Fox-Fordyce disease. **Chest and Back:** Tinea versicolor, pityriasis rosea, acne, seborrheic dermatitis, psoriasis, and secondary syphilis. **Groin and Crural areas:** Tinea infection, candida infection, bacterial intertrigo, scabies, pediculosis, and granuloma inguinale. **Penis:** Contact dermatitis, fusospirochetal and candida balanitis, chancroid, herpes simplex, primary and secondary syphilis, and, less frequently, scabies and balanitis xerotica obliterans. **Hands:** Contact dermatitis, dyshidrosis, id reaction to fungal infection of the feet, atopic eczema, erythema multiforme, secondary syphilis, and fungal infection. **Cubital Fossae and Popliteal Fossae** (elbow and knee pits): Atopic eczema, contact dermatitis and prickly heat. **Elbows and Knees:** Psoriasis, xanthomas, and, occasionally, atopic eczema. **Feet:** Fungal infection, primary or secondary bacterial infection, contact dermatitis from footwear or foot care, and less frequently, psoriasis, atopic eczema, erythema multiforme and secondary syphilis (Sauer '85: 15-23).

Certain dermatoses have an increased incidence in various seasons of the year, winter being the busiest season for dermatologists. **Winter:** Atopic eczema, contact dermatitis of hands, psoriasis, seborrheic dermatitis, nummular eczema, winter itch and dry skin (xerosis), and rarely ichthyosis. **Spring:** Pityriasis rosea, dyshidrosis, erythema multiforme (Hebra), and Acne

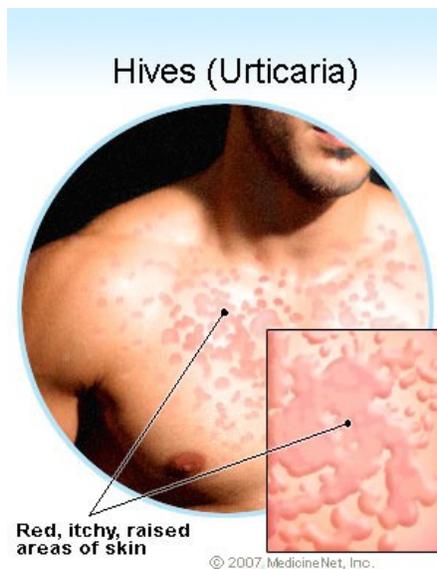
(flares). **Summer:** Contact dermatitis due to poison ivy and oak, tinea of the feet and the groin, candida intertrigo, miliaria or prickly heat, impetigo and other pyodermas, actinic dermatitis, insect bites, tinea versicolor (noticed after suntan), and uncommonly Darier's disease and epidermolysis bullosa. **Fall:** Winter itch, senile pruritis, atopic eczema, pityriasis rosea, contact dermatitis due to ragweed, tinea of the scalp (schoolchildren) and acne (flares). In least developed and war ravaged areas of the world there is an increased incidence of: Scabies, pediculosis, syphilis and other sexually transmitted diseases, bacterial dermatoses, jungle rot in tropical climates: tinea of the feet and the groin, pyoderma, dyshidroses, and miliaria. Some skin diseases are seen with **greater frequency in blacks** than whites: Keloids, dermatosis papulosa nigra, pyodermas of legs in children, pigmentary disturbances from many causes, both hypopigmented and hyperpigmented, traumatic marginal alopecia (from braids and from heated irons used in hair straightening), seborrheic dermatitis of scalp, aggravated by grease on hair, ingrown hairs of beard, acne keloidalis, annular form of secondary syphilis, granuloma inguinale and Mongolian spots. Certain skin conditions **rarely seen in blacks:** Squamous cell or basal cell epitheliomas, actinic keratosis and psoriasis (Sauer '85: 23-28).



**Eczema** is an inflammation of the skin that causes the sensation of itch and makes the sufferer want to scratch. An alternative name for eczema is **dermatitis** – the two terms mean exactly the same thing and it is not uncommon for some doctors to use the term eczema to describe the problem in babies and dermatitis in older children and adults (Mackie '92: 25-28). **Atopic eczemas**, or atopic dermatitis, is a rather common, markedly pruritic, chronic skin condition that occurs in two clinical forms: infantile and adult. The clinical lesions in the infantile form are blisters, oozing and crusting, with excoriation. Adolescent and adult forms marked dryness, thickening (lichenification), excoriation and even scarring. The course varies from a mild single episode to severe chronic, recurrent episodes. The family history is usually positive for one or more of the triad of allergic diseases: asthma, hay fever or atopic eczema. Wool and lanolin (wool fat) commonly irritates the skin of these patients.

Types of **dermatitis** are (1) atopic pleat (Dennie-Morgan fold) an extra fold of skin that develops under the eyes and points to a tendency toward asthma and allergies. (2) Cheilitis is an inflammation of the skin on and around the lips. (3) Hyperlinear palms are increased skin creases on the palms. (4) Hyperpigmented eyelids are eyelids that have darkened in color due to inflammation or hay fever. (5) Ichthyosis dry, rectangular scales on the skin. (6) Keratosis pilaris are small, rough bumps, generally on the face, upper arms and thighs. (7) Lichenification is thick leathery skin due to the constant scratching and rubbing. (8) Papules are small bumps that may open when scratched and become crusty and infected. (9) Urticaria are hives (red bumps) that may occur after exposure to an allergen, at the beginning of flare-ups, or after exercise or a hot bath (Berger & Gordon '04: 258) and (10) lesion(s) caused by methicillin resistant *Staphylococcus aureus* (MRSA) often on the buttocks, but can infect any part of the anatomy, external or internal, and causes toxic shock syndrome when dually exposed to *Streptococcus* spp. treat with an Epsom salt bath. The most common reason for a dermatologic doctor visit is the over-treatment of contact dermatitis. Hydrocortisone ointment, available for \$1, has the broadest spectrum of activity without so much Cushing's disease side-effects of overuse of more powerful corticosteroids.

**Contact dermatitis**, or dermatitis venenata, is a very common inflammation of the skin caused by the exposure of the skin either to primary irritant substances, such as soaps, or to allergenic substances, such as poison ivy resin. The lesion can be of any stage, from mild redness, eczema, or vesicles to large bullae (blisters) with oozing. Crusting from secondary bacterial infection, excoriations, and lichenifications occur. Any agent can affect any area of the body, however, certain agents commonly affect certain skin areas. Corticosteroid-antibiotic ointment can be substituted by hydrocortisone powder) mixed with white petrolatum (15.0) or antibiotic ointment or water-washable bases. This cuts down the cost of the prescription. In chronic cases resistant, to the corticosteroid ointment add, as indicated, sulfur (3% to 5%), coal tar solution (3% to 10%), but these are carcinogenic or an antipruritic agent such as menthol (0.25%) is highly recommended or camphor (2%). Or take an oral corticosteroid therapy, a short course of prednisone will often improve or cure chronic dermatitis (Sauer '85: 69, 73, 75). **Industrial dermatoses** are common. Sixty-five percent of all the industrial diseases are dermatoses. The patient with an average case of occupational dermatitis is compensated for 10 weeks, resulting in a total cost of over \$100 million a year in the United States. The most common cause of these skin problems is contact irritants, of which cutting oils are the worst offenders. Lack of adequate cleansing is a big contributing factor. **Drug eruptions** are a common cause of dermatoses, and any patient with a rather generalized skin eruption should be questioned concerning the use of oral or parenteral drugs. Any drug systemically administered is capable of causing a skin eruption (Sauer '85: 75, 76) the list is too long to quote.



The commonly seen entity of **urticaria**, or hives, can be acute or chronic and due to known or unknown causes and usually clears up with topical hydrocortisone treatment. Poison oak, ivy or sumac should be highly suspected; discoid and systemic lupus erythematosus may be due to chronic, high dose or untreated dermal and respiratory exposure (these toxins tend to be omitted from the medical school literature although they abound in the public library). Urticaria, erythema multiforme and its variants and erythema nodosum are included under the heading of vascular dermatoses because of their vascular reaction patterns. Penicillin is probably the most common cause of acute hives, but any other drug, can cause the reaction. Foods are a common cause of acute hives, the main offenders are seafood, strawberries, chocolate, nuts, cheeses, pork, eggs, wheat, and milk. Chronic hives can be caused by traces of penicillin in milk products. Insect bites and stings

from mosquitos, fleas, spiders and contact with certain moths, leeches and jellyfish cause hives. Hives result from heat, cold, radiation energy, and physical injury. Nasal sprays, insect sprays, dust, feathers, pollens, and animal danders are some offenders. A focus of infection is always considered, sooner or later, in chronic cases of hives. Urticaria has been seen with liver disease, intestinal parasites, cancer and rheumatic fever (Sauer '85: 109-113).



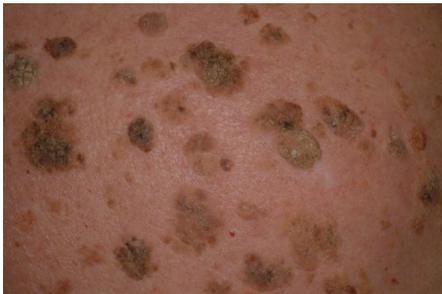
**Systemic lupus erythematosus** produces red, mildly scaly, diffuse, puffy lesions, purpura is also seen. There is no scarring only mild hyperpigmentation. Lesions occur in the face in "butterfly area", arms, fingers and legs and are usually symmetrical. Acute onset with fever, rash, malaise, and joint pains. Systemic complications of nephritis, arthritis, epilepsy, pancarditis, hepatitis, and so on make life difficult. Biopsy is useful, especially fresh tissue immuno-fluorescent studies. Leukopenia, anemia, albuminuria, increased sedimentation rate, positive

ANA test, and biologic false-positive serologic test for syphilis are found. Most cases respond rapidly to corticosteroid and supportive therapy, but the prognosis for life is poor (Sauer '85: 239-242). The term **erythema multiforme** is an uncommon distinct disease of unknown cause characterized by red iris-shaped or bull's eye – like macule, papules, or bullae confined mainly to the extremities, the face and the lips. It is accompanied by mild fever, malaise, and arthralgia. It usually occur in children and young adults in the spring and fall, and has a duration of 2 to 4 weeks and frequently is recurrent for several years. Poison oak, ivy and sumac exposure is highly suspected. Hypersensitivity usually begins after inhalation from a burn-pile and patient can no longer tolerate bush-walking although they often fail to identify exposure to poison oak, ivy or sumac and do not detoxify. **Erythema nodosum** is an uncommon reaction pattern seen mainly on the anterior tibial areas of the legs. It appears as erythematous nodules in successive crops and is preceded by fever, malaise, and arthralgia. The causes of erythema nodosum are streptococcal infection (rheumatic fever, pharyngitis, scarlet fever, arthritis), fungal infection (coccidioidomycosis, Trichophyton infection), pregnancy, lymphogranuloma venereum, syphilis, chancroid, drugs (sulfonamides, contraceptive pills, iodides, bromides) and, rarely, tuberculosis.

**Erythema induratum** is a chronic vasculitis of young women that occurs on the posterior calf area and often suppurates; biopsy shows a tuberculoid-type infiltrate. **Necrobiosis lipoidica diabetorum** is an uncommon cutaneous manifestation of diabetes mellitus, characterized by well-defined patches of reddish yellow atrophic skin, primarily on anterior areas of legs; the lesions can ulcerate. **Periarthritis nodosa** is a rare, fatal arteritis that most often occurs in males; 25% of cases show painful subcutaneous nodules and pupura, mainly of the lower extremities. **Nodular vasculitis** is characterized by chronic, painful nodules of the calves of middle-age women, which rarely ulcerate but recur commonly. **Superficial thrombophlebitis migrans** of Buerger's disease is an early venous change of Buerger's disease commonly seen in males. **Nodular panniculitis** or Weber-Christian disease occurs mainly in obese middle-aged women; tender, indurated, subcutaneous nodules and plaques are seen, usually on the thighs and the buttocks, each crop is preceded by fever and malaise; residual atrophy and hyperpigmentation occur. **Leukocytoclastic vasculitis** includes a constellation of diseases, such as allergic angiitis, allergic vasculitis, necrotizing vasculitis, or cutaneous-systemic vasculitis. Treatment includes bed rest and corticosteroids. **Pityriasis rosea** is a moderately common eruption, mainly of the trunk of young adults. It is mildly pruritic and occurs most often in the spring and the fall. Following the development of a "herald patch" new generalized lesions continue to appear for 2 to 3 weeks. The entire rash commonly disappears within 6 weeks. Recurrences are rare. If the skin becomes too dry from the colloidal bath and lotion, alternate it with Hydrocortisone 1/2% and prednisone, 5 mg or other corticosteroid (Sauer '85: 109-113).

Two common physical irritations of the skin, **photosensitivity dermatoses**, are sunburn, due to ultraviolet radiation and radio-dermatitis, due to ionizing radiation. A sunburn can be mild or severe. The most severe reactions come from prolonged exposure at swimming areas or when the individual falls asleep under an ultraviolet lamp. The degree of reaction depends on the length and intensity of exposure, the person's complexion and previous conditioning of the skin. The reaction can vary from a simple erythema to a measles like rash, to a severe bullous eruption. Varying degrees of redness develop within 2 to 12 hours after exposure to the ultraviolet radiation and reach maximum intensity within 24 hours. Scaling or peeling, is the aftermath of any overexposure. Vesiculation may be complicated by secondary infection.

**Sunlight allergy** (polymorphic light eruption or actinic dermatitis) is manifested clinically by (1) plaquelike erythematous lesions, (2) contact dermatitis like lesions, (3) popular pruritic lesions and (4) erythema multiforme-like lesions. The most frequent **photosensitizers**, accelerating sunburn, are demeclocycline (Declomycin), doxycycline (Vitamycin), chlorpromazine (throzine), hydrochlorothiazide (Hydro-Diuril, Esidrix), sulfonyleureas (Orinase) and nalidixic acid (Negram). Short-term oral chloroquine therapy combined with protection from sunlight is quite effective for polymorphic light eruptions or actinic dermatitis. Application of a sunscreen with sun protective factor (SPF) 15, or better, cream or lotion should be done when planning on spending more than 20 minutes in the sun. Sensible and gradual sun exposure of the skin is the best preventative for sunburn. Sunburn may be treated with moisturizer. Sunburn should be treated with Burow's solution wet dressing in cool water. Menthol 0.25% in nonalcoholic white shake lotion may be applied locally to affected areas. A few days later to prevent secondary infection apply menthol 0.25%, Neosporin or other antibiotic ointment and white petrolatum (Sauer '85: 279, 287, 281).



**Actinic or senile keratosis** appear mainly after the age of 50 but are seen in highly susceptible individuals in their 30s. Chronic sun and wind exposure on the part of a light-complexioned farm, sailor or gardener will lead to the development these superficial, red scaling keratoses on exposed surfaces of the face, the lips (actinic cheilitis), the ear, neck and the dorsum of the hands. Prickle cell epitheliomas arise in an appreciable percentage of these **actinic keratoses**. 5-Fluorouracil solution (Efudex 2% or 5%, fluoroplex 1%) is probably the treatment of choice and should be applied to all sun-damaged area for 2 to 4 week, or to the limits of tolerance, whichever is first. Complete blocking of the sun rays is desired for prevention of actinic keratoses, a flare-up or lupus erythematosus or a sun allergy reaction. Application of a sunscreen with sun protective factor (SPF) 15, or better, cream or lotion should be done when planning on spending more than 20 minutes in the sun. Sensible and gradual sun exposure of the skin is the best preventative for sunburn. Sunburn should be treated with Burow's solution wet dressing in cool water. Menthol 0.25% in nonalcoholic white shake lotion may be applied locally to affected areas. A few days later to prevent secondary infection apply menthol 0.25%, Neosporin or other antibiotic ointment and white petrolatum (Sauer '85: 287, 281). These eruption most often resembles an exaggerated sunburn but may take the form of itching only (from hydrochlorothiazide) or may be present as large bullae (from nalidixic acid). Nail detachment or onycholysis also occurs. Sometimes photoallergy lingers for months or years even without further exposure to the allergen. Topical corticosteroids may afford some relief.

**Porphyria cutanea tarda** (PCT) is common in patients over 40, who drink heavily and often do not complain of undue sensitivity to sunlight. Association with diabetes mellitus is found in 25% of cases and hepatic siderosis in over 80% of cases. Over 90% of untreated patients have abnormal bromsulphalein retention. Increasingly seen in patients undergoing hemodialysis for renal failure. It has also been associated with dioxin intoxication. Cutaneous lesions include hyperpigmentation in exposed areas, hypertrichosis, blisters and erosions from abnormal fragility of the exposed skin, milia, periocular erythema, and scleroderma. The diagnosis rests with demonstrating a greatly elevated urinary uroporphyrin excretion ( $>500 \mu\text{g}/24 \text{ hours}$ ). A tentative diagnosis can be made by finding the characteristic red fluorescence of a fresh acidified urine sample under Wood's illumination, which is usually positive when the urinary uroporphyrin excretion exceeds  $1000 \mu\text{g}/24 \text{ hours}$ . The treatment of choice is multiple phlebotomies over a period of months. Generally, a lasting remission, may be achieved by withdrawal of 500 ml of blood every 2 weeks for three to four times, then every 3 to 6 weeks for a total of 15 to 20 pints of blood. An alternative treatment low-dose chloroquine therapy, 125 mg is given twice weekly for several months. Abstinence from alcohol should be urged.

**Protoporphyrin** is the second most common cutaneous porphyria, protoporphyria, it is inherited and usually begins in childhood. Children complain bitterly of burning and stinging on the exposed areas after only minutes in the sun. For several days after exposure they may display marked erythema, purpura and edema of the face and hands. Photosensitivity may persist well into adult life, but between attacks there are few objective lesions. The diagnosis rests with demonstrating an elevated free erythrocyte protoporphyrin concentration ( $>100 \mu\text{g}/100 \text{ ml}$  of packed red cells). Oral carotene (Solatene) in a dosage of from 60 mg to 180 mg/day is the treatment of choice. Examples of **other photodermatosis** are solar urticarial, Hartnup disease, pellagra, xeroderma pigmentosum, Bloom's syndrome and actinic reticuloid. Poikiloderma approaching that seen in radiodermatitis may also be produced by ultraviolet light, both on an acquired basis (poikiloderma of Civatte) and rarely, on an inherited basis (poikiloderma congenitale). Rosacea is often aggravated by excessive sun exposure (Sauer '85: 283-287).

Ionizing radiation is hazardous. Acute **radiodermatitis** is divided into three degrees of severity. The first degree is manifested by the slow development of erythema, hyperpigmentation and usually hair loss. A single dose of x-rays necessary to produce these changes is called an "erythema dose". All of the changes in the first degree are reversible. The second degree is characterized by vesicle formation, erosions, hair loss, secondary infection and delayed healing. Atrophic and telangiectasis are the end results. The third degree of radiodermatitis includes ulceration, infection and greatly delayed healing. Epitheliomatous changes are very common in the chronic ulcer or scar. Chronic radiodermatitis can follow acute radiation injury or develop slowly, following repeated small radiation exposures. The dosage of ionizing radiation on the skin is cumulative; the effects of previous radiation therapy is never erased by the passage of time. When a complete course of radiation therapy has been given to a particular body area, no further radiation should be administered to this area at any future time. Acute cases of radiodermatitis can be treated symptomatically with bland local measures (Sauer '85: 279-282).

**Pruritis**, or itching, brings more patients to the doctor's office than any other skin disease. Itchy skin is not easily cured or even alleviated. Many hundreds of proprietary over-the-counter and prescription drugs are touted as effective anti-itch remedies, but not one is 100% effective. Pruritis is a symptom of many of the common skin diseases such as contact dermatitis, atopic eczema, seborrheic dermatitis, hives, some drug eruptions, and many other dermatoses. Relief of

itching is of prime importance in treating these diseases. Diffuse itching of the body without perceptible skin disease usually is due to wintertime dry skin, senile skin, or to unknown causes. Senile pruritus is a resistant form of generalized pruritus, most commonly, on the scalp, shoulders sacral areas and legs of the elderly patient. **Essential pruritis** is the rarest form of the generalized itching diseases. Before a diagnosis of essential pruritus is made the following diseases must be ruled out by appropriate studies: drug reactions, diabetes mellitus, uremia, lymphoblastoma (mycosis fungoides, leukemia, or Hodgkin's disease), liver disease, or intestinal parasites. Treatment is the same as for senile and winter pruritus: (1) Limiting general bathing to once a week, (2) sparing use of a bland soap such as Dove, (3) addition of an oil to the tub, such as Lubath, Domol, Nivea, Mellobath, or Alpha-Keri, (4) local application twice daily of white petrolatum, Nivea Skin Oil or Cream, Lowila Emollient, Keri Lotion, Nutraderm, or Lubriderm, (5) oral antihistamines, which are sometimes effective, such as Chlor-Trimeton 4 mg q.i.d., Temaril 2.5 mg q.i.d., or Dimetane 4 mg q.i.d. For some of the more severe localized areas of the itch, a corticosteroid ointment is indicated. The injection of 30 mg trimcinolone acetonide suspension intramuscularly every 4 to 6 weeks, for 2 or 3 injections, is quite beneficial (Sauer '85: 101).

**Pruritis ani**, itching of the anal area is a common malady that can vary in severity from mild to marked. The following irritating foods should be removed from the diet: chocolate, nuts, cheese, and spicy foods. Coffee, because its stimulating effect on any form of itching, should be limited to 1 cup a day. Rarely, certain other foods will be noted. Excessive bathing and scrubbing of the anal area is harmful and irritating and must be stopped. Pruritus ani from antibiotic therapy is seen frequently due an overgrowth of candidal organisms. Treatment involves (1) Burow's solution wet packs, preparation-H or witch hazel, (2) Nonalcoholic white shake lotion, (3) Benadryl, 50 mg, (4) hydrocortisone (1%), (5) intralesional corticosteroid injection, (6) oral corticosteroid therapy for resistant cases. Itching of the female vulva or the male scrotum can be treated in much the same way as pruritis ani.

**Scrotal pruritus** is due to tinea infection, contact dermatitis from soaps, powders, clothing or neurodermatitis. **Vulvar pruritus** is due to *Candida* or *Trichomonas* infections; contact dermatitis from underwear, douche chemicals, contraceptive jellies and diaphragms, chronic cervicitis, neurodermatitis, menopausal or senile atrophic changes, lichen sclerosus et atrophicus, or leukoplakia. Pruritus vulvae is frequently seen in patient with diabetes mellitus and during pregnancy. Treatment can be adapted from that for pruritus ani with the addition of a daily douche, such as vinegar, 2 tablespoons to 1 quart of warm water. **Lichen planus** is an uncommon, chronic, pruritic disease characterized by violaceous flat-topped papules that are usually seen on the wrists and legs. Mucous membrane lesions on the cheeks or lips are whitish. The outbreak is sudden with the chronic course averaging 9 months, some cases last several years. There is no effect on the general health except for itching. Corticosteroids are of definitive value for temporarily relieving the acute cases that have severe etching or a generalized eruption. Patients are to avoid excessive bathing with soap, and use Menthol ¼%, in alcoholic white shake lotion q.s. 120.0 or an antihistamine tablet for itching, but it may cause drowsiness. On subsequent visits, add phenol 0.5%, camphor 25, or coal tar solution 5% (not recommended due to cancer risk) to the lotion and Meprobamate 400 mg (Sauer '85: 105-107, 144).

Seborrheic dermatitis, or **dandruff**, is exceedingly common on the scalp. Seborrheic dermatitis is considered a "condition" of the skin and not a "disease". It occurs as part of the "acne seborrhea complex" most commonly seen in the brown-eyed brunette who has a family history

of these conditions. Dandruff is spoken of as, oily or dry, but it is all basically oily. A differential diagnosis must be made: **Psoriasis**, sharply defined, whitish, dry, scaly patches, typically elsewhere on the body as well, **Neurodermatitis**, usually a single patch on the posterior scalp area or around the ears, intense itching, excoriation and thickening of the skin. **Tinea capitis** usually occurs in a child, broken-off hairs, with or without pustular reaction are seen. **Atopic eczema** usually occurs in children, diffuse dry scaliness, eczema also on the face, arms and legs. **Dandruff** is not contagious and will not cause baldness. An anti-dandruff **shampoo** is often effective. Shampoo hair with three applications of Selsun Suspension, use no other soap. Tar shampoos such as Ionil T, Sebutone, X-Seb T, Vanseb-T and T-Gel require frequent shampooing to keep scaling and itching to a minimum. Other effective shampoos are Head and Shoulders, Sebulex, Ionil and X-Seb. A corticosteroid cream can be applied locally to body lesions (Sauer '85: 117-120).



**Bullous skin diseases** are the most dramatic. **Erythema multiforme bullosum** has no known cause, clinically one sees large vesicles and bullae usually overlying red, irislike macules. It can last from days to months. Slight malaise and fever may precede a new shower of bullae, but for the most part the patient's general health is unaffected. Itching may be mild, or severe enough to interfere with sleep. When the characteristic iris lesions are absent, it is difficult to differentiate this bullous eruption from early pemphigus vulgaris, dermatitis

herpetiformis, bullous hives, and drug eruptions. Corticosteroids orally and by injection are the single most effective drugs in use today. In almost all cases of bullous diseases, it is necessary to examine fresh tissue biopsy for deposits of immune reactants, immunoglobulins (ig) and complement components, at or near the basement membrane zone. Routine histologic examination of a formalin-fixed biopsy is of course also usually indicated. **Pemphigus vulgaris** is a miserable, odoriferous, debilitating skin disease. Prior to the advent of corticosteroid therapy, the disease was eventually fatal. The early lesions of pemphigus are small vesicles or bullae on apparently normal skin. Redness of the base of the bullae is unusual. Without treatment, the bullae enlarge and spread, and new ones balloon up on different areas of the skin or the mucous membranes. Rupturing of the bullae leaves large eroded areas. Bacterial infection with crusting is marked and account, in part, for the characteristic mousy odor. Lesions that heal spontaneously or under therapy do not leave scars. When untreated, pemphigus can be rapidly fatal or assume a slow lingering course, with debility, painful mouth and body erosions, systemic bacterial infection, and toxemia. Spontaneous temporary remissions do occur without therapy.

Three clinical variations of pemphigus exist: **Pemphigus vegetans** is characterized by the development of large granulomatous masses in the armpits and groin. Secondary bacterial infection, is most marked in this form. Pemphigus vegetans must be differentiated from a granulomatous ioderma or bromoderma and from impetigo herpetiformis. **Pemphigus foliaceus** appears as a scaly moist, generalized exfoliative dermatitis. The characteristic mousy odor of pemphigus is dominant in this variant, which is also remarkable for its chronicity. The response to corticosteroid therapy is less favorable in the foliaceus form than in the other types. Pemphigus erythematosus resembles a mixture of pemphigus, seborrheic dermatitis, and lupus erythematosus. The distribution of the red, greasy, crusted and eroded lesions is on the butterfly

area of the face, the sternal area, the scalp and occasionally the mouth. The course is more chronic than for pemphigus vulgaris and remissions are common. Pemphigus must be differentiated from dermatitis herpetiformis and erythema multiforme bullosum. Treatment begins with Triamcinolone, 4 mg, or related corticosteroids, one tablet for 4 days, then reduce the dose slowly as warranted. Local therapy to make the patient more comfortable and decrease the odor by reducing secondary infection is potassium permanganate crystals 2 teaspoonfuls of the crystals in the bathtub with approximately 10 inches of lukewarm water. The crystals should be dissolved completely in a glass of water before adding to the tub. The solution should be made fresh daily. The tub stains can be removed by applying acetic acid. Talc can be applied to bed sheeting and to erosions twice a day. Sulfur, ppt. 3% and Neo-Polycin or other antibiotic ointment can be applied to small infected areas. Supportive therapy includes vitamins, iron, blood transfusions, and oral antibiotics. Methotrexate therapy is also used. Pemphigus is not contagious or infectious (Sauer '85: 222-224).



The mucous membranes of the body adjoin the skin at the oral cavity, nose, conjunctiva, penis, vulva and anus. Histologically, these membranes differ from the skin in that the horny layer and the hair follicles are absent. **Aphthous stomatitis**, canker sores, are extremely common, painful, superficial ulcerations of the mucous membranes of the mouth. One or more lesions develop at the same time and heal without scarring in 5 to 10 days. They can recur at

irregular intervals. Chocolate, nuts and fruits can precipitate the lesions. Little can be done and the ulcers will heal in a few days. Kenalog in Orabase (prescription needed) applied locally before meals will relieve some of the pain. Doxycycline 100 mg therapy, whereby an oral suspension is made with water and kept in the mouth for 2 minutes and then swallowed, daily, is quite healing. Common conditions are infectious diseases, herpes simplex and Fordyce condition. Rarer causes are Phentoin sodium reaction, halitosis, periadenitis mucosa necrotica recurrens, foot and mouth disease, Koplik's spots, Burning tongue (glossodynia), black tongue (hair tongue, lingua nigra), Moeller's glossitis, furrowed tongue (grooved tongue, scrotal tongue glossitis rhomboidea mediana, Sjögren's syndrome, cheilitis glandularis apostematosa). Rarer genital mucous membrane conditions are fusospirochetal balanitis, balanitis xerotica oblitera, lichen sclerosus et atrophicus and ucus vulvae acutum. **Geographic tongue** is an extremely common condition of the tongue that usually occurs without symptoms. Irregularly shaped (map-like or geographic) pale red patches are seen on the tongue. Close examination reveals that the filiform papillae are flatter or denuded in these areas. The patches slowly migrate over the tongue surface and heal without scarring. The disorder may come, go, or persist. Some patients complain of burning and tenderness when eating sour or salty food. There is not effective or necessary treatment (Sauer '85: 273-277).

**Dermatitis herpetiformis** is a rare, chronic, markedly pruritic, popular, vesicular and bullous skin disease of unknown etiology. The patient describes the itching of a new blister as a burning itch that disappears when the blister top is scratched off. The severe scratching results in the formation of excoriations and popular hives, which may be the only visible pathology of the disease. Individual lesions heal, leaving an area of hyperpigmentation that is very characteristic. The duration of the disease varies from months to as long as 40 years, with periods of remission scattered in between. Laboratory tests should include fixed tissue and fresh tissue biopsy. The latter will show in most cases granular IgA in the dermal papillae, along with the third

component of complement (C3). A blood count usually shows an eosinophilia. **Herpes gestationis** is a vesicular and bullous disease that occurs in relation to pregnancy. It usually develops during the second and third trimester and commonly disappears after birth, only to return with subsequent pregnancies. Systemic corticosteroids are usually indicated. Dermatitis herpetiformis must be differentiated from pemphigus, erythema multiforme bullosum, neurotic excoriations, scabies and subcorneal pustular dermatosis. Treatment would consist of local and oral measures to control itching and a course of one of the following quite effective drugs: sulfapyridine (0.5 g) or dapsone (25 mg). These initial doses should be decreased or increased to the patient's response. These drugs can be toxic, and the patient must be under surveillance. Corticosteroids can be used for a short period to give relief in acute flare-ups (Sauer '85: 224-227).

**Stasis dermatitis** is a common condition due to impaired venous circulation in the legs of older patients. Almost all cases are associated with varicose veins. Early cases of stasis dermatitis begin as a red scaly, pruritic patch that rapidly becomes vesicular and crusted, owing to scratching and subsequent secondary infection. The bacterial infection is responsible for the spread of the patch and the chronicity of the eruption. Hyperpigmentation is inevitable following the healing of either simple or severe stasis dermatitis of the legs. Treatment consists of rest and elevation of the affected area, Burow's solution wet packs, an antibiotic-corticosteroid ointment and surgical removal of varicose veins. For the more severe case of stasis dermatitis with oozing, cellulitis, and pitting edema, hospitalization or enforced bed rest for the purpose of applying wet packs for longer periods of time, a course of oral antibiotics, and an Ace elastic bandage, 4 inches wide, No.8.

**Exfoliative dermatitis** is a generalized scaling eruption of the skin. The causes are many but it is a rare skin condition. Various degrees of scaling and redness are seen, ranging from fine, generalized, granular scales with mild erythema to scaling in large plaques, with marked erythema and lichenification. Generalized lymphadenopathy is usually present. Itching is most cases, is intense. The prognosis for an early cure of the disease is poor. The mortality rate is high in older patients to generalized debility and secondary infection. Some authors state that from 35% to 50% of these exfoliative cases, particularly those in patients over the age of 40 are the result of lymphomas. However years may pass before the lymphoma becomes obvious. Biopsy of an enlarged lymph node will reveal lipomelanotic reticulosis. A high protein diet should be prescribed these patients have a high basal metabolic rate and catabolize protein. Some patients prefer a daily cool bath in a colloid solution for relief of itching (1 box of solution starch or 1 cup of Aveeno to 10 inches of water). For most cases, however, generalized bathing dries the skin and intensifies the itching. Locally an ointment is desired but some prefer an oil liquid. White petrolatum can be applied locally and as time progresses more antipruritic effect can be gained by adding menthol 0.25% camphor 2%, phenol 0.55 or coal tar solution 1% to 5%, watch for sensitivity. Zinc oxide 40% can be mixed with olive oil and applied locally with hands or a paint brush, antipruritic chemicals can be added to this. Oral antihistamine, for example, chlorpheniramine, 4 mg, 8 mg or 12 mg, 1 tablet for itching. Subsequent care calls for a systemic steroid. For resistant cases the corticosteroids have consistently provided more relief than any other single form of therapy. For example, Prednisone, 5 mg, 4 tablets every morning for 1 week, then 2 tablets every morning. Systemic antibiotics may or may not be indicated (Sauer '84: 229, 230).

**Purpuric dermatoses** are caused by an extravasation of red blood cells into the skin or mucous membranes. The lesions can be distinguished from erythema and telangiectasia by the fact that

purpuric lesions do not blanch under pressure applied by the finger. Petechiae are small, superficial purpuric lesions. Ecchymoses, or bruises, are more extensive, round or irregularly shaped purpuric lesions. Hematomas are large, deep, fluctuant, tumorlike hemorrhages into the skin. The purpuras can be divided into the thrombocytopenic forms and the nonthrombocytopenic forms. **Thrombocytopenic purpura** may be idiopathic or secondary to various chronic diseases or to a drug sensitivity. The platelet count is below normal, the bleeding time is prolonged, and the clotting time is normal, but the clot does not retract normally. This form of purpura is rare. **Nonthrombocytopenic purpura** is more commonly seen. Henich's purpura is a form of non-thrombocytopenic purpura most commonly seen in children that is characterized by recurrent attacks of purpura accompanied by gastrointestinal pathology. It is thought to be related to Schönleins' purpura. The ecchymoses, or senile purpura, seen in elderly patients following minor injury are very common. Ecchymoses are also seen in patients who have been on long-term systemic corticosteroid therapy. Another common purpuric eruption is that known as **stasis purpura**. These lesions are associated with vascular insufficiency of the legs and occur as the early sign of this change, or they are seen around areas of stasis dermatitis or stasis ulcers. Quite frequently seen is a petechial drug eruption due to the chlorothiazide diuretics. For these pigmented purpuric eruptions, **therapy** with a combination of hesperidin complex, 200 mg t.i.d. and vitamin C, 500 mg, t.i.d. is occasionally effective. Occlusive dressing therapy with corticosteroid cream is also beneficial. **Telangiectases** are abnormal dilated small blood vessels. The primary telangiectases include the simple and compound hemangiomas of infants and the spider hemangiomas. Secondary telangiectasia is very commonly seen on the fair-skinned individual as a result of aging and chronic sun exposure. X-ray therapy and burns can also cause dilated vessels. Treatment for secondary telangiectasias can be accomplished quite adequately with very light electro-surgery to the vessels, which is usually tolerated without anesthesia (Sauer '85: 113-116).

There are two forms of **scleroderma**: localized scleroderma (morphea) a benign disease, and diffuse scleroderma (progressive systemic sclerosis) a serious disease. **Morphea** is an uncommon skin disease of unknown etiology with no systemic involvement. Lesions are single or multiple, violaceous, firm, indurated macules and plaques that enlarge slowly. The progressing border retains the violaceous hue, while the center becomes whitish and lightly depressed beneath the skin surface. Bizarre lesions occur, such as long linear bands on extremities, saber-cut type lesions in scalp, or lesions involving one side of the face or body, causing hemiatrophy. Mild or severe scarring after healing is inevitable. Scalp lesions result in permanent hair loss. Disability is confined to the area involved. Lesions tend to involute slowly and spontaneously. Relapses are rare. No therapy is necessary for most mild cases. For extensive cases, a fluorinated corticosteroid cream is applied locally for months.

**Diffuse scleroderma** (progressive systemic sclerosis) is an uncommon systemic disease of unknown etiology, characterized by a long course of progressive disability due primarily to lack of mobility of the areas and the organs that are affected. The skin becomes hidebound, the esophagus and the gastrointestinal tract semirigid, the lung and the heart fibrosed, the bones resorbed and the overlying tissue calcified. There is usually a long prodromal stage of swelling of the skin with progressive limitation of movement. As months and years pass the limitations of movement become marked, particularly of the hands, the feet and face. The skin becomes atrophic and hidebound and develops sensory, vasomotor and pigmentary changes, and, finally, ulcerations. The prognosis is grave, and most patients die of the disease after years of disability. However, spontaneous or therapy-induced remissions can occur. The disease is more common in females. No specific therapy is known. Protection of the skin from trauma, cold and infection

is important. Physiotherapy may prevent contractures. **Sympathectomy** produces temporary benefits in some patients. Chelating agents are reported helpful for patient with extensive calcification. Corticosteroids are not very beneficial (Sauer '85: 243, 244).

A **granuloma** is a focal chronic inflammatory response to tissue injury manifested by a histologic picture of an accumulation and proliferation of leukocytes, principally of the mononuclear type and its family of derivatives, the mononuclear phagocyte system. Five groups of granulomatous inflammations have been promulgated. Group 1 is the **epithelioid granulomas** which include sarcoidosis, tuberculosis in certain forms, tuberculoid leprosy, tertiary syphilis, zirconium granuloma, beryllium granuloma, mercurial granuloma, and lichen nitidus. Group 2: **histiocytic granulomas**, includes lepromatous leprosy, histoplasmosis, leishmaniasis, and so on. Group 3 is the group of **foreign-body granulomas**, including endogenous products (e.g., hair, fat, keratin), minerals (e.g., tattoos, silica, talc), plant and animal products (e.g., cactus, suture, oil, insect parts), and synthetic agents such as synthetic hair. Group 4 are the **necrobiotic/palisading granulomas**, such as granuloma annulare, necrobiosis lipoidica, rheumatoid nodule, rheumatic fever nodule, cat-scratch disease, and lymphogranuloma venereum. Group 5 is **the mixed inflammatory granulomas**, including many deep fungus infections such as blastomycosis and sporotrichosis, mycobacterial infections, granuloma inguinale, and chronic granulomatous disease.

**Sarcoidosis** is an uncommon systemic granulomatous disease of unknown cause, possibly rat borne illness (hantavirus?) that affects skin, lungs, lymph nodes, liver, spleen, bones and eyes. Lymphadenopathy is the most common single finding. Blacks are affected more often than whites. The superficial lesions consist of reddish papules, nodules and plaques, which may be multiple or solitary and of varying size and configuration. These superficial lesions usually involve the face, shoulder, and the arms. Central healing can result in atrophy and scarring. Most cases are chronic but benign with remission and exacerbations. Spontaneous cures are not unusual. The total blood serum protein is high and ranges from 7.5 g to 10.0 g/dl, owing mainly to an increase in the globulin fraction. Time appears to cure or cause remission of most cases of sarcoidosis, but corticosteroids and immunosuppressant drugs may be indicated for extensive cases. **Granuloma annulare** is a moderately common skin problem with females predominating 2.5 to 1. The usually encountered ring-shaped, red-bordered lesion is often mistaken for ringworm by the inexperienced. The localized form is usually seen in patients in the first 3 decades of life and the generalized form in the fourth to seventh decades. In both forms the lesion is a red asymptomatic papule with no scaling. The papule may be solitary. Most frequently the lesion assumes a ring-shaped or arcuate configuration of papules that tends to enlarge centrifugally. On healing, the red color turns to brown before the lesions disappear. Both forms of granuloma annulare can resolve spontaneously after 1 to several years, but the generalized form is even more long lasting. It must be differentiated from tinea corporis, lichen planus, secondary syphilis, and other granulomatous diseases. Many cases respond to the application of a corticosteroid cream covered for 8 hours a day with an occlusive dressing such as Saran wrap. Intralesional corticosteroids are very effective for a case with only a few lesions (Sauer '85: 213-215).

Many hundreds of medications are available for use in treating skin diseases. The treatment of the majority of the common skin conditions can be made simpler with three basic principles. (1) The type of skin lesion, more than the cause, influences the kind of local medication used. The old adage, "If it's wet, use a wet dressing, and if it's dry use a salve", is true for the majority of cases. An acute oozing dermatitis treated with a lotion can change, in 2 to 3 days, to a dry, scaly

lesion that requires a paste or ointment. Conversely, a chronic dry patch may become irritated with too strong therapy and begin to ooze. (2) The second basic principle in treatment is never do any harm and never over-treat. The most commonly seen dermatitis is the over-treatment of contact dermatitis. The third principle is to instruct the patient adequately regarding the application of the medicine prescribed. The patient does not have to be told how to swallow a pill but does have to be told how to put on a wet dressing. Burow's solution makes a nice wet dressing. A particular topical medication is prescribed to produce a specific beneficial effect.

The formulary: (1) **Antipruritic** agents relieve itching in various ways. Commonly used chemicals and strengths include menthol (0.25%), phenol (0.5%), camphor (2%), and coal tar solution (2% to 10%). Coal tar is not recommended because it is carcinogenic. These chemicals are added to various bases for the desired effect. Unsafe preparations are those that contain antihistamines, benzocaine and related "caine" derivatives. (2) **Keratoplastic** agents tend to increase the thickness of the horny layer. Salicylic acid (1% to 2%) is an example of a keratoplastic agent whereas stronger strengths of salicylic acid are keratolytic. (3) **Keratolytics** remove or soften the horny layer. Commonly used agents of this type include salicylic acid (4% to 10%), resorcinol (2% to 4%) and sulfur (4% to 10%). A strong destructive agent is trichloroacetic acid, full strength. (4) **Antieczematous** agents remove oozing and vesicular excretions by various lotions. The common antieczematous agents include Burow's solution packs or soaks, coal tar solution (2% to 5%) and hydrocortisone (0.5% to 2%) and derivatives incorporated in lotions in salves. (5) **Antiparasitics** destroy or inhibit living infestations. Examples include Eurax lotion and cream, for scabies, and Kwell cream and lotion, for scabies and pediculosis. (6) **Antiseptics** destroy or inhibit bacterial and fungi. Commonly used examples include Vioform (3%), ammoniated mercury (3% to 10%), and antibiotics such as neomycin (0.5%), garamycin (0.1%), aureoycin (3%) and terramycin (3%). **Antifungal** agents include Whitfield's ointment and multiple preparations in various bases that are locally antifungal. Sulfur and ammoniate mercury are older but still effective antifungal chemicals that can be incorporated in several bases or in the newer antifungal reams (Sauer '85: 35, 36). Avoid toftate (antifungal foot powder spray). Use clotrimazole (athlete's foot crème).

The **basic formulary for dermatologic treatments**: (1) Tars: Coal Tar Solution (LCD) (3-10%), Crude Coal Tar (1-5%), Anthralin (0.1-1%); Consider for use in cases of: Atopic eczema, Psoriasis, seborrheic dermatitis, Neurodermatitis, localized; avoid in intertriginous areas (can cause folliculitis). Not recommended because it is carcinogenic. (2) Sulfur (Sulfur, precipitated, 3-10%), Consider for use in cases of Tinea of any area of body, Acne vulgaris and rosacea, Seborrheic dermatitis, Pyoderma (combine with antibiotic salves), Psoriasis; Avoid: do not mix with mercury (causes black mercuric sulfide deposit on skin). (3) Mercury (Ammoniated Mercury, 1-10%); Consider for use in cases of: Psoriasis, Pyoderma, seborrheic dermatitis; Avoid: do not mix with sulfur. Not recommended because it is toxic. (4) Resorcinol (Resorcinol Monoacetate, 1-5%); Consider for use in cases of: Acne vulgaris and rosacea (usually with sulfur), Seborrheic dermatitis, or Psoriasis. (5) Salicylic acid (1-5%, higher with caution); Consider for use in cases of: Psoriasis, Neurodermatitis, localized thick form, Tinea of feet or palms (when peeling is desired), Seborrheic dermatitis; Avoid in intertriginous areas. (6) Menthol (1/4%); Phenol (1/2 – 2%); Camphor (1-2%); Consider for use in any pruritic dermatoses; Avoid use over large areas of body. (7) Hydrocortisone and Related Corticosteroids (hydrocortisone powder, 1/2-2%); Consider for use in cases of: Contact dermatitis of any area, Seborrheic dermatitis, Intertrigo of axillary, crural or inframammary regions, Atopic eczema, Neurodermatitis; Avoid use over large areas of body, because of expense, and possible, but unlikely, internal absorption. (8) Fluorinated Corticosteroids Locally: Not readily available as

powders for personal compounding; Consider for use with or without occlusive dressings, in cases of: Psoriasis, localized to small area, Neurodermatitis, localized, Lichen planus, especially hypertrophic type, Also anywhere that hydrocortisone is indicated. The fluorinated corticosteroids should not be used on the face and intertriginous areas where long-term use can result in atrophy and telangiectasia of the skin (Sauer '85: 45).

Physical medicine embraces therapy with a variety of agents, which include massage, therapeutic exercise, water, air, radiations, heat, light, ultraviolet, x-rays, radium and lasers (vibrations, refrigeration, and electricity of various forms. Many of these agents are used in the treatment of skin diseases. The physical agent most commonly used for dermatoses is **hydrotherapy**, in the form of medicated or non-medicated wet compresses and baths. Distilled water and tap water are the vehicles and may contain any of the following chemicals in varying strengths: sodium chloride, aluminum acetate (Burow's solution), potassium permanganate, silver nitrate, tar, starch, oatmeal (Aveeno) and colloid (Soyaloid). **Open compresses** are used most frequently, since excessive maceration of tissue occurs when the dressings are "closed with wax paper or rubber sheeting. For most conditions, the area to be treated should be wrapped with two or three layers of clean sheeting or muslin. Then gauze 3 inches wide should be wrapped around the sheeting to hold it firmly in place. After that, the dressing can be moistened with the solution by pouring it on or by squirting it on with a bulb syringe. In most instances the dressing is wet with the solution before it is wrapped on the affected area. The indications for wet compresses are any oozing, crusting or pruritic dermatoses, regardless of etiology. **Medicated baths** should last from 15 to 30 minutes. Cool baths tend to lessen pruritis and are prescribed most frequently. Baths can be used for a multitude of skin diseases except those conditions where excessive dryness is to be avoided, such as for patients with atopic eczema, senile or winter pruritus, and ichthyosis (Sauer '85: 47). Saline, Epsom salt bath, swimming in a chlorinated or salt pool or ocean, treats methicillin resistant *Staphylococcus aureus* (MRSA).

## 2. Burns

**Fire** is the fourth greatest cause of accidental death in the United States. It is surpassed only by motor vehicle accidents, falls and drowning as a cause of unintentional injury death. Each year, an estimated 20,000 adults and children die, and an additional 75,000 to 100,000 are hospitalized, from fire-related injuries. Each year more than a million burn injuries require medical care or restriction of activity. Senate resolution 217 declares the first full week of February as "National Burn Awareness Week". Fire Prevention Week is in October of every year. Burn injuries occur in house fires, auto accidents, and work-related accidents, as well as in recreational accidents involving campfires, outdoor grills, boats, aircraft and motorcycles. Anything that involves, heat, chemicals or fires can cause a burn injury. House fires cause three-fourths of all fire injuries. Males account for 74 percent of burn injuries. After the home, the workplace is the second most common place for burn injury to occur, and because of this, adults experience more burn injuries (63 percent) than children (37 percent). Scalds are the second leading cause of burn injury. If the hot-water heater setting is turned up to 159°F, for example, it takes one second, for a full thickness burn to occur. At a setting of 120°F it would take three minutes for this to happen. Bathtub water should not be over 100°F. Electrical injury accounts for about 3 percent of all burns. Chemical injuries are home are usually minor whereas occupational injury from chemicals can be more severe. Smoke inhalation is not a burn per se, but it is a very serious complication of many burn injuries. About 5 percent of all burn injuries involve smoke inhalation. About half of all burn injuries involve 10 percent or less of the body

surface. Another third of the injuries involve from 11 to 30 percent of the body surface (Munster '93: 191, xvii-xxi).

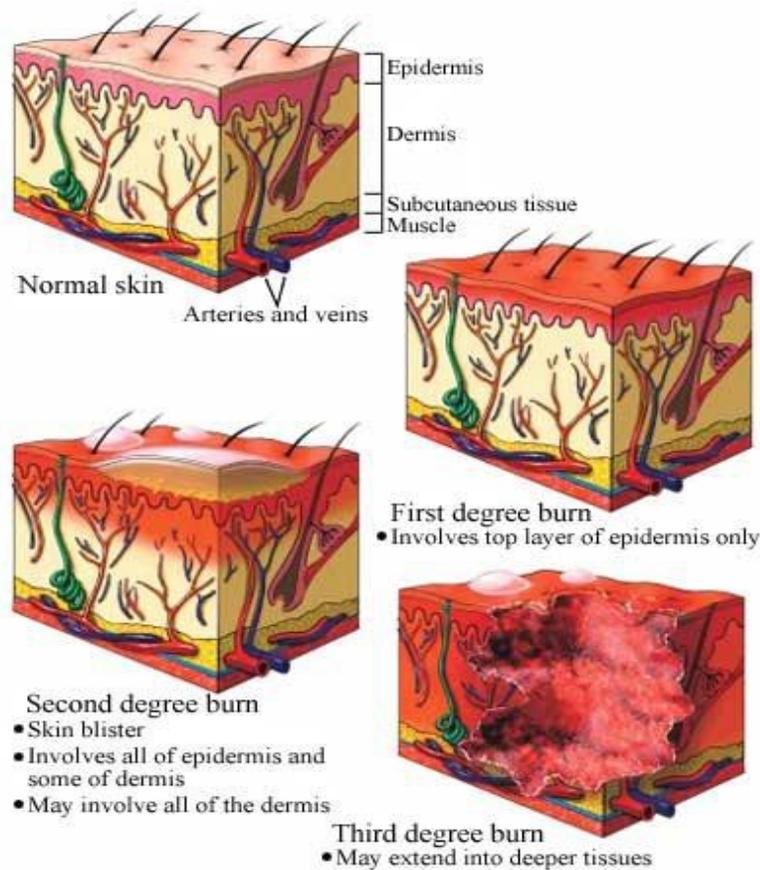
**Shock** is detected by measuring the patient's blood pressure, and urine output. Treatment consists primarily of giving fluids intravenously. The amount of fluid needed is calculated for each individual and is based on the patient's weight and the amount of body area that has been burned. Respiratory insufficiency is defined as the inability of the lungs to supply enough oxygen to the body. This condition is more likely if the patient has **smoke inhalation**. Respiratory insufficiency can have a delayed onset. To determine the presence and severity of smoke inhalation, physicians may run a number of tests, including chest x-rays, measuring the amount of oxygen in the blood, calculating the level of breathing function (spirometry) and looking into the nasal and lung air passages with a lighted flexible scope (bronchoscopy or nasopharyngoscopy). The primary treatment for smoke inhalation is administration of supplemental oxygen, initially given by face mask. If this is not adequate to supply sufficient levels of oxygen or if there is swelling of the air passages, the patient may need to be placed on a ventilator through a tube in the mouth or nose entering the windpipe. If the respiratory insufficiency is severe or prolonged, a tracheostomy may be performed, in which a tube is surgically placed directly into the windpipe through the neck (Munster '93: 8, 9).

The first determinant of **survival** is burn size, measured as a percentage of total body surface involved. Burns involving more than 20 percent of the body surface (less in small babies) or any deep (third-degree) burns over 10 percent of the body surface are classified as critical by the American Burn Association. Certain chemical and high-voltage electrical burns are also classified as critical. Burns classified as critical are best cared for in a burn unit. Even small burns of the hands, face, feet and genitalia are best taken care of in a burn unit, because burns in these areas may impair function and appearance. As the burn size increases, the chances of survival diminish. With burns over 90 percent of the body, even though spectacular survivals are now frequently recorded, the chances of survival are slight. The third-degree component, or how much of the total burn is third-degree, or even a mixed-degree burn, also affects survival. A 50 percent all third-degree burn, or even a mixed-degree burn, is much more serious than a 50 percent all second-degree burn. Age is also another determinant of survival, by age 50, the ability to heal and fight infection is quite diminished, a 30 percent burn in a person who is 80 years old is as life-threatening as an 80 percent burn in a 20 year old. A person's general physical condition, will to live, smoke inhalation and shock determine a person's immediate chances for survival after a burn injury (Munster '93: 8, 9).

Burns are judged by the size of the burn in relation to the whole body and by the depth of the burn. The **size of the burn** is described as a percentage of the total body surface area. The palm of the hand is equal to 1 percent of body surface area. The "Rule of Nines" divides the body into areas equaling multiples of 9 percent of the total body surface. The head and arms are each equal to 9 percent of the body surface. The chest and back are each 18 percent (2 x 9 percent). Each leg is 18 percent (2 x 9 percent). This totals eleven nines, or 99 percent. **Burn depth** is measured in terms of "degrees". A **first-degree burn** is superficial, involving injury only to the outermost layer of skin – the epidermis – and is like a sunburn. The skin becomes red, warm, swollen and painful. The skin may even peel, but the damage to the skin heals within a few days, by a process called epithelialization. A first-degree burn is sometimes called an epidermal burn. **Second-degree burns** are caused by brief contact with fire and by scalds from liquids that are mostly water, such as tea and coffee. A second-degree burn involves a portion of the dermis as well as the epidermis – this is called a partial thickness burn. It can range from superficial to

deep partial thickness, depending on how many of the epidermal accessory structures are left in the remaining dermis. The skin is blistered, moist, discolored, and painful. Spontaneous healing is possible, usually within four to six weeks. Scarring usually can be prevented with an early operation but is only possible when there is enough donor skin and the patient is fit for surgery. **Third-degree burns** destroy the full thickness of skin - all of the epidermis and all of the dermis – and are commonly caused by contact with flame or liquids with a high boiling point (fat, tar, molten metal). A third-degree burn appears dry, pale, and leathery. The skin will not grow back. Skin grafts must be performed to keep infection from entering the body through the burn. Full-thickness burned skin contracts and loses its ability to stretch. It becomes tight around the extremity, eventually restricting the blood supply to the hand or foot or limiting chest expansion during breathing.

### Degrees of Skin Burn



Credit: Howtotreatburnhq.com

Third-degree burns that encircle the arm or leg or chest require an escharotomy. An **escharotomy** is an incision in the burn made through the skin to the underlying fat. Because third-degree burns destroy nerve endings, the burned skin is numb and anesthesia is generally not needed for this procedure, although some sedation or pain medication may be given. **Fourth-degree burns** involve the tissues beneath the skin such as muscle and bone. This term is rarely used, because burns of this depth are rare. They are usually caused by high-voltage electricity or by sleeping too close to a fire for a long time in an altered state of consciousness. The limb is often destroyed and amputation is necessary. Generally speaking, second-degree burns blister and hurt more than third-degree burns, but this is not always true (Munster '93: 10-15).

For the first two or three days after the injury, the patient will receive **fluids** to make up the huge body fluid losses that seep out from the burn (this process is called resuscitation). The patient may be fed intravenously and may receive mechanical assistance with breathing and circulation. The burn would be cleaned by the staff once or twice a day and then dressed, usually with a medication designed to kill germs (a burn cream) and thick dressings. Pain management is an essential concern. The cleansing of the wounds, called **debridement**, is necessary, and involves removing loose, dead skin and old creams or secretions from the skin. After debridement, antibiotic cream or solutions are applied directly to the burn. Silvadene, Sulfamylon, Bacitracin, Mafenide, and silver nitrate are some examples. **Sterile dressings** are then usually placed over the wounds, although sometimes the wounds are left uncovered. Sometimes dressings are changed in a water tub in a procedure called hydrotherapy. Some types of burns require additional specific treatment. **Chemical burns**, for example, are caused by alkalis, acids, oxidants or other agents that destroy tissue upon contact. Chemical burns need to be rinsed with water to remove all traces of the toxic material. This is best done immediately, with shower water. The exception to the rule of rinsing with water is **dry lime**, a substance which reacts with water, that must be brushed off downwind. Occasionally chemical wounds are also treated with specific antidotes such as calcium injections or applications of an ammonium gel (for hydrofluoric acid burns). The chemical burn wound is then treated like any other burn wound.

**Electrical injury** causes damage to tissues beneath the skin surface, heating the bone and causing damage to muscles from the inside out. Blood vessels also become damaged, and delayed muscle death can occur from the lack of circulation over the days to weeks following the initial injury. To prevent swelling that could cause further muscle and nerve injury early surgery is often performed to release pressure on muscle and nerves caused by swollen deep tissues. Repeated trips to the operating room for debridement are often needed for people with high-voltage electrical burns. Once the burn wound is healthy, exposed bone and tendons may need to be covered by local flaps (adjacent healthy tissue transferred over the wound) or microvascular free flaps (healthy tissue transferred from another part of the body). Amputation of damaged fingers, toes, and even parts of limbs is necessary in up to two-thirds of high-voltage injuries. Electrical current can cause arrhythmias or cardiac arrest as well as cessation of breathing. Other injuries, such as fractures and head injuries can result when the body is thrown after receiving the electrical shock. Kidney damage can occur when products are released from damaged muscle cells (myoglobinuria). **Tar burns** cause deep burns because of the high temperatures and prolonged contact with the skin. The tar can be removed with ointments and creams, a procedure that can be done more leisurely if the wound has first been cooled (Munster '93: 15-17).

First-degree burns fade and become pain free within one week. Second-degree or superficial partial thickness burns heal in two to three weeks, although deeper burns can take four to five weeks. Third-degree burns need to be excised or removed surgically and then covered by skin grafts from an unburned area of the body or with the patient's cultured skin. **Sepsis** becomes a serious threat after the first week. Dead tissue from the burn acts as a medium for bacterial growth. Dead tissue also has a poor blood supply so that oral and intravenous antibiotics, which are administered through the bloodstream, have difficulty reaching the burn wound and therefore bacteria are able to multiply despite treatment with antibiotics. Burn wound sepsis can destroy living tissue, converting the wound to a deeper injury. Infection is treated with topical (applied to the wound) and systemic (given intravenously) antibiotics. A further treatment, when the patient is stable, is the surgical removal of dead skin and underlying tissue, called excision of the wound. **Pain control** is important for the patient's comfort and recovery. Pain medication make the pain bearable for the patient so that wounds can be treated properly during dressing changes

and tub baths. Pain medications enable the patient in rehabilitation to cooperate with physical therapy and perform range-of-motion exercises to regain the strength and mobility lost during hospitalization and helps the patient get the rest and sleep needed to recover properly. Pain can be alleviated but not abolished until the burn is healed. Aside from general anesthesia, no pain medication will completely remove a patient's pain (Munster '93: 18-20).

The **burn unit** is a separate unit of the hospital. It is still part of the hospital and shares many facilities with the rest of the hospital – x-ray, computerized tomography scans, magnetic resonance imaging, laboratories for blood tests, food service and operating room. The Shriners Burns Institutes of Boston, Cincinnati and Galveston, which are freestanding, university affiliated burn hospitals, are exceptions to this rule. Some burn units are small, containing 4 to 6 beds, and others are large, having 20 or more beds. Burn units are usually divided into two sections: an intensive care unit (ICU) and a step-down section. In most burn units in the United States, the attending physician is either a general surgeon or a plastic surgeon. Elsewhere in the world, anesthesiologists, internists, and dermatologists may be the specialists in charge of burn units. Sophisticated devices are used through the burn unit to monitor and treat the patient. The **monitor** is an electronic box that monitors four through six inputs at the same time. The most important information is the heartbeat which is monitored by EKG (electrocardiograph). Blood pressure is monitored by a small plastic tube inserted into one of the patient's arteries called the arterial line or A-line which is connected to an electronic device called a transducer, which converts the blood pressure into an electronic signal. Other pressures can be monitored through tubes called catheters. The amount of oxygen in the patient's blood and rate of respiration are also monitored. The oxygen levels of the blood are measured by pulse oximeter attached to patient's ear or finger or by directly measuring the oxygen contents of arterial blood. The **respirator**, also called the ventilator helps a person breathe. First, a tube called an endotracheal tube is placed either through the mouth or nose down the breathing pipe (trachea) and then the ET tube is hooked up to a respirator, which breathes for the patient by pushing humidified oxygen and air into the patient's lungs in a cycle imitating the person's normal breathing. After a number of days, usually between the 10<sup>th</sup> and 20<sup>th</sup> day on the respirator, the ET tube can become very irritating to the nose and mouth, when this happens, a tracheostomy is performed, usually under local anesthetic and a tube is passed (Munster '93: 38, 50-55).

**Surgery** is an essential part of the treatment plan for all patients with third-degree burns and for some patients with second-degree burns. The burn wounds must be covered with new skin both to prevent infection and to limit scarring, which may interfere with the person's ability to function. The principal surgical operation performed on burn patients is **skin grafting**. In this procedure, a sliver of the patient's skin is removed from a healthy, unburned area (the donor area) and attached to the area destroyed by the burn (the recipient area) by stitches, staples, or adhesive paper strips or simply by dressings. The recipient area must be prepared to accept the donor skin. This may be done either surgically, by excision, or by allowing the heat-damaged skin (the eschar) to separate naturally from the underlying, healthy tissue. Excision is performed on the areas of the burn that are not expected to heal on their own. In excision, the **eschar** is removed either tangentially or fascially. Tangential excision involves removing the eschar with a long razor blade in layers until all dead tissue is gone and the surface consists of healthy tissue. Excision down to the fascia involves removing the entire layer of damaged skin and underlying at down to the fascia – the tough covering over the underlying muscle. Excision promotes early healing and eliminates a source of infection. Despite its advantages, this technique is sometimes used reluctantly because the final appearance after removal of fat can be less pleasing, and the blood loss is disconcerting. Natural separation of the eschar takes three to five weeks. Once the

eschar is removed, if there is not enough remaining dermis, which contains regenerating elements (epidermal cells in hair follicles and sweat glands), new skin will not grow. Multiple trips to the operating room are often required before all the eschar is removed and the entire burn wound is grafted (Munster '93: 21- 23).

Skin must be transferred from an unburned part of the body. The patient donates their own skin (**autograft**) in a surgical procedure in which the surgeon removes skin from unburned areas. Only a partial layer of skin is removed from the donor site, so the dermis that remains on the donor site will generate new epidermis. Donor sites can be any part of the body, but since they heal with scarring, inconspicuous areas are used first, such as the thigh, abdomen, trunk and scalp. The donor sites are treated with gauze dressings (dry or medicated, such as Xeriform and Scarlet Red) or plastic dressings (Opsite, Tegaderm, and others) or synthetic gauzes (Biobrane). Donor site healing is usually complete within 7 to 10 days and new skin grafts can be obtained or "harvested" from the same area. The skin from the donor site may be stretched to allow it to cover a larger area than it came from, a procedure called **meshing**. This involves making small slits in the skin which allow it to expand like fish netting. Meshing allows blood and body fluids to drain from under the skin grafts and allows the skin to stretch over a greater area. Meshing works well but on widely meshed skin the mesh marks may be visible forever on the healed burn. When the burn wound covers a large area, the available donor areas (autograft) may not provide enough skin to cover the entire excised wound.

### Mesh Skin Graft



Credit: Google Images

An **allograft** or homograft is human skin donated from a deceased person which is stored after undergoing rigorous testing for transmittable disease in compliance with the standards of the American Association of Tissue Banks. These standards state that the donor's medical history must be screened and the donor tested for HIV and hepatitis virus. The skin is frozen and stored at  $-80^{\circ}\text{C}$ , to provide additional protection against contaminants. Eventually allografts will be rejected by the patient's immune system, but before this they will actually adhere to the wound as in the normal healing process. Allografts keep the wound closed until donor sites have healed sufficiently to allow re-harvesting or until cultured skin is available. Cultured skin, or cultured **autograft**, is a relatively new and expensive method of healing the wound that is used when the patient's own available skin graft donor sites are insufficient. To produce cultured autograft, a tiny piece of skin is taken from an unburned area of the patient's body and its cells are grown in layers in laboratory petri dishes. The skin grows in small sheets that are then applied to the burn.

This method expands the patient's own epidermis from a 1-inch sample up to more than 250 yards of skin – a 10,000 fold increase – over a 30 day period. Cultured skin takes three weeks to grow, it is quite fragile and very expensive. Healed cultured skin is often very fragile, too, it is easily damaged and subject to blistering, since there is no underlying layer of dermis, but only epidermis covering the tissues underneath.

There is no true artificial skin yet. There are however many good temporary artificial wound coverings but all of them eventually must be replaced with autograft. The best of the **artificial skins** developed so far is two-layered product, the inside layer being biologic (that stays on the patient) and the outside being plastic (this part is replaced by autograft). The autograft replacing the plastic is much thinner than conventional autograft so that the donor site heals in 3 to 5 days instead of 7 to 10 days. Commercially processed pigskin and human fetal membranes are used by some surgeons as a temporary covering for the burn wound. Closing wounds with these dressings has the advantages of reducing the loss of protein fluid and electrolytes from the wound, decreasing pain in the wound, and facilitating the healing of partial-thickness burns. Furthermore, if the biologic dressing becomes adherent, it is a sign that the wound is ready to support an autograft. Grafts, auto or allo, are either left open to the air or are wrapped in dressings, sometimes with antibiotic solutions or creams applied. "Take down" is the first dressing change after the grafting procedure and occurs usually two to five days after the procedure. At this point "take" the amount of graft that is viable and adherent is estimated. The take is often expressed as a percentage of the grafted area. A take of more than 85 percent means the procedure was a success. Small open areas can heal in from the surrounding edges. If the take is less than 60 percent, another patching procedure usually must be performed. Grafted areas need to be protected from rubbing by clothing or activity. The healed or grafted skin may also be itchy and dry. Frequent application of moisturizers such as lanolin and Eucerin help make up for the absence of normal oil glands in the skin graft. Grafted skin will always look different from normal skin, healed skin grafts are redder or darker than surrounding skin and have irregular raised areas. Skin that has healed by itself or with skin grafting is less sensitive to touch and will always be somewhat more easily damaged than normal skin. The length of stay in the hospital can be as short as a few hours or as long as many months. The average length of stay in U.S. hospitals is 14 days (Munster '93: 23-27).

**Reconstructive surgery** is the aspect of plastic surgery whose goal is correction of dysfunction an disfigurement resulting from injury. Reconstructive surgery is surgery that deals with the repair or replacement of lost or damaged parts of the body. Reconstructive surgery for burn injuries usually consists of replacing the skin lost or disfigured by the injury in order to correct the pathological scars. Deforming scars are cut out (excised) and the wound is either closed (if sufficient skin exists) or covered with new skin, a procedure called resurfacing. Also in reconstructive surgery, contractures are released (cut across) and skin is placed in the resulting wound after the joint is extended. A graft is tissue that is completely removed from the body, disconnected from its blood supply, and replaced on a wound, where it lives by absorbing nutrients from the wound. The area from which tissue is taken is called the donor site. The recipient site is the wound in need of closure. Blood vessels from the wound generally grow into the graft within three or four days, resulting in the "take" of the graft. Whereas most burn wounds that need to be closed by skin graft surgery are covered with split-thickness skin grafts during acute burn recovery period, full-thickness grafts, composite grafts, and flaps are generally used for reconstructive surgery. When a split-thickness graft is taken, only a portion of the dermis is removed with the epidermis, a full-thickness graft involves removing the entire thickness of the skin for use as a graft. Composite grafts contain more than one type of tissue,

most commonly skin and cartilage from the ear, and are sometimes used to reconstruct facial features such as the nose, eyebrows, and upper lip. Split-thickness donor sites heal by epithelialization, but when a full-thickness or composite graft is taken, the donor site must be closed with sutures or, sometimes, a split-thickness graft. A **flap** is a tissue that maintains its blood supply when moved to another area of the body, they do not contract. A local flap is a flap that is moved to an area adjacent to its original donor site. A distant flap is a piece of tissue which is moved to an area that is not adjacent to the donor site. The most common way of maintaining the blood supply to a distant flap is to disconnect the blood supply to the flap from the original donor site and connect the flap's blood vessels into blood vessels close to the recipient site using microvascular surgery. This is called free flap (Munster '93: 122-124).

In reconstructive surgery burn scars are commonly moved to that they are hidden in the contours or **resting skin tension lines** (RSTL) of the face or body. Scars lying within or parallel to the RSTL are generally better hidden than scars that run perpendicularly to the RSTL. Local flaps are used whenever possible, because they provide the best color match, skin texture, and skin thickness for reconstruction. A **Z-plasty** is one of the most commonly used local flaps. With a Z-plasty, a long, straight line scar is broken into multiple broken lines. This makes the scar less visible and often reorients the scar into the natural lines of the skin. Another method of breaking a long scar into multiple broken lines is a **W-plasty**, which is performed in broad, open areas of skin where there is an excess of tissue, such as the cheek. The limbs of the resulting W are aligned better with the RSTL of the face than the original scar and is less noticeable. A new technique for increasing the amount of local tissue available for flaps is **tissue expansion**, in which a deflated silicone balloon called a tissue expander is placed under normal skin next to the areas to be reconstructed. The balloon is inflated by injecting a saltwater solution into a valve on the balloon which can be felt through the skin. The inflation stretches the skin, and the body responds to this stretching by growing new skin. The procedure may be repeated several times, more saltwater being injected into the expander each time, until enough new skin is grown to reconstruct the adjacent defect after the tissue expander is removed. When the areas of burn scarring are extensive, **full-thickness or split-thickness skin grafts** are used to resurface large areas. These grafts also provide the best means of preserving fine facial features. Thick split-thickness skin is generally used for reconstructing the eyelid, for example, unless full-thickness eyelid skin is available from the eyelid on the opposite side. As a rule, the more dermis the graft contains, the less likely it is that the graft will change postoperatively.. For most surgery performed to release contractures, full-thickness grafts are the first choice (Munster '93: 124-128).

The most common scalp problem addressed by burn reconstruction surgery is the area of the burn scar called **burn alopecia**, where hair and roots have been destroyed. Because scalp skin has a tough underlying layer (galea) it does not stretch like skin in other areas and this limits the areas of scar that can be removed directly. In the past, multiple flap techniques were used to cover larger areas of alopecia, but tissue expansion is increasingly being used for reconstruction of scalp defects. With tissue-expansion the hair-bearing scalp can be expanded, the scarred portion of the scalp excised and the expanded hair-bearing scalp put in its place. No new hair is formed, but the space between hair follicles increases as the scalp expands, causing a thinning of the hair that is usually imperceptible. Less common than alopecia is the complete loss of a portion or all of the scalp, with the result that the underlying skull is exposed. Because the skull has no blood supply on its surface to support a skin graft, a flap that has its own vascular system must be placed in this area. This procedure is generally performed early in the course of recovery to prevent infection of the skull bone (Munster '93: 129, 130).

**Skin replacement of the face** should be performed in aesthetic units, that is, grafts and flaps should be placed so that scars are located within naturally occurring lines of the face. The forehead is a surprisingly large expanse of skin, and although the lines run horizontally a vertical scar in the center of the forehead is often acceptable. When the patient has large forehead scars, the forehead must be resurfaced, generally by placing a thick split-thickness graft as an aesthetic unit (with the scars in the hairline). A hair-bearing full-thickness graft from the temple or behind the ear may yield an acceptable result for reconstruction of an eyebrow, but hair growth is usually sparse and unsatisfactory. The sparseness can be augmented using eyebrow pencil or by medical tattooing. To allow the upper eyelids to move freely, artificial lubricants are applied to protect the patient's corneas until reconstructive surgery can be performed. To reconstruct eyelids, full-thickness skin from the eyelid of the other eye is the ideal replacement. More often, thick split-thickness skin is used to release contractures of the eyelids. The release of the eyelid will be overcorrected in surgery, and frequently this will make the eyelids appear large and droopy, but this overcompensation will correct itself in time, and the eyelids will appear more normal. Scars across the corners of the eyelid can restrict movement, they are corrected using Z-plasty flap techniques or skin grafts. False eyelashes or tattooed eyeliner can be used to substitute for eyelashes. Ear reconstruction is often difficult because of burn scarring next to the ear. When nearby normal skin is available this is used for reconstruction. Portions of the remaining ear can be used to reconstruct the general form of the ear. When the ear is totally missing, a vascularized deep tissue flap from under the scalp is used to cover a framework of rib cartilage, or sometimes plastic. This flap is subsequently covered with a skin graft. Prostheses that look very much like real ears are often the best solution when the entire ear is lost. As with the ear, reconstruction of the nose is difficult. Reconstruction involves releasing the scar contracture, making up the tissue, making up the tissue deficit caused by the burn, replacing the nasal lining in its anatomic location, and resurfacing the nose with local flaps, full-thickness grafts, or sometimes, a composite graft of skin and cartilage. When the nose is missing, skin for the forehead or from other areas of the body is placed over the cartilage framework to shape a new nose. Nasal prostheses are also available (Munster '93: 131, 132)

The **mouth** is a dynamic structure. Small linear contractures can be released by Z-plasty techniques. When large portions of the upper or lower lip are scarred, these areas must be replaced by skin graft applied as an aesthetic unit. Technically the area around the mouth consists of five aesthetic units. The upper lip consists of the dimple in the middle of the lip flanked by two lateral aesthetic units extending out the nasolabial crease (the groove between the nose and the corners of the mouth). The lower lip is an inverted U-shaped aesthetic unit surrounding the prominence of the chin itself, which is the fifth aesthetic unit. The contour of the dimple in the upper lip can be duplicated by using a composite graft of ear skin and cartilage. When the cheeks are scarred, the skin may be discolored and the person may lose facial expression. When tightness occurs as a result of contractures, and when large areas of hypertrophic scarring are present, the cheek is often resurfaced using a full-thickness skin graft or a flap of skin from the neck or shoulder. A tissue expander may be used to expand donor tissue. Small hypertrophic scars and contractures can be corrected or improved through excision of the scars and subsequent closure with Z-plasty or W-plasty (Munster '93: 132, 133).

Burn scar **contractures** can develop across any of the major joints of the body, though they are most common in the neck, across the shoulder joint, or armpit area (axilla) and on the hands, wrists, elbows, knees and feet. Early burn physical therapy strives to prevent these contractures. If the contractures are significant between 6 and 12 months after the burn, reconstructive surgery

is performed to release the contractures. A neck contracture is most frequently released through a simple incision and skin grafting that allows the neck to extend, although Z-plasties and other local flap techniques are also used. The skin graft is placed over the resulting wound, with the size of the graft usually being quite large. Grafts generally take well in neck tissues, with the exception of grafts over the larynx, the movement of which interferes with the healing of the graft. The appearance of tracheostomy scars can be improved through reconstructive surgery. Loose skin on the back of the hand and sensitive, thicker skin on the palm cover the tendons, ligaments, nerves, muscles, bones and joints. Contractures of these many joints and loss of skin sensitivity can interfere with the interactions that allow the hand to function as a fine instrument. Contractures of the fingers are released using grafts and flaps, and sometimes the ligaments around the joints must be released as well, in a surgical procedure called a capsulectomy, in which a portion of the joint capsule is removed. Amputation of fingers is often necessary. The most common effect of burn scars on the feet is contracture of the dorsum (the top or back) of the foot, which causes the toes to be pulled back, resulting in an unnatural gait. When a child's feet have been burned the growth of the foot may be disturbed. Release and grafting usually correct the contracture and the hyperextension of the toes, leaving webbing between the toes. The webbing rarely interferes with function and can be left in place until the child is much older and desires reconstructive surgery. Scar contractures of the trunk can interfere with movement. These contractures are released using grafts or local flaps. When hypertrophic scarring develops over the large areas of the chest, back and abdomen, resurfacing is not possible, since it would require too large a skin graft. Cultured skin autografts are already being used for the treatment of severely burned patients (Munster '93: 133-136).

A major concern of physical rehabilitation is preventing the loss of joint motion in a person who has sustained a burn injury. The inability to move a joint fully because of tightness of the surrounding tissue is called **contracture**. In burn patients, contracture occurs for two reasons. First, because the burned areas are painful, the patient assumes a position that lessens the pain and will remain in that position because it is more comfortable. If a joint is not moved, it will become tight, and eventually the person will not be able to move the joint at all. Second, as the burn heals, scar tissue sometimes develops. This tissue is not pliable and will pull tightly across the joints. Contractures can be prevented by range-of-motion exercises and proper positioning of the involved joints. The technique used most frequently for positioning is splinting. The therapist begins working with the burn patient on an exercise program to restore active movement as soon as possible after the patient is admitted. Three basic exercise techniques are employed: (1) active motion, in which the patient moves on their own, without help, (2) active assisted motion, in which the therapist helps the patient move, and (3) passive motion, in which the therapist moves the patient without the patient's help.

Prolonged bed rest has a substantial negative impact on all the major systems of the body. Bed rest decreases lung volume or "vital capacity" and this can lead to pneumonia. Prolonged bed rest can affect the cardiovascular system as well as the respiratory system. It causes a decrease in blood volume and a decrease in the number of red blood cells. This results in a decrease in the amount of oxygen available to the body and may interfere with the healing of wounds. Since the patient is lying down, gravity can't assist the heart's pumping action. Thus the heart must work harder, blood can pool in veins, leading to blood clots and may contribute to infection and stroke. A rapid drop in blood pressure and fainting, called **orthostatic hypotension**, may occur when the patient who has been lying in bed begins sitting in a chair or standing. The musculoskeletal system can also be adversely affected by bed rest. Muscles can weaken by about 20 percent during one week of inactivity in bed. The muscles actually decrease in size – atrophy. Motor

strength is also affected. Risk of loss of bone density (osteoporosis) and accumulation of excess bone across joint (heterotopic ossification) or in the muscle (myositis ossificans) increases as well. This new bone can cause pain and severely limit motion and may have to be removed surgically. Lying in one position too long can cause pressure sores to develop in the skin over bony prominences in both burned and unburned areas. Prolonged bed rest can also result in decreased appetite and constipation due to slowing of the bowel. Besides physical complication, bed rest can lead to psychological problems (Munster '93: 69, 72, 75).

The body repairs itself by forming **scar tissue**. When an injury first occurs, certain of the body's blood cells are attracted to the wound to help rid it of dead and damaged tissue, foreign substances (such as dirt), and any bacteria that may have entered the wound. This initial phase of healing lasts for five to seven days and is called the **inflammatory phase**. Scar tissue is made up of collagen, a protein that is manufactured and deposited in the healing wound by a cell called a fibroblast. As the first phase of healing ends, fibroblasts migrate into the wound and start laying down collagen to form scar tissue. This second phase is called the **proliferative phase**. Particularly during the first six to eight weeks after injury, a large amount of collagen is formed, resulting in thick scars. Even as the collagen is being laid down, an enzyme called collagenase begins breaking down the collagen. Although this process starts soon after injury occurs, only after two or three months does a balanced state develop, in which the amount of collagen being removed is equal to the amount of collagen being formed. The stage in which the scar fades is known as the **maturation phase**, it can last up to two years following the injury.

Some *scars* become pathological and cause physical problems for the burn patient early on and even after the body has tried to remodel the scar tissue during the maturation phase of healing. Most common pathological scar is the **hypertrophic scar**, that are raised, red and hard. The application of pressure causes the collagen to lay down more normally within the scar and results in a softer, flatter scar. **Keloids** are similar but grow beyond the bounds of the original wound. A third type of pathological scar occurs across a joint, limiting the movement of that joint. If non-operative treatments do not correct the problem a surgeon will cut across the contracture and extend the joint. Scars that remain an abnormal color for a long period of time are also considered pathological scars. **Burn scars** usually differ in color from normal skin early in the healing process and even long after the scar matures, frequently as long as 18 to 24 months. Gradually the color of the burn scar approximates the normal skin color, but it seldom completely matches. Dark-skinned individuals often have persistent depigmentation, resulting in patches of whiteness, or hyperpigmentation, resulting in extra-dark scars. A final category of pathological scars consists of those that are inadequate, most commonly scars that are thin and fragile, resulting in chronic reopening of the wound following minor trauma. Correcting the problem usually requires cutting away the inadequate scar and covering the area with split-thickness skin grafts or flaps in its place. Unless scars pose an urgent functional problem or endanger a vital structure, reconstructive surgery for functional problems is deferred for 6 to 12 months, and reconstructive surgery for the correction of disfigurement is delayed as long as 12 to 18 months after burn injury. Surgery performed on mature scars produces the best results, and the waiting period allows for scar maturation (Munster '93: 116-120, 122).

If left to heal spontaneously, the body will replace its skin cover through two primary healing processes: epithelialization and contraction. When epidermal skin cells (also called epithelial cells) lose contact with the cells that have been destroyed, the healthy cells divide, multiply and move across the open wound to cover it. When the wound is superficial, this process, epithelialization, is the primary mode of healing, and the resulting scar is relatively minimal.

When the wound is deeper, healing elements of the epidermis may have been destroyed and are not available for epithelialization. In this case the body closes the skin defect by drawing on the surrounding skin. This process of pulling the wound margins in toward the center of the wound is called contraction. As the wound heals, it shrinks. Contraction is a natural process that can cause deformities in deep burn injuries, as the same process that leads to contraction of the wound can result in "heaping up" of the burn scar or in the formation of tight scar bands across joints which limit their function. When excess scar tissue accumulates, hypertrophic scars or keloids are formed. Scar bands that limit joint mobility are called contractures. Because they cause dysfunction or deformity, all of these scars are considered pathological scars (Munster '93: 114, 115).

Patients who have deep second-degree burns that heal without grafting, and patients who have burns that require skin grafting, are at risk of developing **hypertrophic scar tissue**. This tissue, which is thick, raised, and hard, may cause both functional and cosmetic problems that can delay or limit the patient's physical rehabilitation. The most critical factor in controlling the scar is the early and continued use of pressure. To be effective, pressure must be applied consistently to all deep burn areas and must be equivalent to at least 25 millimeters of mercury per square inch. Pressure therapy begins as soon as the skin is healed and begins to feel dry. The most effective way to provide adequate pressure is to use specially made **elastic garments** such as gloves, knee-length stockings, full-length tights, long and short sleeve vests and face masks. Jobstskin, Barton-Carey and Bioconcepts are three brands of commercially manufactured elastic garments. Each garment is individually measured so that all burned areas receive consistent pressure. Most patients wear their garments 23 hours a day, with time out only for bathing, and most patients have two sets of garments (one to wash and one to wear). With proper washing, drying and care the garments usually last about 6 to 12 weeks, after which they must be replaced. The garments can be expensive but their cost is generally covered by insurance and medical assistance programs (Munster '93: 81, 82).

### **3. Acne, impetigo, leprosy, bacterial and mycobacterial infections**

**Acne vulgaris** is a very common skin condition of adolescents and young adults. It is characterized by any combination of comedones (blackheads), pustules, cysts, and scarring of varying severity. **Blackheads** are open and non-inflammatory. They result when a pore is partly blocked by dead skin cells. This prohibits the normal drainage of oil, making it accumulate under the skin. When this oil is exposed to air, oxidation occurs. This is when it turns hard and black. To eliminate blackheads, it is key to get rid of extra oil that accumulates. Exfoliating may help, especially when using products with salicylic acid. **Whiteheads** are also non-inflammatory. It develops like blackheads, except the extra oil growth of bacteria is totally blocked with no opening in the skin. The best way to eliminate whiteheads is to maintain a proper skin care routine. Cleaning the skin each day is essential, however it is best to not use plain soap which tends to dehydrate the skin. There are also products on the market which work to treat this condition. Antiseptics that contain aloe vera, witch hazel, or tea tree oil may help the most. **Papules** are a more serious form of acne. They develop when a whitehead gets swollen with a mix of oil and bacteria that ruptures and releases the material into the skin. Since the bacteria has broken through the glandular wall, inflammation occurs as white blood cells rush to the area in hopes of repairing the damage. Pus results and makes its way to the skin's surface. This is known as a pustule. **Nodules and Cysts** are also a severe form of acne. Cysts form when there is a deep rupture of a papule or pustule. These leaks carry infection into the deep part of the skin and leave damaging lesions behind. Individuals with **hormonal acne** can blame an imbalance of hormones

for lesions on the body. It is not something that affects only teenagers. Many times, hormonal acne carries into adulthood. As hormones fluctuate, the sebaceous glands are stimulated to produce large amounts of oil. This extra oil accumulates in hair follicles and combines dead cells and bacteria. This is most likely to occur during certain parts of the menstrual cycle, pregnancy, and times of high stress. The normal way to treat acne brought on by hormones is with birth control pills. This helps to regulate hormone levels. Eating a balanced diet may also help. Spicy, oily, and sugary foods tend to block pores due to the amount of fat they contain. It is also best to rinse the skin daily and avoid chemicals that irritate the skin. Products that contain benzoyl peroxide work best to kill bacteria and treat acne. Any form of pimple is annoying and can be painful. It is important to understand the causes and treatment that will make breakouts occur less. There are many types of acne, but when they become severe, it may be wise to seek the care of a trained dermatologist. **Rosacea** is an uncommon pustular eruption of the butterfly area of the face that may occur in adults in the 40 to 50 year age group. Severe, longstanding cases eventuate in the bulbous, greasy, hypertrophic nose characteristic of rhinophyma. The pustules are recurrent and difficult to heal. Rosacea keratitis of the eye is rare but can be very serious. Treatment is Dial soap twice a day. Sulfur (6%), Resorcinol (5), Colored alcoholic shake lotion q.s. 60.0 applied to face. Doxycycline 100 mg for three days, then for weeks as necessary for benefit (Sauer '85: 120, 125-127).

### Types of Acne



Credit: Healthzillion

**Acne** occurs on the face and neck and, less commonly, on the back, the chest, and the arms. The condition begins at ages 9 to 12 or later, and lasts, with new outbreaks, for months or years. It subsides in the majority of cases by the age of 18 or 19, but occasional flare-ups may occur for years. The residual scarring varies with the severity of the case and response to treatment. Important factors are heredity, hormonal balance, diet, cleanliness and general health. Acne is a disorder in which the oil glands of the skin are overactive. It usually involves the face and, frequently, the chest and the back since these areas are the richest in oil glands. When an oil gland opening becomes plugged, a blackhead is formed and irritates the skin in exactly the same way as any other foreign body, such as a sliver of wood. This irritation takes the form of red pimples or deep painful cysts. These infections destroy the tissues and, when healed, may result in permanent scars. The tendency to develop acne runs in families, especially those in which one or both parents have an oily skin. Acne is aggravated by certain foods, improper care of the skin, lack of adequate sleep, and nervous tension. In girls, acne is usually worse before a menstrual period. Even in boys, acne flares on a cyclic basis. Because acne is so common, is not contagious and does not cause loss of time from school or work, many persons tend to ignore it (Sauer '85: 120, 125-127).

The most obvious effects on the skin of the sudden surge of hormones through the bloodstream between the ages of about 10 and 14 are on the sebaceous, or grease-producing, glands, and the hair. The sebaceous glands have lain dormant since birth but with the stimulus of hormones they suddenly become very active. These glands are found in their greatest numbers on the forehead, the nose, the central part of the cheeks, and the chin. This central panel of the face will become shiny and greasy because the sebum from these very active glands is coming to the skin surface through the small openings of the pilosebaceous follicles, or 'pores'. If this sebum is regularly washed away with soap and water, the skin will usually remain smooth and healthy-looking, but in some teenagers the amount of sebum trying to get to the surface is so great that the opening of the follicle becomes blocked at the skin surface. This blockage quickly becomes blackened, as a result of exposure to the air and the result is a blackhead. If this is not dealt with rapidly, it can be the beginning of acne. Girls will frequently find their greasy skin is particularly troublesome in the week or so before their period is due. The best specific aid to coping with teenage skin is regular use of soap and water. Teenage skin needs the drying effect of soap, and does not require greasy moisturizing agents or emollients. Teenage hair will become greasy and lank if not shampooed frequently. Many teenagers wish to shampoo their hair daily, and this will do no harm. Teenage skin miseries can be partly controlled, if not completely prevented, by a sensible lifestyle. A balanced diet, regular mealtimes, plenty of fresh fruit and vegetables, half-an-hour in the fresh air each day and a regular exercise program are all good for the body in general, including the skin. Late nights, stuffy discos and a diet of sweets and chips do not help anyone to look their best. A deodorant or anti-antiperspirant may be needed in the armpits (Mackie '92: 42, 43).

Studies on teenagers in the UK have suggested that it is normal rather than abnormal to have at least a mild degree of acne, which is not usually called acne at all but just thought of as a few spots at some time during the teenage years. The problem usually begins earlier with girls than with boys. Girls will find their acne problems more troublesome between the ages of 13 and 16, while for many boys the problem does not start until about 15 and goes on until the age of about 19. Some people suffer from lingering problems with acne after the teenage years, but this is the exception. Mild acne usually involves the face, and the area most commonly affected is the central panel – forehead, the nose and the chin. Many teenagers have a few blackheads in these areas. If the problem with obstructed outflow continues, the sebum trapped on the way to the surface of the epidermis may leak into the surrounding dermis. When this happens the problem changes from being just a simple blackhead to being a raised, inflamed papule or spot on the skin. Sometimes these red spots develop unsightly yellow heads. As well as involving the face, acne may involve the front of the chest and, particularly in boys, the back over the shoulder area. Blackhead extractors are sold in pharmacies but must be used with care and should always be sterilized in boiling water after use, they should not be used just before going out to meet friends, as for an hour or two after applying pressure to the skin around blackheads and spots, the skin will be inflamed and red.

**Medical treatment** should be sought to prevent scarring and psychological disturbance. The affected areas should be washed twice a day with a washcloth and Dial soap. Sulfur, ppt. (6%), Resorcinol (4%), Colored alcoholic shake lotion 60.0 should be applied locally at bedtime with fingers. Proprietary substitutions for the above ingredients include Resulin lotion (Almay), Sulfacet-R (Dermik), Komed lotion (Barnes-Hind), Acne-Aid Cream (Stiefel), Acno lotions (Baker-Cummins), and Rezamid lotion (Dermik). Other locally applied preparations of value for acne are Benzoyl peroxide gel (5% or 10%) (Benzagel, Desquem-X, Panoxyl, Persa-Gel, and

others). Apply locally once a day. Some dryness of the skin with once-a-day use is to be expected. Tretinoin gel (0.025%)(Retin-A) q.s. 150 applied locally once a day. Patient toleration varies considerably, it is especially valuable for comedone acne. Isotretinoin (Accutane), for severe, scarring, cystic acne this therapy has proved beneficial. The usual dosage is 1.0 mg/kg/day given for 4 to 5 months. There are many minor and major side-effects with this therapy. Clindamycin 1%, Erythromycin 2% lotion q.s 30.0 applied locally once or twice a day. Remove the blackheads with a comedone extractor in the office. Ultraviolet therapy with increasing sub-erythema doses once or twice a week is used. Tetracycline 250 mg, or similar antibiotic, such as doxycycline 100 mg, the once a day antibiotic, can be continued at this dose for weeks, months or years (Sauer '85: 120-125).

**Foods to avoid** are chocolate, nuts, milk products, fatty meats and spicy foods. One important method of treatment is the proper removal of blackheads. This is part of the doctor's job and should not be done by the patient. Pimples that have pus in them. They can be extracted with surgical instruments designed for the purpose and do not damage tissues or cause scars. Picking pimples by the patient can cause scarring and should be avoided. When the blackheads are removed and the pustules are opened in the doctor's office, the skin heals faster and scarring is minimized. Doxycycline is frequently prescribed for the acne patient who is developing scars or pits. This antibiotic therapy may be continued by the physician for many months or even years. Occasionally one develops an upset stomach, diarrhea, or a genital itch from an overgrowth of yeast organisms. If these problems develop, stop the medication and call the physician. Doxycycline makes the skin more sensitive to sunlight. Therefore, if going skiing or to a sunny climate, lower the dosage or stop the tetracycline 4 days before the trip. Tetracyclines may make oral birth control slightly less effective. Do not take tetracycline or doxycycline if pregnant, because, after the fifth month of pregnancy, to the age of 9 years, it can permanently discolor the adult teeth of the child (Sauer '85: 125-127).

Treatments applied to the skin are very often based on **benzoyol peroxide**, which is a drying, mildly antiseptic preparation. When first used it can cause some dryness, redness and minor irritation. This is part of the treatment, and the preparation should not be stopped because this happens. After about a week the redness usually disappears, as do the blackheads. Another approach to managing mild acne is the use of oral antibiotics. These are prescribed not because acne is an infection, but because, among other things, antibiotics appear to alter the movement of the white cells normally found in the blood vessels, and it is these white cells – leucocytes – that are responsible for the yellow tops of spots on the skin. By altering the way in which they move into the skin, antibiotics make inflamed spots less likely. Tetracycline antibiotics, ideally **doxycycline** 'the once a day antibiotic', are prescribed for the treatment of acne. However, tetracycline cannot be prescribed if there is any possibility of pregnancy, or in children under the age of 8, because it can cause yellow stain on the bones and permanent teeth. Ideally it should be taken with a glass of water half-an-hour or so before a meal, so that it can be absorbed through the lining of the stomach; if it is taken with food it may not be absorbed. Treatment applied directly to the skin usually takes a week or two to have an effect, and the usual waiting time for an oral antibiotic is 1-2 months. For acne a low dose of antibiotic is prescribed for along period of time. Many acne sufferers have to take tetracyclines for 6, 9 or even 12 months. Fortunately, tetracyclines are safe preparations (in children over 8 as it causes permanent yellowing of developing permanent teeth) and there are no long-term side-effects (Mackie '92: 45-48).

For girls the use of a **hormonal combination** similar to that found in the oral contraceptive pill may well be of value in the management of acne. The hormonal combination most commonly prescribed for acne is **Dianette**, starting 5 days after the period has begun and continuing for 21-22 days. As with other forms of treatment for acne, there is usually a large period of 2 to 3 months before any benefit can be expected, and most should be discontinued after 9 months to a year, to be sure their own hormones are still working in the normal manner, and they have not developed any small cysts, common in those receiving hormonal therapy. An alternative treatment for acne in both sexes is a synthetic, vitamin A-like drug called Roaccutane in Europe and **Accutane** in the US. This has a very dramatic effect on the sebaceous glands. If small samples of skin are removed before and 4 months after oral Roaccutane and compared under microscope, it will be seen that after Roaccutane treatment the sebaceous glands have shrunk dramatically to a size similar to that found in small children before puberty. As the sebaceous glands shrink, their secretion of sebum dries up. The lips tend to dry and crack in the way which they may do when exposed to cold winter weather, and the lining of the nose may become dry, giving a permanent feeling of a stuffy nose and sometimes resulting in nose bleeds. The secretion of tears is also affected and there are complaints of dry-feeling, gritty eyes. The level of circulating fats in the blood may also become elevated, it is therefore necessary to get a blood sample checked, it is rare to have to cut treatment short because of this, but the levels return rapidly to their pretreatment state. All of these side-effects are relatively easy to put up with provided the acne sufferer has severe acne and knows the treatment is doing good. Accutane can damage an unborn child if taken by a young woman who is in the early stages of pregnancy, resulting in very serious defects of the heart, the hearing system and other organs. A standard course of Roaccutane usually lasts 4 months and the risk to an unborn child is so serious that most specialists will not prescribe Roaccutane unless the girl who wishes treatment for her acne is prepared to take the oral contraceptive for a month before starting Roaccutane, continue the oral contraceptive for the full 4 months of Roaccutane treatment and for another month after the Roaccutane course ends. Thus a 4 month course of Roaccutane involves a 6 month course of treatment with an oral contraceptive (Mackie '92: 48-50).

The most common causative agents of the primary skin infections, **pyodermas**, are the coagulase-positive micrococci (staphylococci) and the  $\beta$ -hemolytic streptococci. Superficial or deep bacterial lesions can be produced by these organisms. In general, improve bathing habits and use bactericidal soap, such as Dial. Clothing and bedding should be changed frequently and the patient should have a separate towel and wash cloth. Chocolate, nuts, cola drinks, cheeses, iodides, bromides and lithium should be restricted. Rule out diabetes.



**Impetigo** is a very common superficial bacterial infection seen most often in children. The lesions vary from small vesicles to large bullae that rupture and discharge a honey-colored serous liquid. New lesions can develop in a matter of hours. Crusts form from the discharge and appear to be lightly stuck on the skin surface. When removed, a superficial erosion remains. In debilitated infants bullae may coalesce to form an exfoliative type of infection called Ritter's disease or

pemphigus neonatorum. In infants massive bullae can develop rapidly, particularly with

staphylococcal infection. Impetigo is a skin infection caused by bacteria. If any child has a cut or graze, particularly on the face, certain types of bacteria – mainly staphylococci and streptococci – can enter the abrasion and give rise to impetigo. This is usually recognized as a moist, weeping, crusted sore, often on the face around the mouth. Impetigo responds well to antibiotics, either applied as an ointment to the skin surface or as a syrup given by mouth for a few days. Although the rash of impetigo can be widespread, it affects only the most superficial layers of the epidermis. No permanent damage will be done to the child's skin – the impetigo lesions will heal with no scarring because the basal layer of keratinocytes is undamaged and will build a new and perfect epidermis. However, picking and scratching can damage the underlying dermis and could in turn give rise to scarring (Mackie '92: 38, 39).

The severe but not too serious form of the impetigo infection is known as the **staphylococcal scalded skin syndrome**. The lesion is treated with Neo-Polycin or other antibiotic ointment with Sulfur, ppt. 4% advised to continue the local treatment for 3 days after the lesions apparently have disappeared. Systemic antibiotic therapy with oral penicillin or erythromycin in children and people with penicillin allergies respectively, or doxycycline in adults for 10 days would be effective to heal these lesions and also to prevent chronic glomerulonephritis (Sauer '85: 145-148). **Ecthyma** is another superficial bacterial infection, but it is seen less commonly and is deeper than impetigo. It is usually caused by  $\beta$ -hemolytic streptococci and occurs on the buttocks and the thighs of children. A vesicle appears and rapidly changes into a piled-up crust, 1 cm to 3 cm in diameter, overlying a superficial erosion or ulcer. In neglected cases scarring can occur. Systemic antibiotics are commonly given to children with impetigo, if there is a low-grade fever and evidence of bacterial infection in other organs, such as the kidney. If so penicillin by injection (600,000 units/day for 3 to 4 days) or one of the antibiotic syrups orally q.i.d. for 6 to 1 days.

**Folliculitis** is a very common pyogenic infection of the hair follicles, usually caused by coagulase-positive staphylococci. The physician is not often consulted unless there are recurrent and chronic pustular lesions. The folliculitis may invade only the superficial part of the hair follicle, or it may extend down to the hair bulb. Hair oils, bath oils or suntan oils should be avoided. A superficial form has the appellation *acne necrotica miliaris* that is an annoying pruritic, chronic, recurrent folliculitis of the scalp in adults. Treatment is Selsun Suspension 120.0 shampoo twice a week as directed. Use no other shampoo or rinse. Antibiotic-corticosteroid ointment may be applied to the scalp. The deep form of scalp folliculitis is called **folliculitis decalvans** it is a chronic, slowly progressive folliculitis with an active border and scarred atrophic center. The end result, after years of progression, is patchy, scarred areas of alopecia, with eventual burning out of the infection and differential diagnosis with chronic discoid lupus erythematosus, alopecia cicatrisata, and tinea of the scalp (Sauer '85: 148, 149).



A **furuncle**, or boil, is a more extensive infection of the hair follicle, usually due to *Staphylococcus*. It is treated with Burow's solution hot packs, incision and drainage, oral antistaphylococcal penicillin, such as dicloxacillin, for 5 to 10 days. Oral doxycycline therapy 100 mg for weeks, as for acne patients, is very effective in breaking the cycle of recurrent cases. A **carbuncle** is an extensive infection of several adjoining hair follicles that drains with multiple openings onto the skin surface. Fatal cases were not unusual in the preantibiotic days. Treatment is the same as that for a boil but

with greater emphasis on systemic antibiotic therapy and physical rest. **Sweat gland infections** are rare, however, prickly heat, a sweat-retention disease, very frequently develops secondary bacterial infection. **Apocrinities** denotes infection of a single apocrine gland, usually in the axilla, and is commonly associated with a change in deodorant. A shake lotion containing a powdered antibiotic aids in keeping the area dry. The second form of apocrine gland infection is **hidradenitis suppurativa**. This chronic, recurring, pyogenic infection is characterized by the development of multiple nodules, abscesses, draining sinuses, and eventual hypertrophic bands of scars. It does not occur before puberty. Two other diseases may be present in the same patient (1) a severe form of acne called acne conglobate and (2) dissecting cellulitis of the scalp. Hot packs should be used locally and oral antibiotics taken for several weeks (Sauer '85: 149-152).

**Erysipelas** is an uncommon  $\beta$ -hemolytic streptococcal infection of the subcutaneous tissue that produces a characteristic type of cellulitis, with fever and malaise. Recurrences are frequent. A red, warm, raised, brawny, sharply bordered plaque enlarges peripherally. Vesicles and bullae may form on the surface of the plaque. Usually a preexisting skin wound or pyoderma will be found that initiated the acute infection. Multiple lesions of erysipelas are rare. Most commonly lesions occur on the face and around the ears (following ear piercing), but no area is exempt. Untreated cases last for 2 to 3 weeks, but when treated with antibiotics, the response is rapid. Recurrences are common in the same location and may lead to lymphedema of that area, which eventually can become irreversible. The lip, the cheek and the legs are particularly prone to this chronic change, which is called elephantiasis nostras. Differential diagnosis with cellulitis, that lacks a sharp border; recurrences are rare and contact dermatitis, sharp border absent fever and malaise absent; eruption predominantly vascular. Bed rest is instituted and therapy is directed toward reducing the fever. If the patient is hospitalized, semi-isolation procedures should be initiated. Give appropriate systemic antibiotic orally and/or by injection for 10 days. Apply local cool wet dressing, as necessary for comfort. **Erythrasma** is a rather uncommon bacterial infection of the skin that clinically resembles regular *tinea* or *tinea versicolor*. It affects the crural area, axillae, and webs of the toes with flat, hyperpigmented, fine scaly patches. If the patient has not been using an antibacterial soap these patches fluoresce a striking orange reddish color under the Wood's light. The causative agent is a diphtheroid organism called *Corynebacterium minutissimum*. The most effective treatment is erythromycin, 250 mg, twice a day, for 5 to 7 days. Locally the erythromycin lotions are quite effective (Staticin, T-Stat, Ery-Derm and A/T/S lotion) applied for 10 days (Sauer '85: 152 153).

**Secondary infection** develops as a complicating factor on a preexisting skin disease. Any type of skin lesion, such as hand dermatitis, poison ivy dermatitis, atopic eczema, chigger bites, fungus infection, traumatic abrasion, and so on, can become secondarily infected. The treatment is usually simple. Add an antibacterial agent to the treatment. For extensive secondary bacterial infection, the appropriate systemic antibiotic is indicated. Ulcers are deep skin infections due to injury or disease that invade the subcutaneous tissue and, on healing, leave scars. Primary ulcers result from gangrene due to pathogenic streptococci, staphylococci and *Clostridium* species; *Helicobacter pylori*, syphilis, chancroid, tuberculosis, diphtheria, fungi, leprosy anthrax, cancer and lymphoblastomas. Secondary ulcers can be related to vascular disorders (arteriosclerosis, thromboangiitis obliterans, Raynaud's phenomenon, phlebitis, thrombosis), neurologic disorders (spinal cord injury with bedsores or decubiti, CNS syphilis, spina bifida, poliomyelitis, syringomyelia), diabetes, trauma, ulcerative colitis, allergic local anaphylaxis and other conditions. There is also a group of secondary ulcers called phagedenic ulcers, that arise in diseased skin or on the apparently normal skin of debilitated individuals. These ulcers

undermine the skin in large areas, are notoriously chronic and resistant to therapy. For primary ulcers the response to antibiotic therapy is usually quite rapid. For secondary ulcers, appropriate therapy should be directed toward the primary disease whereas the response to medicine is slow. Treatment involves rest and bandaging of the ulcer. Burow's solution wet packs, in warm water. Debridement can be accomplished by enzymes, such as Santyl (collagenase) ointment, Varidase jelly or Elase ointment, applied twice a day and covered with gauze. Gentian violet (1%) in distilled water. Neosporin or other antibiotic ointment. Doxycycline 100 mg therapy, once a day for 10 days. Metronidazole (Flagyl ER) 400 mg, twice a day, for 10 days, is particularly good at healing ulcers of the alimentary canal. Low-dose oral corticosteroid therapy prednisone, 10 mg, 1 or 2 tablets every morning for 3 to 4 weeks, then 1 tablet every other morning for months (Sauer '85: 153, 156).

**Infectious eczematoid dermatitis** is an uncommon disease characterized by the development of an acute eruption around an infected exudative primary site, such as a draining ear, mastitis, a boil, or a seeping ulcer. Widespread eczematous lesions can develop at a distant site from the primary infection. Vesicles and pustules in circumscribed plaques spread peripherally from an infected central source. Central healing usually does not occur, as in ringworm infection. Crusting, oozing and scaling predominate in widespread cases. Coagulase-positive staphylococci are frequently isolated. Passage of the infective material to another individual rarely elicits a reaction. Differential diagnosis with contact dermatitis with secondary infection, nummular eczema and seborrheic dermatitis. Clean with Burow's solution wet packs and warm water. Apply antibiotic-corticosteroid cream, locally, after the wet packs are removed.

**Bacterial intertrigo** is caused by the presence of friction, heat and moisture in areas where two opposing skin surfaces contact each other leading to a secondary bacterial or fungal infection. The factors of obesity, diabetes, and prolonged contact with urine, feces and menstrual discharges predispose to the development of intertrigo. Differential diagnosis with Candidal intertrigo, Tinea and Seborrheic dermatitis. Bathe one a day in lukewarm water with antibacterial soap. Dry affected areas thoroughly. Apply sulfur (4%) and nonalcoholic white shake lotion 90.0 or sulfur (4%) and Hydrocortisone-antibiotic cream, to affected areas (Sauer '85: 157, 158). Scarlet fever is a moderately common streptococcal infection characterized by a sore throat, high fever and a scarlet rash. In untreated cases the rash reaches its peak on the fourth day, and scaling commences around the seventh day and continues for 1 or 2 weeks. The "strawberry tongue" is seen at the height of the eruption. The presence of petechiae on the body is a grave prognostic sign. Differential diagnosis with measles and drug eruptions. Complications are numerous and common in untreated cases. Penicillin or a similar systemic antibiotic is the therapy of choice.

The most common **rickettsial disease** in the United States is Rocky Mountain spotted fever which is spread by ticks of various types. The skin eruption occurs after 3 to 7 days of fever and other toxic signs and is characterized by purpuric lesions on the extremities, mainly the wrists and ankles. The Weil-Felix test using *Proteus* OX19 and OX2 is positive. Tetracycline and chloramphenicol are effective. The typhus group of rickettsial diseases includes epidemic or louse-borne typhus, Brill's disease and endemic murine or flea-borne typhus. Less common forms include scrub typhus (tsutsugamushi disease), trench fever, and rickettsial-pox, which is caused by a mite bite. The mite ordinarily lives on rodents. Approximately 10 days after the bite a primary lesion develops in the form of a papule that becomes vesicular. After a few days of fever and other toxic signs are accompanied by a generalized eruption that resembles chickenpox. The disease subsides without therapy.

**Actinomycosis** is a chronic, granulomatous, suppurative infection that characteristically causes the formation of a draining sinus. The most common location of the draining sinus is in the jaw region. But thoracic and abdominal sinuses do occur. A red, firm, non-tender tumor in the jaw area slowly extends locally to form a "lumpy jaw". Discharging sinuses become infected with other bacteria and, if untreated, may develop into osteomyelitis. General health is usually unaffected. *Actinomyces israelii*, which is an anaerobic bacterium that lives as a normal inhabitant of the mouth, particularly in individuals who have poor dental hygiene, is the causative agent. Injury to the jaw or a tooth extraction usually precedes the development of the infection. The disease is twice as frequent in males as in females. A Gram stain of the pus will show masses of interlacing gram-positive fibers with or without the club-shaped processes at the tips of these fibers. Differential diagnosis with pyoderma, tuberculosis and neoplasm. Treat with penicillin, 2.4 million units intramuscularly, daily, until definite improvement is noted. Then oral penicillin in the same dosage should be continued for 3 weeks after the infection apparently has been cured. In severe cases, 10 million or more units of penicillin given intravenously, daily may be necessary. Incision and drainage is performed on the lumps and sinuses. In resistant cases, broad-spectrum antibiotics can be used alone or in combination with the penicillin (Sauer '85: 161, 162). Doxycycline is indicated for the treatment of rickettsial diseases.

**Granuloma inguinale** is due to *Calymmatobacterium granulomatis*. Prior to the use of antibiotics, particularly streptomycin and tetracycline, was one of the most chronic and resistant afflictions of humans. Granuloma inguinale should be considered a venereal disease, although other factors may have to be present to initiate infection. An irregularly shaped, bright red, velvety appearing, flat ulcer with rolled border is seen. Scarring may lead to complications and squamous cell carcinoma can develop in old, chronic lesions. Genital lesions are most common on the penis, scrotum, labia, cervix and inguinal region. Without therapy, the granuloma grows slowly and persists for years, causing marked scarring and mutilation. Under modern therapy, healing is rather rapid, but recurrences are not unusual. Differential diagnosis with Granuloma pyogenicum, primary syphilis, chanroid, and squamous cell carcinoma. Doxycycline 100 mg is continued until all the lesions are healed.

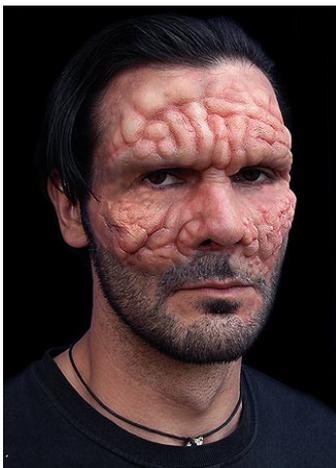
**Chancroid** is a venereal disease with a very short incubation period of 1 to 5 days. It is caused by *Hemophilus ducreyi*. A small, superficial or deep erosion occurs with surrounding redness and edema. Multiple genital or distant lesions can be produced by autoinoculation. Deep, destructive ulcers form in chronic cases, which may lead to gangrene. Without therapy most cases heal within 1 to 2 weeks. In rare cases, severe local destruction and draining lymph nodes result. Syphilis must be considered in any patient with a penile lesion. It can be ruled out only by darkfield examination or blood serology tests. Herpes simplex progenitalis, lymphogranuloma enereum and granuloma inguinale must also be ruled out in a differential diagnosis. **Gonorrhea** is considerably more prevalent than syphilis. Skin lesions with gonorrheal infection are rare. The therapy schedule suggested by the United States Public Health Service is 4.8 million units of aqueous procaine penicillin intramuscularly divided into two doses injected at two sites on the first visit. For penicillin sensitive individuals, spectinomycin, 2 g to 4 g intramuscularly, or tetracycline, orally in a dose of 9 g given over 4 days, can be prescribed. Untreated or inadequately treated infection due to *Neisseria gonorrhoeae* can involve the skin through metastatic spread. Metastatic complications are treated with intravenous penicillin for 10 days with 5 to 10 million units/day (Sauer '85: 158, 159, 161).

**Skin tuberculosis** is rare in the United States. *Lupus vulgaris* is a chronic, granulomatous disease characterized by the development of nodules, ulcers and plaques. Scarring in the center of active lesions or at the edge, in severe untreated cases, leads to atrophy and contraction, resulting in mutilating changes. The course is often slow and progressive, in spite of therapy. The histopathology shows typical tubercle formation with epithelioid cells, giant cells and a peripheral zone of lymphocytes. The causative organisms, *Mycobacterium tuberculosis*, is not abundant in the lesions. The 48-hour tuberculin test is usually positive. Differential diagnosis with other granulomas, such as those associated with syphilis, leprosy, sarcoidosis, deep fungus disease and neoplasm. Early localized lesions can be treated by surgical excision. For more widespread cases, long term systemic therapy offers high hopes for cure. Isonicotinic acid hydrazide is usually prescribed along with another antituberculous drug.

In order to diagnose **syphilis**, the physician must have a high index of suspicion for it. Syphilis mimics many other conditions. Cutaneous lesions of syphilis occur in all three stages of the disease. The first stage of acquired syphilis usually develops within 2 to 6 weeks (average 3 weeks) after exposure. The primary chancre most commonly occurs on the genitalia, but extra-genital chancres are not rare and are often misdiagnosed. Without treatment the chancre usually heals within 1 to 4 weeks. The blood serologic test for syphilis (STS) may be negative in the early days of the chancre but eventually become positive. A cerebrospinal fluid examination during the primary stage reveals invasion of the spirochete in approximately 25% of cases. The chancre may vary in appearance from a single small erosion to multiple indurated ulcers of the genitalia. Primary syphilis commonly goes unnoticed in the female. Bilateral or unilateral regional lymphadenopathy is common. Malaise and fever may be present. Early secondary lesions may develop before the primary chancre has healed or after latency of a few weeks. Late secondary lesions are more rare and usually are seen after the early secondary lesions have healed. Both types of secondary lesions contain the spirochete *Treponema pallidum*, which can be easily seen with the darkfield microscope. The STS is positive, and approximately 30% of cases have abnormal cerebrospinal fluid findings. **Condylomata lata** is the name applied to the flat, moist, warty lesions teeming with spirochetes found in the groin and the axillae. The late secondary lesions are nodular, squamous and ulcerative and are to be distinguished from the tertiary lesions only by the time interval after the onset of the infection and by the finding of the spirochetes in superficial smears of serum from the lesions. Following the secondary stage, many patients with untreated syphilis have only a positive STS. After 4 years of infection, the patient enters the late latent stage. This time span of 4 years arbitrarily divides the early infectious stages from the later noninfectious stages, which may or may not develop. Tertiary syphilis is the late stage manifested by subjective or objective involvement of any of the organs of the body, including the skin. Tertiary changes may be precocious but must often develop 5 to 20 years after the onset of the primary stage. Approximately 15% of the patients who acquire syphilis and receive no treatment die of the disease. Congenital syphilis is acquired in utero from an infectious mother. The STS required of pregnant women by most states has lowered the incidence of this unfortunate disease. Stillbirths are not uncommon from mothers who are untreated. After the birth of a live infect child, the mortality rate depends on the duration of the infection, the natural host resistance, and the rapidity of initiating correct treatment (Sauer '85: 163-168).

The etiologic agent, *Treponema pallidum*, can be found in the serum from the lesion. However, a darkfield microscope is necessary. A considerable amount of experience is needed to distinguish *T. pallidum* from other *Treponema* species. A rather simple and readily available test is the serologic test for syphilis (STS). When a report is received from the laboratory that the

STS is positive, a second blood specimen should be submitted. The cerebrospinal fluid is frequently positive in the primary and secondary stages of the disease. Invasion of the central nervous system is an early manifestation, even though the perceptible clinical effects are a late manifestation. If the cerebrospinal fluid is negative in a patient who has had syphilis for 4 years, central nervous system syphilis will not occur, and future cerebrospinal fluid tests are not necessary. If the test is positive, repeat tests should be done every 6 months for 4 years. A white count, total protein and nontreponemal flocculation test are run on the cerebrospinal fluid. Differential diagnosis of primary syphilis from chancroid, herpes simplex, fusospirochetal balanitis, granuloma inguinale and any primary chancre-type disease. Secondary syphilis from any of the papulosquamous diseases, fungal diseases, drug eruptions and alopecia areata. Tertiary skin syphilis from any of the granulomatous disease, particularly tuberculosis, leprosy, sarcoidosis, deep mycoses, and lymphoblastomas. Congenital syphilis from atopic eczema, lymphadenopathy, hepatomegaly, and splenomegaly. A true-positive syphilitic serology is to be differentiated from a biologic false-positive reaction. Treatment involves soaking the site in saline solution for 15 minutes twice a day, Neosporin topical ointment and advising against sexual intercourse. Primary and secondary syphilis are treated with 2.4 million units of benzathine penicillin G, half in each buttock, single session. Latent syphilis is treated with 7.2 million units benzathine penicillin G divided into three weekly injections. If cerebrospinal fluid examination is nonreactive: 2.4 million units in single dose. For neurosyphilis or cardiovascular syphilis 9 to 12 million units of a long-acting penicillin. For early congenital syphilis under 6 months of age aqueous procaine penicillin G, ten daily intramuscular doses totaling 100,000 to 200,000 units/kg. Six months to 2 years of age as above, or benzathine penicillin G, 100,000 units/kg intramuscularly in one single dose. For ages 2 to 11 years or weighing less than 70 pounds same as for 6 months to 2 years. Twelve years or older, but weighing more than 70 pounds same treatment as for adults acquired syphilis. Any patient treated for gonorrhea should have serologic test for syphilis (STS) 4 to 6 weeks later. Seventy-five percent of the persons who acquire syphilis suffer no serious manifestations (Sauer '85: 168-172).



**Leprosy** or Hansen's disease is to be considered in the differential diagnosis of any skin granulomas. It is endemic in the southern part of the United States and in semitropical and tropical areas the world over, wherever there is tuberculosis. Two definite types of leprosy are recognized: lepromatous and tuberculoid. **Lepromatous leprosy** is the malignant form, which represents minimal resistance to the disease, with a negative lepromin reaction, characteristic histology, infiltrated cutaneous lesions with ill-defined borders, and progression to death from tuberculosis and secondary amyloidosis. **Tuberculoid leprosy** is generally benign in its course because of considerable resistance to the disease on the part of the host. This is manifested by a positive lepromin test, histology that is not diagnostic, cutaneous lesions that are frequently erythematous with elevated borders, and minimal effect of the disease on the general

health. Early lesions of the lepromatous type include reddish macules with an indefinite border, nasal obstruction, and nosebleeds. Erythema nodosum-like lesions occur commonly. The tuberculoid type of leprosy is diagnosed early by the presence of an area of skin with impaired sensation, polyneuritis, and skin lesions with a sharp border and central atrophy. The causative organism is *Mycobacterium leprae*. **Mycobacteria** are pathogenic and saprophytic. *Mycobacterium marinum* can cause the swimming pool granuloma and also granulomas in fishermen and those involved with fish tanks. The source of infection is thought to be from

patients with the lepromatous form. Infectiousness is of a low order. The bacilli are usually uncovered in the lepromatous type but seldom in the tuberculoid type. The lepromin reaction, a delayed reaction test similar to the tuberculin test, is of value in differentiating the lepromatous from for the tuberculoid form of leprosy. False-positive reactions, including tests for syphilis, can occur. Dapsone (diaminodiphenyl sulfone, DDS) to specifically treat leprosy lesions and rifampin, and isoniazid to treat tuberculosis are all quite effective (Sauer '85: 160, 161). A leper said to Jesus, "if you are willing you can heal me" (Mark 1:40)(Luke 5:12)

#### 4. Warts, herpes and viral infections

Viral diseases of the skin are exceedingly common. The exanthems of children include: (1) herpes simplex, (2) Kaposi's varicelliform eruption, (3) zoster, (4) chickenpox, (5) smallpox, vaccinia, and cowpox, (6) warts, (7) molluscum contagiosum, (8) lymphogranuloma venereum, and (9) exanthematous disease; measles, German measles, roseola, and erythema infectiosum.



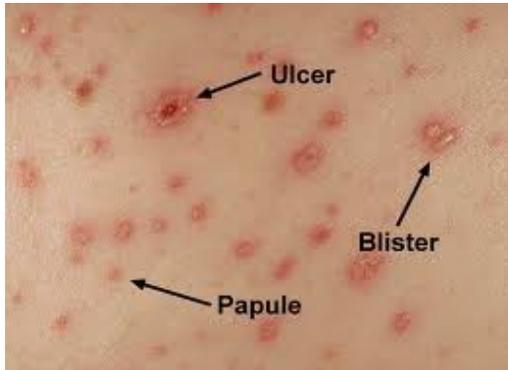
**Herpes simplex** (fever blister) is an acute, moderately painful, viral eruption of a single group of vesicles that commonly occurs around the mouth or the genitalia. A group of vesicles appears on the lips, mouth, genital region of both males and females (herpes progeneralis), eye (marginal keratitis or corneal ulcer) or any body area may be involved, erosions and secondary bacterial infection are seen. The vesicles last for 2 to 3 days before the tops come off. The residual erosions or crusted lesions last for another 5 to 7 days. Recurrences are common in the

same area. The disease is caused by a relatively large DNA virus, the herpes simplex virus (HSV). There are two antigenically and biologically different strains of the virus. Type 1 HSV is associated with most non-genital herpetic infections.

Type 2 HSV occurs chiefly in association with genital infection and is venereally transmitted. However, herpetic pharyngitis in homosexual men is frequently caused by type 2 virus. Either viral type will "take" at any site on the body, if appropriately inoculated. Certain precipitating factors are important in producing the recurrent eruptions. These factors include, fever, common cold, sunlight, psychic influences, stomach upsets, and trauma, apparently activate a dormant phase of the virus in the dorsal root ganglia. The disease can be spread through intimate contact. On the average, recurrent herpes lesions "shed" infectious HSV for approximately 5 days after onset of the lesions. However asymptomatic shedding of the HSV also occurs and is a major epidemiologic problem. The virus may be isolated from the lesions. Cytodiagnosis slides reveal large bizarre mononucleate and multinucleate giant cells and nuclear changes of ballooning degeneration. The giant cells contain eight to ten nuclei. Differential diagnosis with aphthous stomatitis in mouth, zoster and tinea of the body in body lesions and primary syphilis in genital lesions. Treatment is Acyclovir (Zovirax) therapy 200 mg 5 capsules a day, in divided doses every 4 hours while awake, for 5 days. Zovirax ointment (5%), Neo-Synalar or other antibiotic-corticosteroid ointment and Burow's solution wet compress for 20 minutes three times a day relieve much of the pain and irritation (Sauer '85: 175-178).

**Kaposi's varicelliform eruption** is an uncommon viral disease with severe complication in children who have atopic eczema. It results from self-inoculation by scratching, due to the virus

of either herpes simplex (eczema herpeticum) or vaccinia. With either type, the child is acutely ill, has a high fever, and has generalized, umbilicated, chickenpoxlike skin lesions. Acyclovir administered intravenously has proved beneficial in halting the progression of the disease and in promoting faster healing. Supportive therapy consists of antibiotic systemically, intravenous infusions, and a claminelike shake lotion. Locally. For severe cases due to the vaccinia virus, vaccinia immune globulin (VIG) is available from several centers in the United States through the American National Red Cross. **Herpesvirus infection in immunocompromised** patients can present as severe, ulcerative life-threatening herpes simplex infections in children and adults who have undergone organ transplantation, have lymphomas or advanced metastatic carcinoma, or are receiving systemic corticosteroid or antimetabolite therapy. Intravenous acyclovir therapy is proving helpful in controlling the viral proliferation (Sauer '85: 178, 179).



**Zoster**, shingles, is a common viral disease characterized by the appearance of several groups of vesicles distributed along a cutaneous nerve segment. Zoster and chickenpox are thought to be caused by the same virus. Susceptible children who are exposed to cases of zoster often develop chickenpox. Less commonly, older individuals exposed to chickenpox may get zoster. New crops of vesicles may appear for 3 to 5 days. The vesicles then dry up and form crusts, which take 3 weeks, on the average, to disappear. The general health is seldom affected, except for low-grade

fever and malaise. Recurrences are rare. Treatment consists of alcoholic white shake lotion, triamcinolone, 4 mg, 1 tablet for 6 days, then 2 tablets every morning, and corticosteroid therapy, for which there is evidence that early systemic use can decrease the post-herpetic pain problem, and can be prescribed Prednisone, 10 mg, 2 tablets every morning for 6 days, then decrease dose slowly as symptoms subside. **Chickenpox** is a common viral disease of childhood characterized by the development of tense vesicles, first on the trunk and then spreading, to a milder extent, to the face and extremities. New crops of vesicles appear for 3 to 5 days, and healing of the individual lesions occurs in a week. The disease occurs 10 to 14 days after exposure to another child with chickenpox or to an adult with zoster. The clear vesicle becomes a pustule and then a crusted lesion before dropping off. Itching is more prominent during the healing stage. Usually no treatment is indicated. Menthol (0.25%) may be combined with nonalcoholic white shake lotion. Benadryl hydrochloride elixir 60.0 1 teaspoon for moderately severe itching (Sauer '85: 179, 180).

**Smallpox** is an apparently eradicated viral disease characterized by the development, after an incubation period of 1 to 3 weeks, of prodromal symptoms of high fever, chills, and various aches. After 3 to 4 days a rash develops, with lowering of the fever. The individual lesions are most extensive on the face and the extremities; they come out as a single shower and progress from papule to vesicle, and, in 5 to 10 days, to pustule. With the occurrence of the pustule the fever goes up again, with a high white blood cell count. Hemorrhagic lesions usually indicate a severe form of the disease. Alastrim is a mild form of smallpox resulting from a less virulent strain of the virus. Varioloid is a mild form of smallpox that occurs in vaccinated individuals, this strain is very virulent, and when transmitted to a non-vaccinated person often causes a fulminating disease. Severe systemic complications of smallpox include pneumonia, secondary bacterial skin infection and encephalitis. Prophylactic treatment consists of vaccination. The

best technique is multiple puncture. Never vaccinate a patient who has active eczema, scratching of the vaccination can lead to development of eczema vaccinatum.

**Vaccinia** is produced by the inoculation of the vaccinia virus into the skin of a person who has no immunity. The primary vaccination reaction begins as a red papule on a red base that develops on the fourth day, becomes vesicular in 3 more days and pustular in 2 to 3 more days, and then gradually dries to form a crust, which drops off within 3 to 4 weeks after the vaccination. A mild systemic reaction may occur during the pustular stage. The vaccination site should be kept dry and uncovered. A biologic false-positive serologic test for syphilis develops in approximately 0% of vaccinated persons. The test becomes negative within 2 to 4 months. A vaccinoid reaction develops in a partially immune individual. A pustule with some surrounding redness occurs within 1 week. An immune reaction consists of a papule that develops in 2 days, which may or may not persist for 1 week. An absent reaction indicates that the vaccine was inactivated by the procedure. A successful vaccination offers protection from smallpox within 3 weeks, and this immunity lasts for approximately 7 years or longer. Jenner used the **cowpox** virus to vaccinate humans against smallpox. The vaccinia virus and the cowpox virus are however different, presumably as a result of a change in the vaccinia virus through years of passage. The term cowpox is now reserved for the viral disease of cows that occurs in Europe. Humans can get the disease from infected teats and udders. A solitary nodule appears, usually on the hand, which eventually suppurates and then heals in 4 to 8 weeks (Sauer '85: 180-181).

Warts, or **verrucae**, are very common small tumors of the skin. There are 30 to 40 types of human papillomavirus (HPV) that will affect an estimated 75% to 80% of males and females in their lifetime. For most, HPV clears on its own, but, for others HPV could cause cervical cancer in females and other types of HPV could cause genital warts in both males and females. The human papillomavirus (HPV) is a DNA virus. In 1985, 15 types of HPV had been identified by immunocytologic and molecular biologic techniques. Several of the types can cause clinically similar warts. For instance, types 3 and 10 cause flat warts. The **common wart** appears as a papillary growth, slightly raised above the skin surface, varying from pinhead size to large clusters of pea-sized tumors. These warts are seen most commonly on the hands. Rarely, they have to be differentiated from seborrheic keratosis (flatter, darker, velvety tumors of older adults) and pigmented verrucous nevi (projections are not dry and rough to touch). Single small (under 6 mm) warts in adults or older children are best removed by electrosurgery. The recurrence rate is minimal, and one treatment usually suffices. The technique is to cleanse the area, anesthetize the site with 1% procaine or other local anesthetic, destroy the tumor with any form of electrosurgery, nip off or curette out the dead tissue, and desiccate the base. Recurrences can be attributed to failure to remove the dead tissue. No dressing should be applied. The site will heal in 5 to 14 days with only minimal bacterial infection and scar formation. Warts around the nails have a high recurrence rate, and cure usually requires removal of part of the overlying nail.

Liquid nitrogen therapy is simple, effective but moderately painful, admonished to freeze lightly and not deeply. Alternatively, Salicylic acid (10%) in flexible collodion 30.0 may be applied to warts every night for 5 to 7 nights. The dead tissue can then be removed with scissors. This type of treatment may be used for patients with 20 or more warts, or for larger warts to avoid scarring. Another form of treatment for multiple warts or warts in children is a mild corticosteroid cream 150.0 applied in very small quantity to each wart at night. Then cover the wart with Saran Wrap or Blenderm tape and leave the occlusive dressing on all night or for 24 hours. Repeat nightly. This treatment has the advantage of being painless and quite effective. Salicylic acid (2% to 4%) can be added to the cream for further benefit. Vitamin A, 50,000 units, 1 tablet a day for no

longer than 3 months, is safe, for the resistant case, and warts have disappears after such a course of treatment (Sauer '85: 181-183). Gardasil is a vaccine that helps protect against 4 types of HPV. In girls and young women ages 9 to 26 Gardasil helps protect against 2 types of HPV that cause about 75% of cervical cancer cases, and 2 more types that cause 90% of genital warts cases. In boys and young men ages 9 to 26 Gardsasil helps protect against 90% of genital warts cases.

**Filiform warts** are warts with long, fingerlike projections for the skin that most commonly appear on the eyelids, the face and the neck. They are differentiated from cutaneous horns (which are seen in elderly patients with actinic keratosis or prickle cell epithelioma at the base and have a hard keratin horn and from pedunculated fibromas (which occur on the neck and the axillae of middle-aged men and women. The warts can be snipped off without anesthesia, with a small scissors. Apply trichloroacetic acid solution (saturated) cautiously to the base. This method is fast and effective, especially for children. Electrosurgery can be done. An annoying variant of this type of wart if multiple small filiform warts of the beard area. Electrosurgery without anesthesia is well tolerated, however, to achieve a permanent cure, the patient should be seen every 3 to 4 weeks for as long a period as necessary to remove the young warts that are in the process of enlarging. Flat warts are small, flat tumors that are often barely visible but can occur in clusters of 10 to 30 or more. They are commonly seen on the horsehead and the dorsum of the hand and should be differentiated from seborrheic keratosis or nonpigmented nevi. Alcoholic white shake lotion 60.0 has been effective. Electrosurgery or liquid nitrogen may be used.

### Types of Warts



**Moist warts** (condylomata acuminata) are characteristic, single, or multiple, soft, nonhorny masses that appear in the anogenital areas and, less commonly, between the toes and at the corners of the mouth. They are not always of a venereal nature. Treatment involves Podophyllum resin in alcohol (25% solution). Apply once to the warts, cautiously. Second or third treatments are usually necessary at weekly intervals. To prevent excessive irritation, the site should be bathed within 3 to 6 hours after the application (Sauer '85: 183, 184). Gardasil helps protect against 4 types of HPV. In girls and young women ages 9 to 26 Gardasil helps protect against 2 types of HPV that cause about 75% of cervical cancer cases, and 2 more types that cause 90% of genital warts cases. In boys and young men ages 9 to 26 Gardsasil helps protect against 90% of genital warts cases.

**Plantar warts** occur on the sole of the foot, is flat, extends deep into the thick skin, and, on superficial trimming reveals small pinpoint-sized bleeding points. Varying degrees of disability can be produced from the pressure type of pain. Single or multiple lesions may be present. The name mosaic wart is applied when the warts have coalesced into larger patches. Plantar warts are to differentiated from a callus (no bleeding points visible on superficial trimming) and frm scar tissue form a previous treatment (no bleeding points seen). Never treat a plantar lesion as a

wart until proven by trimming. A number of remedies are effective. The **trichloroacetic acid-tape technique** is useful for children and cases with multiple or large plantar warts. The procedure follows, pare down the wart with a sharp knife, apply trichloroacetic acid solution (saturated) to the wart, then cover the area with plain tape. Leave the tape on for 5 days without getting it wet. Remove the tape and curette out the dead wart tissue. Usually, more wart will remain and the procedure is repeated until the wart is destroyed. Treatment may take several weeks. **Fluorinated corticosteroid-occlusive dressing therapy** is applied to the wart(s) at night and covered with Sran Wrap, Handi-Wrap, or Blenderm Tape. Leave on for 12 to 24 to 48 hours and reapply. This form of treatment is painless. **Cantharidin tincture** is applied by the doctor to the pared wart. Cover with adhesive tape and leave on for 12 to 24 hours. This treatment can cause pain and infection, but is quite effective. The resulting blister can be trimmed off in 1 week and the medicine reapplied, if necessary. Liquid nitrogen is applied, a blister will form in 24 hours and deep peeling of the wart will ensue. This can be quite painful but effective. X-ray therapy is a painless form of therapy that can be used for single small warts. The dose should never be repeated to that side. The cure rate is fairly high (Sauer '85: 184, 186).

**Molluscum contagiosum** is an uncommon viral infection of the skin characterized by the occurrence, usually in children or sexually active young adults, of one or multiple small skin tumors. These growths occasionally develop in the scratched areas of patients with atopic eczema. The causative agent is a large DNA-containing poxvirus. An umbilicated, firm, waxy, skin-colored raised papule, varying in diameter from 2 mm to 5 mm and, rarely, larger. The skin may be inflamed by secondary bacterial infection. The papules most commonly appear on the trunk, face, arms, and genital area but can occur anywhere. The onset of lesions is insidious, owing to lack of symptoms, trauma or infection of a lesion causes it to disappear. Recurrences are rare, if lesions are removed adequately. It is contagious by contact or autoinoculation. The differential is with warts, keratoacanthoma, most commonly in older adults, larger lesion and basal cell epithelioma. Treat by curettage, treat with trichloroacetic acid. A drop of Verrusol may be applied on each lesion. A blister will form. Electrosurgery is an effective option.

**Lymphogranuloma venereum** is an uncommon venereal disease characterized by a primary lesion on the genitals and secondary changes involving the draining lymph channels and glands. The primary erosion or blister is rarely seen, especially in the female. Within 10 to 30 days after exposure, the inguinal nodes, particularly in the male, enlarge unilaterally. This inguinal mass may rupture if treatment is delayed. In the female the lymph drainage most commonly is toward the pelvic and the perirectal nodes, and their enlargement may be overlooked.

Lymphogranuloma venereum is caused by the obligate intracellular parasite *Chlamydia trachomatis*, serotypes L<sub>1</sub>, L<sub>2</sub> and L<sub>3</sub>. A complement fixation test (LGV-CFT) becomes positive 3 to 4 weeks after the onset of the disease in 80% to 90% of the patients. Tetracycline, 500 mg and minocycline 100 mg and doxycycline 100 mg are drugs of choice. These are most effective in the early stages and should be continued for at least 3 weeks. Fluctuant inguinal nodes should be aspirated to prevent rupture (Sauer '85: 185, 186).

**Measles** is a common childhood disease. The incubation period averages 14 days before the appearance of the rash. The prodromal stage appears around the 9th day after exposure and consists of fever, conjunctivitis, runny nose, Koplik spots and even a faint red rash. The Koplik spots measure from 1 to 3 mm in diameter, are bluish white on a red base, and occur bilaterally on the mucous membrane around the parotid duct and on the lower lip. With increasing fever and cough the "morbilliform" rash appears, first behind the ears and on the forehead, then spreads over the face, neck, trunk and extremities. The fever begins to fall as the rash comes out.

The rash is a faint, reddish patchy eruption, occasionally popular. Scaling occurs in the end stage. Complications include secondary bacterial infection and encephalitis. The differential diagnosis is with German measles, scarlet fever, drug eruption, and infectious mononucleosis. Prophylactic treatment is the measles virus vaccine, attenuated. Supportive therapy for the cough, bed rest, and protection from bright light are measures for the active disease. Antibiotics have eliminated most of the bacterial complications. Corticosteroids are of value for the rare but serious complication of encephalitis.

**German measles** (rubella) is a benign disease of children, it is serious if it develops in a pregnant woman during the first trimester, since it causes anomalies in a low percentage of newborns. The incubation period is around 18 days, and, as in measles, there may be a short prodromal stage of fever and malaise. The rash also resembles measles but the redness is less intense and the rash disappears within 2 to 3 days. Serious complications are rare. The rubella virus vaccine, live, attenuated can be administered prophylactically. Active treatment is usually unnecessary.  $\gamma$ -globulin given to an exposed pregnant woman in the first trimester of pregnancy may prevent the disease. Congenital rubella syndrome in infants born to mothers who had rubella in the first trimester of pregnancy can cause multiple system abnormalities. The skin lesions include thrombocytopenic purpura, hyperpigmentation of the navel, forehead and cheeks, acne, seborrhea, and reticulated erythema of the face and extremities (Sauer '85: 186, 187). The live rubella virus used in the vaccine is known to have caused significant deforming injuries and is under investigation for attenuation to reduce risk.

**Erythema infectiosum**, also known as "fifth disease" is an exanthema that occurs in epidemics and is thought to be caused by a virus. It primarily affects children, but in a large epidemic many cases are seen in adults. In the Kansas City epidemic of the spring of 1957, over 1,000 cases occurred. The incubation period varies from 1 to 7 weeks. In children the prodromal stage lasts from 2 to 4 days and is manifested by low-grade fever and occasionally by joint pains. When the red macular rash develops, it begins on the arms and the face and then spreads to the body. The differential diagnosis is with drug eruption and measles. No treatment is necessary.

**Coxsackievirus infection** are identified by type specific antigens that appear in the blood 7 days or so after the onset of the disease. **Roseola** is a common exanthema of children of 6 to 18 months of age. The incubation period is 10 days, but a contact history is rarely helpful. Characteristically, there is a high fever up to 105°F for 4 to 5 days. With the appearance of the rash the fever and the malaise subside. The rash is mainly on the trunk as a faint, red, macular eruption. It fades in a few days. There are no severe complications. Roseola is thought to be caused by coxsackievirus B<sub>5</sub>. It must be differentiated from measles, scarlet fever, infectious mononucleosis and drug eruptions. No treatment is necessary except to reduce the high fever with Aspirin.

**Herpangia** is an acute febrile disease occurring mainly in children in the summer months. The first complaints are fever, headache, sore throat, nausea, and stiff neck. Blisters are seen in the throat that are approximately 2 mm in size and surrounded by an intense erythema. These lesions may coalesce, and some may ulcerate. The course is usually 7 to 10 days. The cause of herpangina is primarily coxsackievirus A, but echovirus types have also been isolated from sporadic cases. It must be differentiated from aphthous stomatitis, drug eruption, primary herpes gingivostomatitis, and hand-foot-and-mouth disease. Treatment involves soothing mouthwashes and antipyretics. **ECHO** (enteric cytopathic human orphan), the label given to the virus before it was known to be causative of any disease. Echovirus exanthema complaints include fever, nausea, vomiting, diarrhea, sore throat, cough and stiff neck. A measles-like eruption occurs in

one third of cases. Small erosions may develop on the mucous membranes of the cheek. Echoviruses 9 and 4 have been isolated from most cases with skin lesions. Treatment is symptomatic. The infection usually lasts 1 to 2 week (Sauer '85: 188, 189). If the infection is life threatening or lasts longer Human Immune Globulin IV is known to be effective.

## 5. Tinea and fungal infection

**Fungi** can be present as part of the normal flora of the skin or as abnormal inhabitants. Pathogenic fungi have a predilection for certain body areas: most commonly it is the skin, but the lungs, the brain and other organs can be infected. Pathogenic fungi can invade the skin superficially and deeply. The superficial fungi live on the dead horny layer of the skin and elaborate an enzyme that enables them to digest keratin, causing the superficial skin to scale and disintegrate, the nails to crumble, and the hairs to break off. Under the microscope in wet preparation two structural elements will be seen: the spores and the hyphae. Spores are the reproducing bodies of the fungi. Sexual and asexual forms occur. Spores are rarely seen in skin scrapings. Hyphae are threadlike, branching filaments that grow out from the fungus spore. The hyphae are the identifying filaments seen in skin scraping in potassium hydroxide (KOH) solution. Mycelia are matted clumps of hyphae that grow on culture plates. The latest classification divides the superficial fungi into three genera: *Microsporum*, *Epidermophyton* and *Trichophyton*. Only two of these species invade the hair: *Microsporum* and *Trichophyton*. *Microsporu* causes an extothrix infection of the hair shaft, whereas *Trichophyton* causes either an ectothrix or an endothrix infection. The extothrix fungi cause the formation of anexternal spore sheath around the hair, whereas the endothrix fungi do not. The filaments of mycelia penetrate the hair in both types of infection. The clinical types of superficial fungal infections are Tinea of the feet (*Tinea pedis*), Tinea of the hands (*Tinea manus*), Tinea of the nails (*Onychomycosis*), Tinea of the groin (*Tinea cruris*), Tinea of the smooth skin (*tinea corporis*), Tinea of the scalp (*Tinea capitis*), Tinea of the bears (*Tinea barbae*) and Tinea of the ear (External Otitis) (Sauer '85: 191, 192).



The most common problem associated with sporting activity are fungal infections, and the most common of these is **athlete's foot**, which develops between the toe webs and may also involve the nails. Small particles of skin may be rubbed form the soles of the feet onto the floor of changing rooms, swimming pools, etc. and may be picked by the next person who walks over the area. If the skin infection is recognized and treated promptly, it can usually be clearly relatively easily. If, however the infection on the skin is not recognized or is ignored ,the same fungal infection may spread to involve the nails. When this happens the nail becomes rough, crumbles and develops irregular white patches. The nail may become very thick and difficult to cut. This can lead to pain and difficulty finding comfortable shoes. Once the nails are involved with fungal infection, curing the problem is very much more difficult. It takes from 1 to 2 years for a toe-nail to grow right out, and treatment for fungal infection of the toe-nail needs to be continued for this entire period of time. Even then it is very easy to re-infect to-nails from shoes, and many people who developed fungal infection of toe-nails when they were teenagers still have the problem 20, 30 and even 40 years later. For many years the most effective oral treatment available was friseolfulvin. This was very effective in the treatment of infections of the skin, although less effective for treatment of the nails. As the present time there

are some exciting new developments in the treatment of fungal infection of the skin, and newer drugs which are very effective in the treatment of fungal infection of the nail, are now becoming available. One of these is terbinafine (Lamisil) (Mackie '92: 51-53).

**Tinea of the feet** (athlete's foot or ringworm of the feet) is a very common skin infection. Blisters occur on the soles and sides of the feet or between the toes. In the chronic form the lesions are dry and scaly. Secondary bacterial infection is common, maceration and fissures are also seen. If the toenails become infected, a cure is highly improbable. The species of fungus influences the response to therapy. Most vesicular, acute fungal infections are due to *Trichophyton mentagrophytes* and respond readily to treatment with clotrimazole athlete's foot crème. The chronic scaly type of infection is usually due to *T. rubrum* and is exceedingly difficult, if not impossible, to cure. Males are more susceptible than females. A differential diagnosis is needed with contact dermatitis, atopic eczema, psoriasis, pustular bacteria, hyperhidrosis of feet, symmetric lividity of the soles and pitted keratolysis (keratolysis plantare sulcatum). Treatment involves hygiene, debridement, the skipping off the tips of the blister enabling pus to drain out and medication to reach the organisms. The edges of any blister should be kept trimmed, since fungi spread under these edges. Follow debridement with foot soak in Burow's solution. Neosporin or other antibiotic ointment and sulfur (antifungal) ppt. 5% may be applied locally to feet after soaking. Subsequent treatment should include an antifungal crème such as clotrimazole, Lotrimin, Monistat-Derm, Loprox, Spectazole, Tinactin, Halotex, Desenex, and so on. A combination of an antifungal cream and a corticosteroid, as in Lotrisone cream (Schering) is very beneficial. Antifungal solutions, such as Lotrimin or Mycelex solutions, are quite effective. Apply a few drops on affected skin and rub in. Griseofulvin and ketoconazole therapy are not recommended for acute tinea of the feet because (1) response to oral agents is slow, (2) recurrence rate is high and (3) the cost of oral therapy is much greater (Sauer '85: 193-197). Sporanox (itraconazole) and Lamisil (affordable oral) are indicated in severe infections.

A primary **fungal infection of the hand** is quite rare and must be differentiated from contact dermatitis, atopic eczema, pustular bacteria, or psoriasis. Blister on the palms and the fingers are seen at the edge of red areas in acute cases. In chronic cases lesions are dry and scaly, and usually there is a single patch, not separate patches. This gradually progressive disease spreads to the fingernails and is usually non-symptomatic. Unless the cost is prohibitive Griseofulvin therapy should be used for very case. Griseofulvin, ultrafine, (330 mg or equivalent) for three months is usually curative. Rarely does the dose have to be higher or for a longer term. Ketoconazole therapy, monitoring for the possibility of liver and other toxicity, 200 mg tablet once a day for 3 months might be curative.

**Tinea of the nails**, particularly the toenails are very common. Once infected the nail serves as a resistant focus for future skin infection. Detachment of the nail occurs with subsequent thickening and deformity. Bacterial infection can result from the pressure of shoes on the deformed nail and surrounding skin. The infection usually begins in the fifth toenail and may remain there or spread to involve the other nails. Tinea of the toenails can rarely be cured. Aside from the deformity and an occasional mild flare-up of acute tinea, treatment is not necessary. Progression is slow and spontaneous cures are rare. Tinea of the fingernails can be cured, but the treatment usually takes months. This type of tinea of the nails is usually due to *T. rubrum* and less importantly *T. mentagrophytes*. Differential diagnosis with nail injury, psoriasis of fingernails or toenails, candidiasis of fingernails, or green nails, an infection yielding *Candida albicans* or *Pseudomonas aeruginosa* most commonly. Griseofulvin ultrafine (330 mg or equivalent) therapy is the oral treatment of choice, it is used for approximately 9 months.

Therapy is stopped when there is no clinical evidence of infection and no cultural evidence of fungi. Ketoconazole therapy 200 mg once a day for 9 months might be curative. For the tinea of the toenails 12 months of therapy. Antifungal solution, 15 ml or athlete's foot crème (clotrimazole) applied locally for several months might help some milder cases. Debriding of thick nails offers relief from discomfort (Sauer '85: 198, 199).

**Tinea of the groin** is a common, itching, annoying fungal infection of the groin, appearing usually in males and often concurrently with tinea of the feet. Bilateral, fan-shaped, red scaly patches with a sharp, slightly raised border occur. Small vesicles may be seen in the active border. Oozing, crusting, edema and secondary bacterial infection are evident. The infection extends to involve the scrotum, penis, thighs, perianal area and buttocks. Tinea of the groin is commonly due to the fungi of tinea of the feet, *T. rubru*, and *T mentagrophyties* and also the fungus *Epidermophyton floccosum*. It is minimally contagious even between husband and wife. Differential diagnosis is needed with Candidiasis, contact dermatitis, prickly heat, neurodermatitis, psoriasis, and Erythrasma due a diphtheroid organisms called *Corynebacterium minutissimum*. Treatment is to advise drying the feet after the groin, Griseofulvin oral therapy 330 mg 1 tablet a day for 6 to 8 weeks. Vinegar 1 part to 2 parts water can be applied to the area for 15 minutes twice a day. Sulfur ppt. 5% and nonalcoholic white shake lotion can be applied locally. Subsequently, antifungal solution 15 ml or a mix of Sulfur ppt. 5%, Hydrocortisone powder 1% an antifungal crème 15.0 may be applied locally. A small amount of the following solution may be applied in the office with a cotton swab Chrysarobin 3% and Chloroform 15.0, it is quite effective for resistant dry scaly patches but stings after application. Caution patient to avoid touching the area with their fingers and then rubbing their eyes (Sauer '85: 199, 200). 1% Clotrimazole (athlete's foot crème) or hydrocortisone crème may be effective.

**Tinea of the smooth skin**, the familiar ringworm of the skin most commonly seen in children because of their intimacy with animals and other children. Round, oval or semicircular scaly patches have a slightly raised border that commonly is vesicular. Rarely, deep, ulcerative, granulomatous lesions are due to superficial fungi. Bacterial infection is common in association with certain fungi, such as *M. canis* and *T. mentagrophytes*. Infection is short lived, if treated correctly and seldom recurs. This disorder is most commonly due to *M. cani* from kitten and puppies, to *M. audouini* frm other children, who usually also have scalp infection and less commonly due to *E. floccosum* and *T. mentagrophytes*, from groin and foot infections. It is very contagious. There is a differential diagnosis with pityriasis rosea, impetigo, and contact dermatitis. Treatment is with antifungal solution 15 ml or a cream sulfur ppt. 5%, antifungal salve 15.0 applies locally. Antifungal bases that can be used are Clotrimazole, Lotrimin, Monstat-Derm, Loprox, Spectazole, Halotex, Tinactin, and so on. On subsequent visits Griseofulvin (ultrafine can be given in tablet or oral suspension form. The usual dose for children is 165 mg but the product information sheet should be consulted. Therapy should be maintained for 3 to 6 weeks or until lesions are gone (Sauer '85: 201-202).

**Tinea of the scalp** is the most common cause of patchy hair loss in children. Griseofulvin orally finds it greatest therapeutic usefulness in the management of tinea of the scalp. Ketoconazole is available for griseofulvin resistant cases. Tinea capitis infections can be divided into two clinical types noninflammatory and inflammatory. The **noninflammatory type** has grayish, scaly, round patches with broke-off hairs causing balding areas. The incubation period is short by clinical evidence of the infection cannot be expected under 3 weeks after inoculation. Spontaneous cures are rare in 2 to 6 months but after that time occur with greater frequency. Some cases last for years, if untreated. Infection of the scalp is most common between the ages of 3 and 8 and is

rare after the age of puberty. The adult resistance to infection is attributed in part to the higher content of fungistatic fatty acids in the sebum after puberty. This finding led to the development of Desenex, Timofax, Salundek and other fatty acid ointments and powders. The noninflammatory type of scalp ringworm is caused most commonly by *M. audouini*, occasionally by *M. canis* and rarely by *T. tonsurans*. *M. audouini* and *T. tonsurans* are anthropophilic fungi (human-to-human passage only), whereas *M. canis* is a zoophilic fungus (animals are the original source, mainly kittens and puppies). Hair infected with *M. audouini* and *M. canis* fluoresce with a bright yellowish green color in Wood's light. Over 90% of the tinea capitis in the United States and Canada is due to these fungi. Infected individuals may go to school provided that the child wears a cotton stockinette cap at all times and a note must be presented from the physician every 3 weeks. Griseofulvin oral therapy ultrafine (Fulvicin U/F, Grifulvin V, and Frisactin) can be administered in tablet form or liquid suspension. The usual dose for a child aged 4 to 8 is 250 mg. The duration of therapy is usually 6 to 8 weeks. Near the end of therapy the remaining infected and fluorescent hairs can be plucked out, or the involved area can be shaved closely. Duration of the **inflammatory type** of tinea of the scalp is much shorter than the non-inflammatory type of infection. Spontaneous cures will result after 2 to 4 months in majority of cases, even if untreated. The inflammatory type of scalp ringworm is most commonly caused by *M. canis*, occasionally by *M. audouini*, and rarely by *M. gypseum*, *T. mentagrophytes* and *T. verrucosum*. Except for *M. audouini* the species are zoophilic, that is, passed from infected animals or soil. The incidence is high in children and farmers. It is endemic, except for cases due to *M. audouini*. Griseofulvin oral therapy may be used as in the noninflammatory type. Local therapy can be used where drug cost is an issue, with good results, Sulfur ppt. 5% Vioform ointment q.s. 15.0 shampooed nightly. If kerion is severe, with or without griseofulvin therapy: Burow's pack we solutions in warm water, antibiotic therapy orally helps to eliminate secondary bacterial infection (Sauer '85: 202).



**Tinea versicolor** is a moderately common skin eruption with characteristics of tannish colored, irregularly shaped scaly patches causing no discomfort that are usually located on the upper chest and back. It is caused by a lipophilic yeast. The skin does not tan when exposed to sunlight, and it is this cosmetic defect that often brings patients to the doctor's office. The causative agent is a lipophilic yeast, *Pityrosporum orbiculare*, which has a hyphae form called *Pityrosporum* or *Malassezia furfur*. A scraping of the scale is placed on a microscopic slide, covered with a 20% solution of potassium hydroxide and a coverslip will show the hyphae. Under the low-power lens

of the microscope, very thin mycelia filaments are seen. Diagnostic grape-like clusters of spores are seen best with the high-power lens. This dimorphic organism does not grow on routine culture media. It is treated with Selenium Suspension 2 ½% 120.0 applied after bathing and drying. Bathe again in 24 hours and wash off the medicine. Repeat procedure again at weekly intervals for four treatments. Recurrences can be re-treated. Depigmented spots may remain after the tinea is cured, but if desired, can be tanned by gradual exposure to sunlight or ultraviolet light (Sauer '85: 135).

**Tinea of the beard** is a rare cause of dermatitis in the beard area. Farmers occasionally contract it from infected cattle. Differential diagnosis with bacterial folliculitis. The primary lesions are follicular pustular or sharp-bordered, ringworm-type lesions or deep-boggy, inflammatory

masses are seen. Treatment begins with Burow's solution wet packs in 2 pint of hot water, apply wet cloth to area for 15 minutes. Apply sulfur ppt. 5% and antifungal ointment locally. Griseofulving oral therapy ultrafine 330 mg for 6 to 8 weeks or longer, depending on clinical response or negative Sabouraud's culture. **Dermatophytid**, is an allergic reaction to a fungal infection. During an acute episode of any fungal infection an id eruption can develop over the body. The most common id reaction occurs on the hands during an acute tinea infection on the feet. To assume a diagnosis of an id reaction, the following criteria should be followed: (1) the primary focus should be acutely infected with fungi, not chronically infected, (2) the id lesions must not contain fungi, and, (3) the id eruptions should disappear or wane following adequate treatment of the acute focus. Vesicular eruption of the hands (primary lesion on the feet) and papulofollicular eruption on body (primary lesion commonly is scalp kerion) are found; pityriasis rosea – like id eruptions and others are seen less commonly. Excoriation and infection occur, when itching is severe, which is unusual. Treat the primary focus of infection. Burow's solutions soaks in quart of cool water. For an id reaction on the body that is moderately pruritic, Linit starch or Aveeno oatmeal bath once daily. Alcoholic white shake lotion with menthol 0.25%, phenol 0.5% or camphor 2% could be added. For a severely itching, generalized id eruption, prednisone 10 mg or related corticosteroid tablets (Sauer '85: 205-206). Hydrocortisone crème should be effective.

**Deep fungal infections** are those fungi that invade the skin deeply and go into organic and skeletal tissue. Only the skin manifestations of Candidiasis, Sporotrichosis and North American blastomycosis, are discussed here. **Candidiasis** is a fungal infection caused by *Candida albicans* that produces lesions in the mouth, vagina, skin, nails, lungs or the gastrointestinal tract or occasionally a septicemia, in patients on long-term, high dose antibiotic therapy and in those who are immunosuppressed. Since *C. albicans* exists commonly as a harmless skin inhabitant, the laboratory findings of this organism is not adequate proof of its pathogenicity and etiologic role. Candida commonly seed preexisting disease conditions. Cutaneous candidiasis, or **candida paronychia**, is a common candida infection characterized by development of painful, red swellings of the skin around the nail plate. In chronic infections the nail becomes secondarily thickened and harded. Candidal paronychia is commonly seen in housewives and those individuals whose occupations predispose to frequent immersion of the hands in water. This nail involvement is to be differentiated from superficial tinea of the nails (the candida infection does not cause the nail to lose its lust or to become crumbly, and debris does not accumulate beneath the nail) and from bacterial paronychia (this is more acute in onset and throbs with pain). Apply antifungal imidazole type solution (Lotrimin or Mycelex Solution 1%) to base of nail for several weeks. At night apply sulfur ppt. 5% in Benzoic and salicylic acid ointment (USP) locally (or Mycostatin cream can be used as the base).

**Candidal intertrigo** is a moderately common characterized by well-defined, red, eroded patches, with scaly, pustular or pustulovesicular diffuse borders. The most common sites are axillae, umbilicus, genital area, anal area and webs of toes and fingers. Obesity and diabetes predispose to the development of this intertriginous type. It is to be differentiated from superficial tinea infections, which are not as red and eroded, and seborrheic dermatitis. Apply Sulfur, ppt. 5%, Hydrocortisone 1% and Mycostatin cream locally. Mycostatin dusting powder can be used over cream. **Generalized cutaneous candidiasis** is a rare infection involving the smooth skin, mucocutaneous orifices, and intertriginous area. It follows in the wake of general debility, as seen in immunosuppressed patients, and was very resistant to treatment prior to the discovery of ketoconazole.



**Mucous membrane candidiasis**, oral candidiasis is either Thrush and Perlèche. Thrush is characterized by creamy white flakes on a red, inflamed mucous membrane. The tongue may be smooth and atrophic, or the papillae may be hypertrophic, as in "hairy tongue". Perlèche is seen as cracks or fissures at the corners of the mouth, usually associated with candida disease elsewhere, and dietary deficiency. It is usually effectively treated with over-the-counter anticandidal medicine but

ketoconazole and other antifungal drugs are often prescribed by physicians and Amphotericin B intravenously in severe systemic infections. **Candidal vulvovaginitis** is an oozing, red, sharply bordered skin infection surrounding an inflamed vagina that contains a buttermilk-like discharge. This type of candida infection is frequently seen in pregnant women and diabetics. It is to be differentiated from an allergic condition or from trichomonal vaginitis. It is treated with Mycostatin vaginal tablets 100,000 units inserted into the vagina. Or Monostat-Derm lotion or Sulfur, ppt. 5%, Hydrocortisone 1% and Mycostatin cream 30.0. For chronic mucocutaneous candidiasis, ketoconazole can heal dramatically (Sauer '85: 209, 210).

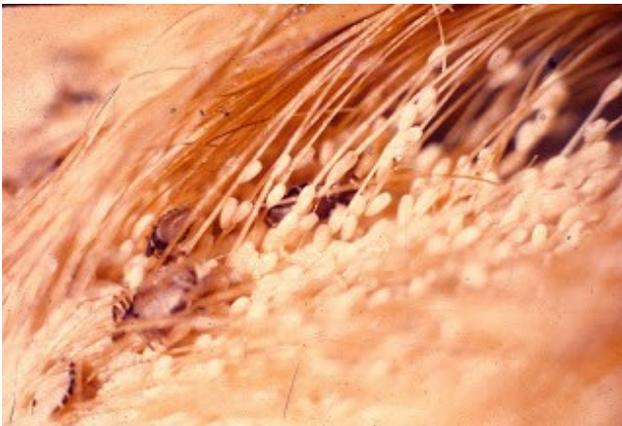
**Sporotrichosis** is a granulomatous fungal infection of the skin and the subcutaneous tissues. Characteristically, a primary chancre develops at the site of the skin inoculation, which is commonly the hand and less commonly the face or the feet. The chancre begins as a painless, movable subcutaneous nodule that eventually softens and breaks down to form an ulcer. Within a few weeks subcutaneous nodules arise along the course of the draining lymphatics and form a chain of tumors that develop into ulcers. The development of the skin lesions is slow and rarely affects the general health. The causative agent is *Sporothrix schenckii*, a fungus that grows on wood and in the soil. It invades open wounds and is an occupational hazard of farmers, laborers and miners. Differentiate with any of the skin granulomas, such as pyodermas, syphilis, tuberculosis, sarcoidosis and leprosy. An ioderma or bromoderma can cause a similar clinical picture. Treat with saturates solution of potassium iodide 60.0 ml. On the first day, 10 drops added to milk or water. Second day, 15 drops, third day, 20 drops, and increased until 30 to 40 drops are given. Watch for gastric irritation and ioderma. Continue this very specific treatment for 1 month after apparent cure. Ketoconazole therapy (Nizoral) 200 mg 2 tablets a day for 8 weeks.

North American **Blastomycosis** presents as two cutaneous forms (1) primary cutaneous blastomycosis and (2) secondary localized cutaneous blastomycosis. Primary cutaneous blastomycosis occurs in laboratory workers and physicians following accidental inoculation. A primary chancre develops at the site of the inoculation, and the regional nodes enlarge. In a short time the primary lesion and nodes heal spontaneously, and the cure is complete. The lesions begin as a papule that ulcerates and slowly spreads peripherally, with a warty, pustular, raised border. The face, hands and feet are involved most commonly. Central healing of the ulcer occurs gradually with resultant thick scar. A large lesion develops over several months. The fungus *Blastomyces dermatitidis* is thought to invade the lungs primarily and the skin secondarily as a metastatic lesion. High native immunity prevents the development of more than one skin lesion. This immunity is low in the rare systemic form of blastomycosis in which multiple lesions occur in the skin, the bones and other organs. This fungal disease affects adult males most frequently. It must be differentiated from any of the granuloma-producing diseases,

such as tuberculosis, syphilis, iodide or bromide drug eruption, pyoderma, and neoplasm. It is treated with surgical excision and plastic repair of early lesion. Amphotericin B suppresses the chronic lesion more effectively than any other drug. It is administered by intravenous infusion, daily, in varying schedules. Ketoconazole therapy on a long-term basis is also beneficial. Since the discovery of specific systemic antifungal agents, griseofulvin and ketoconazole correct diagnosis of a fungal infection is necessary. Griseofulvin or ketoconazole are of no value in treating atopic dermatitis, contact dermatitis, psoriasis, pityriasis rosea, and so on. Oral griseofulvin or ketoconazole therapy should not be used to treat tinea of the feet or toenails, the recurrence rate after therapy is very high, Lamasil, is preferred for serious foot fungus. Tinea versicolor does not respond to oral griseofulvin therapy (Sauer '85: 212, 191).

## 6. Lice, mites and parasitic infestations

**Dermatologic parasitology** is extensive and includes dermatoses due to three main groups of organisms: protozoa, helminthes and arthropods. The protozoal dermatoses are exemplified by the various forms of trypanosomiasis and leishmaniasis. Helminthic dermatoses include those due to roundworms (round itch, creeping eruption, filariasis, and other rare tropical diseases) and those due to flatworms (schistosomiasis, swimmer's itch, and others). Arthropod dermatoses are divided into those caused by two classes of organisms, the arachnids (spiders, scorpions, ticks and mites) and the insects (lice, bugs, flies, moths, beetles, bees and fleas).



There are between 6 and 12 million cases of **head lice** in the United States every year. Head lice are highly contagious and if one person in a family becomes infected, everyone in the household must be treated. Lice are the insects, nits are the eggs. Nits are harder to eliminate than lice. Dead nits are white, live nits are hair colored so they are harder to see. Nearly all lice treatments are available over-the-counter. A single application will usually kill all head lice, taking about 12 hours to clear the problem. A

second application is necessary 10 days later to kill any newly hatched nits. Alcohol-based solutions are the most effective, but water-based alternatives are available for small children and eczema and asthma sufferers. Many oils, including eucalyptus, geranium, parsley, Scotch pine, rosemary, lavender, thyme and tea tree, will kill lice. The safest to use on children are tea tree and lavender. In a small bottle mix 1 tsp pure tea tree or lavender essential oil, with 5 tbs warm water, 2 tbs pure alcohol or vodka and 1 tsp castor oil. Shake the bottle well, then make a series of ½ in. partings in the hair. Apply the lotion over the scalp covering approximately 2 in. up the hair shaft from the roots and leave for 12 hours or overnight. Shampoo using warm water, massaging well into the scalp. Comb through the hair with a nit comb to remove dead lice and egg cases. Let hair dry naturally, heat will evaporate the active ingredients. Repeat every three days for two weeks and check regularly for any reinfestation. Swimming pool chlorine, perms and hair dyeing can reduce the effectiveness of the treatment (Davenport et al '03: 58, 59).

**Pediculosis**, lice infestation, affects persons of all ages but usually those in the lower-income strata, because of lack of cleanliness and infrequent changes of clothing. It is also seen as a

sexually transmitted disease. Three clinical entities are produced (1) infestation of the hair by the head louse *Pediculus humanus capitis*, (2) infestation of the body by *P. humanus corporis* and (3) infestation of the pubic area by the pubic louse *Phthirus pubis*. Since lice bite the skin and live on the blood, it is impossible for them to live without human contact. The readily visible oval eggs or nits are attached to hairs or to clothing fibers by the female. After the eggs hatch, the newly born lice mature within 30 days. Then the female can live for another 30 days and deposit a few eggs daily. The bite is not unusual but is seldom seen because of the secondary changes produced by the resulting intense itching. In the scalp and pubic form, nits are found on the hairs, but the lice are found only occasionally. The lice can be found after careful searching in the seams of the clothing. In the scalp, the skin is red and excoriated, with such severe secondary bacterial infection, in some cases, that the hairs become matted together in a crusty, foul-smelling "cap". Regional lymphadenopathy is common. A morbilliform rash on the body, an id reaction, is seen in longstanding cases. In the body form linear excoriations and secondary infection, seen mainly on the shoulders, the belt-line, and the buttocks, mask the primary bites. In the pubic form the secondary excoriations are again dominant and produce some matting of the hairs. This louse can also infest body, axillary, and eyelash hairs. An unusual eruption on the abdomen, the thighs and the arms, called maculae cerulae, because of the bluish, pea-sized macules, can occur in chronic cases of public pediculosis. Pediculosis must be differentiated from bacterial infection seborrheic dermatitis or dandruff, hair casts resembling nits, scabies, senile or winter itch, or pyoderma. Treatment for pediculosis capitis and pubis is lindane shampoo (Kwell or Scabene) 60.0 shampoo and comb hair thoroughly, leave on the hair for 4 minutes. Shampoo again in 3 days. For secondary scalp infections trim hair as much as possible, shampoo once a day with an antiseborrhea-type shampoo. Neosporin or other antibiotic ointment. Change and clean bedding and headwear after 24 hours of treatment. Storage of headwear for 30 days will destroy the lice and the nits. Pediculosis corporis is treated with phenol (0.5%) in calamine lotion 120.0 applied locally for itching. Have the clothing laundered or dry cleaned. If this is impossible, dusting with 10 lindane powder will kill the parasites. Care should be taken to prevent re-infestation. Storage of clothing for 30 days will kill both nits and lice (Sauer '85: 219, 220).



**Scabies** is a parasitic infestation usually more prevalent in a populace ravaged by war, famine or disease, when personal hygiene become relatively unimportant. In normal times scabies is rarely seen except in schoolchildren or in poorer populations under crowded conditions. A burrow caused by the female of the mite *Sarcoptes scabiei* measures approximately 2 mm in length and can be hidden by the secondary eruption. Small vesicles may overlie the burrow. Excoriations of the burrows may be the only visible pathology. In severe, chronic cases bacterial infection may be extensive and may take the form of impetigo cellulitis and furunculosis. Itching is intense, particularly at night, when the patient is warm and in bed and the mite is more active. However, many skin diseases itch worse at night. The mite can persist for months and years (seven-year itch) in untreated, unclean individuals. The female scabies mite, ova and fecal pellets may seen in curetted burrows examined under the low-power magnification of the microscope. Potassium hydroxide (20% solution) can be used to clear the tissue, as with fungus smears. Another method of collection is to scrape the burrow through immersion oil and then transfer the scraping to the microscopic slide. Skill is necessary to uncover the mite by curetting or scraping. Differentiate from pyoderma, pediculosis pubic, winter itch, dermatitis herpetiformis, neurotic

excoriations, and parasitophobia. Apply lindane lotion (Kwell or Scabene) to the entire body from the neck down. Old clothes may be reworn. Do not bathe for 12 to 24 hours after application. After 24 hours bathe carefully and change to clean clothes and bedding. Itching may persist for a few days or even for 2 to 3 weeks in spite of the destruction of the mite. For itching apply sulfur (4%), camphor (1%) in Alcoholic white shake lotion or Eurax cream that has scabidical power and antipruritic action (Sauer '85: 217-219). Contaminated fabrics have been reported to be sterilized when cleaned with an Eucalyptus essential oil solution.

## 7. Psoriasis



**Psoriasis** is a common, chronically recurring papulosquamous disease, characterized by varying sized whitish, scaly patches seen most commonly on the elbows, knees and scalp. The scale is usually thick and silvery and bleeds from minute points when it is removed by the fingernail. Psoriasis is notoriously chronic and recurrent. However, cases have been known to clear up and not recur. Approximately 30% of patients with psoriasis have a family history of the disease. Only 30% of patients with psoriasis itch. Psoriasis is usually worse in winter. It is not

contagious. Psoriatic lesions may develop or flare up in area of skin injury. The differential diagnosis is with Tinea corporis, seborrheic dermatitis, pityriasis rosacea, secondary or tertiary syphilis, or lichen planus. Patients can be reassured that psoriasis is not contagious but there is no "cure". It might help if psoriasis were not to be considered as a disease but thought of as a hobby. Psoriasis is treated with Fluorinated Corticosteroid Cream or Ointment q.s. 30.0. For scalp lesions Pragmatar ointment 15.0 applied to scalp in water-washable base such as Unibase, Neobase, Dermovan, and so on). Selsun Suspension 120.0, or a tar shampoo, twice a week. Triamcinolone (Kenalog) Spray 63 g applied to scalp with plastic tube applicator at night. Methotrexate therapy is used in cases of severe psoriasis, for instance psoriasis covering >65% of the body surface, with good results (Sauer '85: 129-135). Mild psoriasis is often managed quite easily without medical supervision. A shampoo designed to remove scale from the scalp, for example Polytar or Capasal, and a simple ointment, for example, white soft paraffin, after a bath or shower, will remove the excessive scaling. Creams and ointments prescribed for psoriasis contain tar, dithranol and for limited parts of the body, topical steroids (cortisone-containing creams, ointments and lotions). The modern way to use dithranol preparations is to apply them to the skin for only 15-30 minutes each day, either in the morning or just before bedtime. Most people spend this time in an older dressing gown, on which any staining from the ointment does not matter. The dithranol is then washed off in the bath or shower and normal clothes can be worn without staining the clothes. A further recent development is an ointment containing an active ingredient very similar to vitamin A, which appears to be effective, clean, odor-free, and non-staining (calcipotriol or Dovonex) (Mackie '92: 66, 67).

Psoriasis is an ancient disease that was probably amongst the scaly eruptions described by Hippocrates (460-377 B.C) in his collection of medical dissertations known as the Hippocratic Corpus. At the beginning of the first century psoriasis was described by the Roman scholar Aurelius Celsus (25 B.C.-A.D. 45) in his *De re medica* who referred to it as "impetigo" from impeto meaning attack. He treated the disease with "red nitre and sulfur. Subsequently Galen (A.D. 133-200) was the first to use the term "psoriasis" (from psora meaning to itch), but was

probably referring to seborrhoeic eczema. In the Bible, psoriasis (and other skin disorders) was considered to be the same as leprosy. The Syrian Naaman the leper was cured of his skin lesions by bathing in the river Jordan, most probably had psoriasis. In the Middle Ages, this confusion between psoriasis and leprosy became more established. True leprosy, known to the Greeks in the 2<sup>nd</sup> century as "elephantiasis graecorum", became confused with "lepra graecorum" when Arabic texts were translated into Latin. The term "lepra" was derived from the Greek *lepos* (epidermis) and *lepo* and included dry scaling conditions such as psoriasis, pityriasis and ichthyosis. Thus there were probably thousands of people suffering from psoriasis who, during the 13<sup>th</sup> and 14<sup>th</sup> centuries in Europe, were forced to carry a bell or clapper to warn the healthy population, wore special clothing, and were banned from touching, talking above a whisper, or eating with anyone other than a leper. In 1313 it is rumored that Philip the Fair of France ordered individuals with psoriasis to be burnt at the stake. During the Byzantine period, a change in the attitude towards the sick with disfiguring diseases such as leprosy led to them being fed and cared for in monasteries. The inability to distinguish psoriasis from leprosy was to continue for a further five hundred years (Baker '08: 1, 2).

It had been recognized as early as the 19<sup>th</sup> century that psoriasis was an inherited disease, with the first analysis of the genetic basis carried out in 1931. However it was not until the establishment of the Human Genome Project during the first half of the 1990s that it became feasible to begin a systematic search for the genes determining psoriasis. In 1996, a gene map of the human genome containing 16,000 of the 50,000-100,000 genes then estimated to be present was published. Stronger HLA associations had been found in patients with an age of onset younger than 40 years, and who showed a higher frequency of affected first-degree relatives, than patients with a later onset whose HLA associations were much weaker. The strongest association observed in psoriasis was that of HLA-Cw6, an allele rarely increased in frequency in patients with other inflammatory diseases. However, only a proportion (approximately 10%) of HLA predisposed individuals go on to develop psoriasis, suggesting that inheritance of a particular HLA allele is not sufficient by itself for initiation of the disease. Several additional psoriasis genes, triggered by environmental factors, are involved. The first genome wide linkage study of psoriasis families was published in 1994 and reported a susceptibility locus on chromosome 17q25. None of the families with linkage to chromosome 17q however, showed any association with Cw6, providing the first evidence for the existence of genetic heterogeneity. Two to three years later, susceptibility loci for familial psoriasis were reported on chromosomes 4q21 and 6p. The susceptibility locus on chromosome 6 was located in the MHC region p21.3, close to the HLA-C, as predicted from the HLA association studies. This locus, named PSOR1 (psoriasis susceptibility 1), was subsequently confirmed by several research groups and found to confer significant risk (35-50%) for development of psoriasis. However, since all psoriatic patients carry Cw6, it seems more likely that the PSORS1 gene was a gene close to HLA-Cw6 rather than Cw6 itself; subsequent studies using more precise mapping methods were consistent with this assumption. The identification of 11 further linkage sites on 10 different chromosomes followed and were numbered PSORS-2-PSORS7.

It has been established over the last two decades that psoriasis is a T cell mediated disease. CD4<sup>+</sup> T cells are essential for initiating and maintaining the psoriatic process, and, when removed by treatment, the disease is temporarily switched off. Both dermal CD4<sup>+</sup> T cells and epidermal CD8<sup>+</sup> T cells each consist of small numbers of dominant clones that have expanded in situ, suggesting that unidentified antigens drive the disease process, namely *Streptococcus* and *Staphylococcus*. It is likely that other components derived from yeasts (*Malassezia* and *Candida albicans*) or viruses (HIV, retroviruses, papillomaviruses) which are associated with the

triggering and/or exacerbation of psoriasis. Peptiglycan is a strong activator of innate immunity, the immediate, non-specific response to pathogens which precedes the T cell response. Innate immunity in psoriasis has become a current focus of research as evidence is emerging that the response to pathogens dysregulated, with a marked increase in the production of anti-bacterial peptides. Overall, the findings suggest that psoriasis may be an autoimmune T cell disease, triggered by infection (Baker '08:" 92-94, 110, 111).

The use of **balneotherapy** (immersion of patients in mineral water baths or pools) and spa therapy as accompaniments to psoriasis treatment first emerged during the 19<sup>th</sup> century. Since that time, three unique locations for balneotherapy have become established the Blue Lagoon in Iceland, the Kangal hot spring in Turkey, and most importantly, the Dead Sea in Israel. The healing properties of the Dead Sea (Sea of Salt in Hebrew) were recognized as early as the second century by Galen who described "the potency of this medicine (asphalt produced in the Dead Sea) consists in its drying and next its healing capabilities; it is indeed appropriate that people use it for closing bleeding wounds". Dostrovsky and coworkers published the first preliminary report of the beneficial effects of exposure of the Dead Sea on psoriasis in 1959, followed by numerous reports during the 1970s which confirmed the ameliorative properties of the Dead Sea environment in large numbers of patients. More than 80% of the psoriasis patients treated with daily exposure to solar UV light and regular bathing in the Dead Sea had either complete or nearly complete clearance of their skin lesions. Furthermore, patients with psoriatic arthritis also showed significant improvement in their symptoms. These beneficial effects were attributed to several factors. Firstly, the Dead Sea is the lowest and most saline lake on earth, being 400 m below sea level with an approximately 30% salt content. The salts (magnesium, calcium, potassium and bromine) present in the lake water which are used in the production various health products, contribute to the resolution of skin lesions. Mud packs and sulphur baths may also be included in the treatment regime. Secondly, UV light is attenuated by traversing an extra 400 m of atmosphere and a haze of water vapor and aerosols overhanging the lake. This changes the spectral balance, affecting UVB more than UV, allowing longer exposure times. Thus the well known beneficial effects of UV lights can be experience with a reduced risk of burning. Furthermore, psychological benefits are attributed to the social nature of the treatment regime. Fellow patients stay in the same hotels and share experiences, whilst the general success of the treatment generates a more optimistic outlook to living with the disease. The success of the treatment causes thousands of psoriasis patients continue to go to this unique location every year (Baker '08: 75-76). Epsom salt baths are advised.

Two new types of treatment for skin diseases became available after World War II; glucocorticosteroids and folate analogues. Despite its anti-inflammatory effects in RA, topical applications of cortisone for the treatment of skin diseases was not found to be beneficial, despite the fact that it penetrated the skin as well as clinically effective hydrocortisone and was converted to the latter in the skin. However, the availability of synthetic derivatives of corticosteroids hormones, at the beginning of the 1950s, revolutionized the treatment of skin diseases. These anti-inflammatory drugs were more potent than their natural counterparts and, administered topically in ointments and creams, avoided the side-effects experienced when the drugs were taken orally. In 1954-5 prednisolone and fluorocortisone were introduced. Prednisolone was 4 times as powerful as cortisone, whilst the replacement of the 9-hydrogen atom by halogen fluoride in fluorocortisone results in a 8-fold increase in its anti-inflammatory properties. Topical preparations of fluorocortisone, although clinically superior, were soon abandoned because of their effects on electrolyte balance.

The additional substitution of hydroxyl or methyl groups at position 16 on the steroid molecule was subsequently found to greatly reduce the unwanted side effects induced by the fluoride atom, leading to the development of a wide variety of fluorinated steroids, including triamcinolone, dexamethasone and betamethasone. Triamcinolone became available in 1958 and was administered systemically and topically in psoriasis with favorable results, over a period of 7-8 weeks, during which time the dose was reduced. Itching was relieved within 7 days, whilst clearance was observed within 3-7 weeks of commencing treatment in all but 2 of the patients. A third of the patients remained clear 10 weeks after the end of treatment, minor side effects affected only two patients in this study but serious side effects such as "buffalo hump", hairy red face, decalcification of bone and hypertension were reported with higher doses of steroids and led to the discontinuation of the use of systemic steroids in psoriasis over the next few years. Triamcinolone acetonide was also used locally to treat psoriasis, either by intralesional injection, or combined with other treatments such as tar, which was more effective than steroid alone. However, together with increased potency came the increased likelihood of local side effects such as striae and atrophy of the skin, steroid-induced acne, purpura and glaucoma. Furthermore, systemic side effects could also be a problem (especially in children) if sufficient amounts of a potent steroid were absorbed (Baker '08: 51, 52).

During the 1940s in New York, the Lederle Pharmaceutical company were testing various compounds known as anti-folates or folate analogues which inhibit the body's use of folic acid, a vitamin essential for cell growth. These compounds exert their effects by blocking the reduction of folic acid to tetrahydrofolic acid (citraovorum factor), preventing synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins. The first of these anti-folates (or anti-metabolites) that showed potential as a chemotherapy drug was aminopterin, which was first reported in 1948 to produce temporary remission of acute leukemia of children. Subsequently, it was used experimentally to treat RA, and long-standing, extensive psoriasis with or without arthritis, inducing improvement in both skin and joints within 2 weeks after the start of treatment. However, toxic effects such as ulceration of buccal mucosa, cramps and diarrhea (due to inhibition of epithelial cell proliferation in the oral cavity and gastrointestinal tract), commonly accompanied the improvement in skin lesions. This necessitated a rest period between courses of treatment to allow the symptoms to disappear, usually after a few days. Topical aminopterin was also tested but found to be replaced by its methyl derivative, amethopterin, or methotrexate as it is now known. Clinical trials showed that, aminopterin, methotrexate was effective in causing remission in childhood leukemia and also in the fast growing, pregnancy related cancer, choriocarcinoma, via its inhibition of the metabolism of rapidly dividing cells. Methotrexate was first used to treat psoriasis in the late 1950s, and became popular throughout the following decade. In one study, three-quarters of the patients receiving the folic acid antagonist showed 50-100% improvement in their skin lesions that was maintained for at least 6 months. However, toxicity was a major concern associated with the use of these drugs, whose side effects included modification of the liver function, bone marrow depression, gastrointestinal ulcerations and bleeding, alopecia and damage to embryonic tissue when given in high doses. In psoriasis (and RA), therapeutic effects without demonstrable toxic effects were achieved with much lower doses of methotrexate than those used in leukemia, in which, conversely, there was a direct relationship between therapeutic and toxic effects. Concomitant use of alcohol, as well as increased age and body weight were identified as being significant contributors to adverse hepatic outcomes including cirrhosis. Despite three decades of study into its clinical effects, it was not until 1988 that methotrexate was approved by the U.S. Food and Drug Administration for use in adults for the treatment of immunological diseases.

Although methotrexate is commonly prescribed by rheumatologists it is still not, even now, licensed for use in psoriatic arthritis (Baker '08: 53-55).

Three types of biological have been tested in psoriasis, monoclonal antibodies, fusion proteins and recombinant cytokines. The latter were produced by cloning human cytokine genes into a bacterial genome, allowing the proteins to be produced in large quantities, a technique first introduced in 1973. Monoclonal antibodies, up until this time, had been predominately mouse in origin, which had the disadvantage of inducing neutralizing antibodies when used therapeutically. Genetic engineering advances allowed new types of monoclonal antibodies to become available for therapeutic use. These were either chimeric (fused mouse and human sequences, designated "-ximab"), humanized (human backbone with intermittent mouse sequences, designated "-zumab"), monkey sequences (primatized) or fully human. Fusion proteins on the other hand, were usually human constructs, often between the constant (Fc) portion of an immunoglobulin molecule and the binding site of a receptor (designated "-cept"). These agents were targeted at T cells (or the antigen-presenting cells they interact with) with the aim of blocking T cell activation and proliferation, or were used to inhibit specific cytokines. The first genetically engineered antibodies used to treat psoriasis was efalizumab (Raptiva), an antibody raised against the LFA-1 (leukocyte-function-associated antigen-1) molecule expressed on the surface of T cells. Binding of efalizumab to LFA-1 blocks T cell interaction with other cell types, preventing T cell activation and migration through the skin. At the same time alefacept (Amevive), a fusion protein consisting of LFA-3 linked to human IgG, was developed and tested in psoriasis patients. The structure of the fusion protein was designed so that it bound specifically to the target molecule, CD2, expressed by T cells, and was soluble in plasma. The binding of alefacept via its LFA-3 domain to CD2 prevents T cell activation by blocking its interaction with LFA-3 on antigen-presenting cells, and results in the death of the cell. The majority of patients treated with the drug show improvement and remissions can be prolonged, but total clearing is observed in only a small proportion of patients.

The other main targets for these new biological agents are the cytokines released as a result of T cell activation. These mediators play an important role in the psoriatic process by exerting their effects on various cell types in psoriatic skin. The focus of this strategy is the cytokine TNF- $\alpha$  (Tumour Necrosis Factor- $\alpha$ ), both because of its increased levels in lesional skin, and the demonstrated efficacy of anti-TNF- $\alpha$  agents such as the fusion protein etanercept (Enbrel), and monoclonal antibody infliximab (Remicade) in RA and/or Crohn's disease. Etanercept and infliximab have the same mechanism of action, they bind to and inactivate TNF- $\alpha$ , preventing the cytokine from binding to receptors expressed on the surface of most types of cells, both have been shown to be effective in psoriasis and psoriatic arthritis. The development of biological therapies has heralded a new era in the treatment of psoriasis. They have proved both effective and relatively safe in the short to intermediate term; however, it is not known whether there may be side-effects associated with long-term use. Furthermore, the high cost of the treatments may be prohibitive (Baker '08: 96-99).

Retinoic acid was first used to treat psoriasis in the 1970s. Second generation retinoids, etretinate and its active metabolite acitretin, came into use during the 1980s, most commonly combined with UVB or PUVA, but highly effective as a monotherapy for pustular psoriasis. However, they were only administered to patients with severe and recalcitrant forms of psoriasis, because of their attendant toxic side-effects. These side-effects were thought to arise from the non-specific interaction of etretinate and acitretin with several retinoic acid receptors in the skin. In the 1990s, this led to the development of a new class of retinoids called acetylene retinoids,

the first of which were tazarotene and taarotenic acid, which were designed to selective for RARs. Tazarotene was developed in a topical gel formulation, providing the first topical retinoid for use in psoriasis. Unlike the oral retinoids, the gel was well-tolerated, showing low systemic absorption and was not harmful to fetal development. Furthermore, its beneficial effects in psoriasis were rapid and sustainable over several weeks. Although retinoids were originally believed to act primarily on epidermal cell growth and differentiation, it became evident that their immunomodulatory and ant-inflammatory properties contribute to the resolution of psoriatic skin lesions. Ascomycin derivatives, a novel class of anti-inflammatory macrolactams, were first introduced in the late 1990s for the treatment of skin diseases. In common with cyclosporine and tacrolimus, ascomycins act by inhibiting cytokine production by T cells, but had the advantage over those two drugs of being effective when applied topically. The main ascomycin compound tested, pimecrolimus, was shown to be effective not only in atopic dermatitis and allergic contact dermatitis, but also in psoriasis under semi-occlusive conditions. It proved to be as effective as topical corticosteroids in these diseases, but had a better safety profile and did not induce skin atrophy (Baker '08: 95, 96).

The first use of the administration of plant extracts, followed by sun exposure (**photochemotherapy**) in the treatment of skin disease was by the Hindus in about 1400 B.C. In 1947, the active ingredients in these plant extracts were isolated, 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP) and used in combination with sun exposure to treat patients with vitiligo. After it had been determined that long wavelength ultraviolet radiation (320-400 nm, UVA) was the most efficient from activating 8-MOP, artificial sources of UVA were developed. This highly effective procedure developed became known as PUVA (psoralens +UVA) and is one of the mainstays of psoriasis therapy. **Excimer lasers** were first used as a form of phototherapy in psoriasis in the late 1990s. Excimer lasers operate in the UV range and use a mixture of a noble gas and a halogen, which are induced to form unstable "excited dimers" by high energy electric current. The high energy dimers quickly dissociate to their ground states giving off laser light, which is delivered to its target via a fibre optic cable. These lasers could precisely ablate the surface of a variety of tissues without an apparent thermal effect, termed "cold ablation", but were used only briefly for resurfacing the skin as they were found to be unsuitable due to technical reasons. The first use of a 308-nm xenon chloride excimer laser as a form of phototherapy in psoriasis was in 1997. Clearance of psoriatic plaques was achieved in 7 to 11 treatments with the laser compared to over 30 treatments with conventional narrow band UVB therapy. In addition to the faster therapeutic effect, the use of the excimer laser has several other advantages, including the sparing of surrounding normal skin from unnecessary UV exposure, long remission times (up to 2 years), and a smaller total cumulative dose needed to clear psoriasis than in conventional phototherapy, thus reducing the potential long-term risk of carcinogenicity from UV exposure (Baker '08: 74, 94, 95).

Although treatments have improved greatly during the last century, largely because they became evidence-based, patient dissatisfaction was still high, as shown by a large patient survey carried out by the National Psoriasis Foundation in 1998. Traditional treatments for moderate to severe psoriasis, some of which have been in use for several decades, have many limitations including immunosuppressive effects leading to an increased risk of infection and cancer, toxicity, a requirement for continual monitoring and inconvenience of use. This has contributed to an increasing use by psoriatic patients of over the counter medications, and complementary or alternative forms of medicine. Herbal remedies, nutrition therapy, traditional Chinese remedies, acupuncture or homeopathy are used by around half of psoriatic patients, mainly as a complementary treatment rather than as an alternative to conventional therapies. The

introduction of biological therapies at the end of the 20<sup>th</sup> century represented a new, more specific approach to the treatment of psoriasis, based upon an increased understanding of the role of the immune system in the pathogenesis of the disease. Alefacept, efalizumab, etanercept and infliximab have all now been approved by the US FDA and its European equivalent (EMA) for use in psoriasis; the latter two are also approved for psoriatic arthritis. Assessments of the performance of these agents in psoriasis over a 3 to 5 year period concluded that they were not only effective, but non-toxic and relatively safe. Furthermore, their use required less monitoring, and they were more convenient and easy to administer. Thus biological agents appear to provide a safe and effective alternative to traditional therapies, although long-term safety data is lacking. Despite these obvious advantages biological therapies, in common with all previous treatments, cannot induce permanent remission of the disease (Baker '08: 112).

## 8. Lupus erythematosus

The onset of the collagen diseases, lupus erythematosus, scleroderma and dermatomyositis, is insidious and the prognosis as to life is serious. Systemic and discoid lupus erythematosus are clinically dissimilar but basically related diseases. The two diseases differ in regards regard to characteristic skin lesions, subjective complaints and other organ involvement, blood and tissue test findings, response to treatment and prognosis. **Discoid lupus erythematosus** is red, scaly, thickened, well-circumscribed patches with enlarged follicle and elevated border leading atrophy, scarring and pigmentary changes. Most lesions are on the face, mainly in "butterfly" area, but also on scalp, ears, arms and chest, may not be symmetrical. Very chronic aggravated by intense sun exposure or radiation therapy. Twice as common in females. Laboratory findings are negative. Treatment of lesions includes the application of Fluorinated corticosteroid cream locally to lesions, but not on the face for long periods because atrophy and telangiectasia can develop. Sunscreen cream with SPF 15. **Systemic lupus erythematosus** produces red, mildly scaly, diffuse, puffy lesions, purpura is also seen. There is no scarring only mild hyperpigmentation. Lesions occur in the face in "butterfly area", arms, fingers and legs and are usually symmetrical. Acute onset with fever, rash, malaise, and joint pains. Systemic complications of nephritis, arthritis, epilepsy, pancarditis, hepatitis, and so on make life difficult. Biopsy is useful, especially fresh tissue immuno-fluorescent studies. Leukopenia, anemia, albuminuria, increased sedimentation rate, positive ANA test, and biologic false-positive serologic test for syphilis are found. Most cases respond rapidly to corticosteroid and supportive therapy, but the prognosis for life is poor (Sauer '85: 239-242). Unwitting exposure to poison oak or poison ivy, after inhaling large quantities of such substances from burn piles, is highly suspected.



In 1966, Edmund Dubois, in Los Angeles, published the first comprehensive medical textbook on SLE. In 1971, diagnostic criteria for SLE were established. These were further refined in 1982 by the American College of Rheumatology (ACR). The first international conference on SLE was held in Calgary, Alberta, in 1986. Since then, conferences have been held in Singapore, London, Jerusalem, Cancun, Barcelona and New York. In 1991, the first international scientific journal on SLE was published in London, England. The diagnosis of SLE is never made on the basis of a single

symptom or abnormal test – other abnormalities must be present. The American College of Rheumatology (ACR) has defined SLE as the presence of any combination of four out of eleven possible criteria. These criteria are: (1) Malar rash – fixed red rash over the cheeks (also known as the "butterfly rash"); (2) Discoid rash – red, raised, scaling patches anywhere on the body; (3) Photosensitivity – rash that develops after sun exposure; (4) Oral ulcers – sores in the mouth or nose, usually painless; (5) Arthritis – inflammation of the joints; (6) Serositis – inflammation of the lining around the lungs or heart; (7) Renal disorder – kidney involvement with blood cells or protein in the urine; (8) Neurological disorder – seizures or severe psychiatric problems; (9) Hematologic disorder – low numbers of red cells, white cells or platelets in the blood; (10) Antinuclear antibody (ANA) – a laboratory test screening for autoantibodies. It can be present in any disorders, but suggests SLE if it is present in high levels and is associated with other SLE criteria; and (11) Immunologic disorder – a positive laboratory test for various autoantibodies – one is the anti-DNA autoantibody test, which is more specific than the ANA Survival in SLE has improved dramatically in the last few decades and continues to do so. In the 1950s, SLE was considered a fatal disease. Studies have shown that survival in SLE has improved significantly from the reported 50 percent survival at five years in 1955 to 80 percent survival at twenty years in 1995. The widespread use of corticosteroids and other treatments, better medical care, more timely diagnosis and closer follow-ups are all working to help patients with SLE live longer (Bernatsky & Senécal '05: 19, 17-18).

### **Monitoring for Lupus Medication Side Effects**

<b>Drug</b>	<b>Blood tests</b>	<b>How often</b>	<b>Other tests</b>
Corticosteroids	Glucose, electrolytes (sodium, potassium)	Depends on dose	Blood pressure at each visit
Methotrexate	CBC, liver enzymes, creatinine	Every 8-12 weeks (may be more often in first 3 months or if dose adjustments)	
Aathioprine, Mycophenolate mofetil	CBC, liver enzymes	Every 1-2 weeks with changes in dose and every 1-3 months thereafter	
Cyclophosphamide pills	CBC	Every 1-2 weeks with changes in dose and every 1-3 months thereafter	Urine changes
Cyclophosphamide intravenous injection	CBC	At the time of injection, and two weeks after	Urinalysis (as often as the blood work)
Cyclosporine A	Creatinine, CBC, Potassium levels and liver enzymes occasionally)	Every 2 weeks until dose is stable, then monthly	Blood pressure (as often as the blood work)
NSAIDs and COX-II inhibitors	Creatinine, CBC	Depends; 2 weeks after starting and thereafter, at each visit.	Blood pressure, liver enzymes and urine analysis

Source: Bernatsky & Senécal '05: 62

Many forms of SLE skin disease can be treated with **corticosteroid creams** applied to the affected skin until the rash has cleared up. Very powerful corticosteroid creams should only be used for a short period of time; a milder topical corticosteroid should be prescribed as the rash begins to respond to treatment. Like any medication, corticosteroids can cause side effects. Side effects are more likely to begin with doses of corticosteroids greater than the equivalent of about 7.5 mg of prednisone per day. The higher the dose and the more prolonged the treatment, the more likely it is that side effects will occur. Side effects of corticosteroids can include osteoporosis and osteonecrosis, facial changes and weight gain, moodiness, acne, facial hair, upset stomach, glaucoma and cataracts, adrenal insufficiency, high blood sugar (hyperglycemia), high blood pressure (hypertension), increased risk of infection and swelling or water retention necessitating salt elimination and calcium supplementation diet. Stopping prednisone suddenly when the body has become used to it, is very dangerous and could be fatal. Corticosteroids such as prednisone are very similar to the cortisone produced naturally by the body's adrenal glands. These two small glands, located close to the kidneys, produce hormones that regulate water and salt balance, along with many other functions. During corticosteroid treatment, because it notes the presence of prednisone, the body may "turn off" its own production of the hormones that drive the natural production of cortisone. Some difficulties can occur when the dose of prednisone is tapered below about 7.5 mg per day if the adrenal glands can't keep up. Difficulty can also occur when experiencing some very significant physical stressor, such as an infection or serious injury. In states of severe stress, the body normally produces doses of cortisone that equal at least about 15 mg of prednisone. In general, if a drug can be used in pregnancy, it is safe in breastfeeding. NSAIDs such as naproxen and ibuprofen can be used safely when breastfeeding. The same holds true for corticosteroids, provided the dose does not exceed 40 mg per day. Antimalarials appear to be safe but are a little more controversial. Women have taken azathioprine with little risk to the infant, but cyclophosphamide and methotrexate should be avoided (Bernatsky & Sénécal '05: 38, 48-52, 86).

**Antimalarial medications** (for example, hydroxychloroquine, chloroquine) are very helpful in the treatment of SLE rashes because they are relatively non-toxic but often effective. Regular follow-ups are necessary. Occasionally, patients with severe SLE skin disease need treatment with corticosteroids given as pills (for example, prednisone) or, rarely, intravenously. Sulfa drugs and tetracyclines should be avoided because they can cause sun sensitivity. Antimalarial drugs, most commonly hydroxychloroquine, chloroquine and quinacrine, have been used in the treatment of SLE since the 1950s. They are called antimalarials because they were originally used against malaria, an infectious disease that is common outside North America and Europe. Stories among British troops in World War II who took antimalarial drugs to treat malaria and saw an improvement in their skin condition. The beneficial effects on rashes can be seen in as soon as a few weeks and may take up to six months to fully appreciate the beneficial effects. (Bernatsky & Sénécal '05: 43).

**Steroid-saving drugs** are immunosuppressive drugs that, usually in combination with corticosteroids such as prednisone, are very useful to control severe SLE both on a short term and a long-term basis. Azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate are four drugs that can be steroid-sparing. **Azathioprine** is a useful immunosuppressive drug that is available in tablet form only and the dose varies according to weight, that has been used for several decades, but serious blood toxicity is not uncommon and potentially serious liver toxicity requires liver enzyme monitoring, and it has been replaced by intravenous cyclophosphamide and now MMF for the initial treatment of lupus nephritis.

**Mycophenolate mofetil** (MMF) has been used since the early 1990s for the prevention of acute rejection of transplanted organs such as the kidney or heart. Since 200, MMF has gained popularity as a steroid sparing drug in the treatment of people with lupus nephritis. MMF is taken by mouth usually as a tablet (an oral suspension is also available) and appears to be as effective as intravenous cyclophosphamide in the treatment of major forms of lupus glomerulonephritis (involving the kidneys). Although not devoid of potentially severe side effects, MMF is clearly safer than cyclophosphamide in most circumstances.

**Cyclophosphamide** (CYC) is one of the most potent immunosuppressive therapies available, and it is available in tablet form (taken daily), and by intravenous injection (given outpatient at four week intervals). CYC is the preferred treatment for several types of SLE nephritis, however, intravenous CYC remains an important treatment option in SLE when prompt control of the underlying disease is needed, to limit the extent and severity of the damage. CYC can cause hemorrhagic cystitis. To decrease bladder-related problems increase intake of fluids before going to bed to wake up in the night to empty the bladder, Bone marrow toxicity and regular blood tests (e.g. complete blood counts CBC) should be done. Nuisance side effects, such as nausea and hair loss, can also occur. The hair grows back. Even years after stopping CYC seems to increase the risk for bladder cancer and ovarian failure (Bernatsky & Senécal '05: 55-58).

Certain people with milder SLE manifestations can improve on **methotrexate** (MTX) the front line anti-neoplastic drug, that needs to be taken only once a week. MTX is considered for people whose SLE causes arthritis or pleuritis (inflammation of the lining of the lungs) that requires frequent use of corticosteroids. MTX is usually started at 2.5 mg in tablet form and increases as needed to 15 mg per week. The development of mouth sores and moderate hair loss are possible side-effects that are reduced by taking small doses of vitamin B<sub>9</sub>, folic acid. Persistently abnormal liver function tests may lead to a procedure called a liver biopsy. Alcohol should be avoided. MTX should be avoided if there is pre-existing kidney damage and kidney function is also periodically monitored. A rare but potentially serious side effects of MT is the development of lung inflammation. Also, sexually active women who are of childbearing age should not take methotrexate unless they are on a reliable birth control, because this drug can cause miscarriages and birth defects if taken during a pregnancy (Bernatsky & Senécal '05: 59, 60).

## 9. Pigmentary disorders



There are two variants of pigmentation of the skin: hyperpigmentation and hypopigmentation. The common clinical example of abnormal hyperpigmentation is chloasma, but secondary melanoderma can result from many causes. The most common form of hypopigmentation is vitiligo, but secondary leukoderma does occur. **Chloasma** (Melasma) is an irregular hyperpigmentation of the skin that varies in shades of brown. The lesions usually occur on the sides of the face, forehead and sides of the neck. The disorder is slowly progressive, but remissions do occur. It is more obvious in the summer.

The differential diagnosis must rule out drug eruption, hyperpigmentation due to hormones and secondary melanoderma. Sunlight intensifies the pigmentation so a sunscreen should be used. Melanex solution 3% (Neutrogena) 30.0 or Eldopaque Forte Cream (elder) 30.0 can be applied

locally. Stop if irritation develops. The treatment with either of these hydroquinone preparations should be at least 3 months. Response to therapy is slow. A salve containing 5% ammoniated mercury in white petrolatum can be prescribed is allergic contact reactions to hydroquinones occurs.



**Vitiligo** is irregular areas of depigmented skin with a hyperpigmented border. Most commonly the lesions occur on the face and the dorsum of hands and feet, but they can occur on all body areas. The disease is slowly progressive but remissions are frequent. It is more obvious during the summer. The cause is unknown, heredity is a factor in some cases. The use of covering or staining preparation is recommended such as Covermak, Vitadye (Elder); walnut juice stain or potassium permanganate solution in appropriate dilution. Corticosteroid cream therapy is effective for

early cases of vitiligo, especially when one is mainly concerned with face and hand lesions. Betamethasone valerate cream 0.1% (Valisone cream) can be prescribed for use on the hands for 4 months or so and for use on the face for only 3 months. Do not use on eyelids or as full-body therapy. **Psoralen** derivatives were used for many years by Egyptians along the Nile River who chewed certain plants to cause the disappearance of white spots of vitiligo. Extraction of the chemicals from these plants reveals the psoralen derivatives to be the active agents, and one of these, 8-methoxypsoralen (8-MOP) was found to be the most effective. This chemical is now manufactured under the name Oxsoralen (Elder) in 10 mg capsules and also a topical liquid form. The oral form is to be ingested 2 hours before exposure to measured sun radiation. A short 2 week course of Oxsoralen capsules (20 mg/day) has been advocated for the purpose of acquiring a better and quicker suntan. Trisoralen (Elder) is a synthetic psoralen in 5 mg tablets. The recommended dosage is 2 tablets taken 2 hours before measured sun exposure for a long-term course. PUVa involves the combination of oral psoralen (P) therapy with ultraviolet A (UVA) radiation has been somewhat successful in repigmentating vitiligo (Sauer '85: 233-236).

Some of the earliest signs of aging of the skin are the development of hyperpigmented macular lesions known as freckles and lentigines. These can begin in individuals in their 40s. They develop most commonly on the dorsum of the hands and on the face, in direct proportion to the genetically determined fair complexion of the individual and the dosage of sun gained through the earlier years of life. On the face, and to a lesser extent on the rest of the body, wrinkling of the skin also progresses with age. Diffuse hyperpigmentation of the face and hands, again in the sun-exposed areas, becomes more definite with age. Hyperpigmentation on the side of the neck, which is a combination of red and brown discoloration, seen particularly in women, is called **poikiloderma of Civatte** (Sauer '85: 343). Ultraviolet radiation from the sun is divided into three different wavelengths – UVA, UVB, and UVC. The UVA waves are the longest and the UVC the shortest. UVB rays do not penetrate further than the basal layer of the epidermis, but UVA rays go much deeper than this – into the mid-dermis. UVC is prevented from reaching the earth's surface by the ozone layer, and is not therefore a natural hazard. Ozone currently absorbs all UVC and a proportion of UVB from the sun's rays, but emission of chlorofluorocarbons (CFCs) from aerosols and other sources is destroying this protective ozone layer and will continue to do so if further national and international action is not taken. It would take up to 50 years or more for the ozone mantle to repair itself and is regarded as a matter of major ecological importance. The main ultraviolet component of natural sunlight that does reach the earth's surface is UVB. This

penetrates the epidermis and reaches the more superficial layer of the dermis – the papillary dermis. UVA is also present in sunlight and, in the early spring, a high proportion of natural sunlight in countries at latitudes 50 degrees or more north or south of the Equator (e.g. the more northern states of the US, Europe and New Zealand is composed of UVA. As the summer develops, the proportion of UVA falls. UVA is the main, but not the only, wavelength found in the long tubes in UVA sunbeds. The effects of UVA go deeper into the skin than those of UVB. A simple rule of thumb is that chronic over-exposure to UVB cause wrinkles, chronic over-exposure to UVA causes sagging, and chronic over-exposure to both increases the risk of developing skin cancer. One of the important points between UVB and UVA exposure is that acute overexposure to UVB causes the redness and soreness recognized as sunburn. This is maximal 12-24 hours after the exposure has taken place, and is a useful warning that the skin should be protected for a few days until the redness has disappeared. In contrast, however, acute over-exposure to UVA may show no warning redness and even if a little pinkness develops, it takes up to 72 hours for this to show. So there is no immediate warning that the damaged skin had an excess of UVA and needs protection for a day or two. There are at present no widely accepted scaled by which UVA protection is measured, although a system of stars has been proposed by the UK (Mackie '92: 80-82, 89).

A number of biologically important events are triggered when skin is exposed to **ultraviolet radiation**. Short-lived structures called free radicals, which consist of a few atoms, are generated and, although these are very quickly destroyed by a number of scavenging systems in the skin, they do some damage. When this happens rough scaly patches of skin – actinic keratoses – develop, with irregular patches of brown color – sometimes called age spots, liver spots or sunspots. These are often seen on the backs of the hands and other chronically sun-exposed parts of the body. The underlying elasticity of the dermis is lost. This dermal damage causes wrinkles if the damage is done by UVB and sags if it has been caused by UVA. Chronically sun-exposed skin tends to look leathery and thickened because of the deposition of this elastic-tissue-like material. The next stage in the gradual build-up of chronic sun-induced damage is the development of skin cancers. These are usually of the non-melanoma type – the basal and squamous cell cancers. They are relatively easily cured by surgery but, once one develops, it is highly likely that more will follow. In Australia, where it is difficult to keep out of strong sunshine, two-thirds of the population currently develop some form of skin cancer during their lifetime. Because of this a very large proportion of that country's expenditure on health care is devoted to skin cancer treatment. Before sun-induced skin damage reaches the stage of frank cancer it causes considerable discomfort with dry itchy skin (Mackie '92: 82-84).

### Types of Skin Pigmentation

Skin Type	Description
1	Always burns – never tans; this is quite rare.
2	Usually burns at first. Tans slowly and with difficulty. This is a common skin type in the north of Europe and in Americans with British or Scandinavian ancestry.
3	Tans easily, burns rarely.
4	Tans easily, never burns. Rare in the UK but common in Mediterranean countries and in Americans of Italian, Spanish or Greek descent.
5	Indian or similar shade of brown skin.
6	Black Afrocaribbean skin.

People with **skin types 1 or 2** will never achieve a deep, golden tan and will cause themselves a lot of discomfort, if not actual pain, and their skin some damage, if they try to do this. The midday sun should be avoided at home and abroad, and a shady hat should be worn. Clothing is an excellent sunscreen as long as it is closely woven. A sun-screening preparation with an SPF of 10 or more should generously re-applied every 2 hours and after swimming. A preparation that also states it protects against UVA is even better. One of the ingredients to look for when seeking UVA protection is microfine titanium dioxide. Those with skin types 3 and 4 can safely allow themselves more sun exposure, but again should avoid the noonday sun, and require some sun-screen protection with an SPF of around 8. Skin types 5 and 6 of those born with a darker brown or black skin have a good in-built sunscreen, but even they may need to use a sunscreen in very strong sunshine. Preparations with SPFs of 4-6 are recommended. Whatever the skin type and skin color, most people notice that their skin is dry after a lot of sun exposure so plenty of emollients and moisturizing creams are a good idea. After-sun preparations are generally good moisturizers, but the usual moisturizing preparation will be just as effective. The important point is to apply generous quantities of these preparations after a day on the beach and for a week or two after returning home. **Polymorphic light eruption** used to be a relatively rare problem but is now seen much more frequently. It consists of small, very itchy blisters on the light-exposed areas of skin, chiefly the face and hands. It mainly affects young females, and is thought to be triggered by UVA. It is most often seen in the early spring. To avoid this, choose a sun-screen that protects against UVA as well as UVB. Useful, relatively new, preparations include Sun E45 with an SPF of 15 or 25. These have good UVB and UVA protection (Mackie '92: 90, 91, 93). If the skin becomes sunburned, plenty of soothing moisturizer applied to the skin and aspirin taken by mouth will help. Aspirin has a specific effect in reducing the causes of sunburn-induced inflammation, so is preferred to a paracetamol (UK) or Tylenol (US). A tepid bath with added bath oil may help. Hydrocortisone cream or ointment in small quantities for a day or two, is helpful. Other soothing remedies include aloe vera. The inflamed and sore areas of skin should be protected from further damaging sunburn until the redness and any peeling that develops have settled. A number of skin problems have been associated with using a sunbed including; skin fragility, blistering, large unattractive freckles, and the possibility of skin cancer. In addition, UVA can interact with some oral drugs and cause an uncomfortable rash; such drugs include water pills (diuretics), anti-rheumatics, and some antibiotics. UVA sun-beds are not good for the skin and tan developed on a sun-bed, if such a tan develops at all, will only have the protection of a factor 2 or 3 SPF sun-cream when the skin is exposed to natural sunlight. If a sun-bed must be used, it should be only for one course of 10 30 minute exposures annually and goggles would always be worn, as the eyes can be badly damaged by UVA (Mackie '92: 96, 98).



Most **skin cancer** are curable, provided they are recognized and treated early. Those at greatest risk of skin cancer are Caucasians, i.e. white-skinned, usually aged over 40, but may be younger in sunny climates, have usually spent a fair amount of time in a sunny climate, either born there, worked there, or on holiday, are most likely to develop non melanoma skin cancer on the face, or the hands, may first notice rough, dry skin on the head and neck, a useful warning sign, may also have flat brown marks, sometimes referred to as age spots or

sunspots, on their skin at these sites. There are three types of malignant tumors of the skin (1) squamous cell carcinomas (2) basal cell carcinoma and (3) malignant melanoma. Basal cell carcinomas rarely metastasize and squamous cell carcinomas are slow to do so, however malignant melanomas metastasize rapidly with deadly effect. There are four main types of malignant melanoma (1) lentigo maligna melanoma most common on older faces, develop as raised bumps in an irregular flat brown mark, a lentigo maligna, after a year or two, untreated, (2) superficial spreading melanoma, most common, malignant change in nevi, (3) nodular melanoma, a rapidly growing lump or bump found anywhere on the skin and (4) acral melanoma, the rarest type in white-skinned people, found mainly on the soles of the feet more common in Asian skin. Individuals who have had a skin cancer of any kind are at an increased risk of developing further skin cancers and should wear a broad-brimmed hat to protect the head and shoulders and a sun-screen with an SPF of 15 or higher. (Mackie '92: 99-100, 106-110, 96). Treatment for all skin cancers is wide surgical excision with 2 cm to 3 cm margins. Topical 5-FU may be effective.

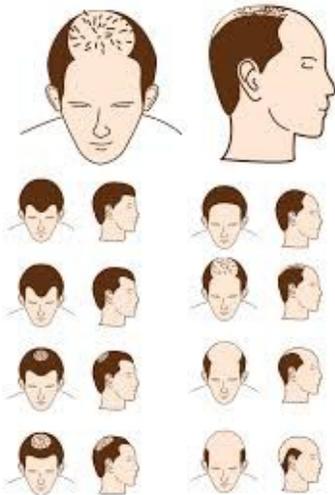
The many shades of **hair color** are produced by pigment, a brownish material called melanin. If it is abundant the hair is dark; if in moderate quantity the hair is brownish and if totally absent the hair is white. The pigment is formed in the cells of the follicle, and is exactly comparable with that occurring in the other skin cells. However, once the melanin has been deposited in the hair shaft, it tends to be bleached by strong sunlight. The granules of melanin in the hair cannot be replaced as they can in the skin. Gradual greying of the hair with age is not a disorder. It is normal for the pigmentation to alter in density with age, and its reduction need not be associated with any lack of vigor in the hair growth. Even white hair should remain thick and vigorous until a really advanced age. If either parent greyed early there is a probability of it occurring in the offspring. Sudden greying is a different matter and can only occur if bleaching by a chemical or by light happens. Ordinarily it must take at least a day for non-pigmented hair to become visible above the surface but the process of turning a head of white hair is a gradual one taking weeks or months and depending on genetics may only be partial, salt and pepper. Whether loss of color takes place slowly or dramatically, it is far less amenable to remedial treatment than conditions which involve the growth and vitality of the hair. A diet adequate in fresh and wholesome foodstuffs, plus attention to breathing and the muscles of the neck – to encourage oxygenation and circulation – are possibly the most immediately significant remedial measures. Hair dyes are regarded with some suspicion and so-called tonics for the hair and scalp have a bad record. Outdoor activity such as brisk walking, plus a daily cold water splash and a scalp bath three or four times a day; vigorous massage of the scalp, combing, brushing and pulling the hair, daily vegetable salad and nightly scalp compress will do much to encourage a return of natural coloring (Thomson '69: 60-67).

## **10. Hair loss, dandruff and nail infections**

The **hair** is continually being shed and replaced. The hair follicles respond to male and female hormones circulating in the bloodstream. In general, female hormones encourage hair growth, so that during pregnancy a higher proportion than usual of the hair follicles are in the growth phase. Male hormones have a more varied effect but on certain areas of the scalp, particularly the temples and the top of the head, they tend to inhibit hair growth, so that some males lose hair from these sites quite early in life. The tendency of **male hair loss** tends to run in families and is a result of the hair follicle ceasing to make a long strong terminal hair of the type normally seen on the scalp. Instead, it produces a villous hair – a small fine downy hair – of the type usually seen on the forearms. Scalp hair varies in its thickness. In general, fair hair is finer and darker

hair is thicker, giving a fuller look to the head of hair. With age, hair tends to get thinner and more brittle and cannot tolerate perms, bleaching, heat or vigorous back combing. Hair varies greatly in its straightness or tendency to form curls and waves (Mackie '92: 126, 127).

A common and comparatively minor, sign of disorder of the hair is **splitting** at the ends, called scissura pilorum in Latin. It occurs most usually in long hair, and is thus seen mainly in women or men with full beards or long hair. Splitting seems to indicate that the hair was produced under less than ideal conditions. There seem to be a link with deep ridges in finger and toe-nails which is caused by overworked kidneys, too much tea, coffee or water. **Atrophy**, wasting large-scale splitting of the hair, involves a more rapid and complete loss of hair growth than any other condition. In atrophy, the hairs become rough, dry, lusterless and brittle, and give the general appearance of being "dead". The splitting which occurs in the hair shaft is usually into three or four segments – rather than the division into two which occurs in less serious conditions. Another symptom is the appearance of hairs that are much thinner than their neighbors and the bulbs of the thin hairs, if pulled out and observed, will be found to be small and shriveled. Very little can be expected from any local treatment of true atrophy, since its causes lie deep within the individual's general condition, such as prolonged fever or any other comparable disorder affecting the system as a whole (Thomson '69: 48, 51-53).



**Hair loss (Alopecia)** can be caused by chemotherapy that kills rapidly dividing cells; other medications may cause hair to thin. These are most often temporary effects: hair usually starts to regrow a few weeks after the last treatment, and sometimes can change color, texture, thickness and style. Sometimes hair has a tendency to curl after regrowth, resulting in "chemo curls." Severe hair loss occurs most often with drugs such as doxorubicin, daunorubicin, paclitaxel, docetaxel, cyclophosphamide, ifosfamide and etoposide. Permanent thinning or hair loss can result from some standard chemotherapy regimens. Hair loss (**alopecia**) in the scalp can be diffuse or patchy. Patchy alopecias can be of the nonscarring or scarring variety. In the scarring variety, the hair cannot regrow because of destroyed follicle. Diffuse hair loss most commonly occurs as male-pattern hair loss. The earliest hair loss extends back on both

sides of the forehead in an M-shape to meet a slowly enlarging area of similar hair loss on the vertex of the scalp. The degree of hair loss varies with the individual, as does the age at which it begins. The dominant factors are heredity, age of the individual, and hormones. Hormonal therapy in safe disease has no beneficial effect. Castrated males do not have male-pattern hair loss, but castration is not recommended as a form of treatment. **Male pattern hair loss** must be differentiated from patchy hair loss from alopecia areata or trichotillomania. Treatment involves explaining this is an unalterable factor of heredity, treatment is of little value, and the surgical procedures of hair transplantation and scalp reduction are possible therapeutic modalities. Suggest the use of a dandruff-removing shampoo, such as Selsun Suspension, to keep the scalp as healthy as possible. Female-pattern hair loss is mild, diffuse hair loss that occurs in a small percentage of women, most commonly after the age of 50. There is no effective form of therapy. Treatment consists of pointing out the causative factor of anesthetic use, and reassuring the patient she will not become bald and regrowth will take at least 6 months. **Trichotillomania** is a rare form of hair loss thought of when exclamation-point hairs, scaliness and infection are not seen and self-mutilation from a "pulling tendency" is suspected. Alopecia due to secondary

syphilis is uncommon patchy, moth-eaten form without exclamation point hairs (Sauer '85: 257-261, 263).



**Alopecia areata**, a patchy, nonscarring hair loss, is a common disease of unknown causes. Loss of hair is a slowly enlarging area or areas. No scaling or evidence of infection is present. The hair breaks off at a point 2 mm to 3 mm above the scalp surface. The broken hairs are called "exclamation-point hairs". When healing begins, the new hairs are commonly white, but eventually they regain their normal color. Any hairy area of the body can be affected. The most common areas are the scalp, the eyebrows, the eyelashes and the beard. The great majority of cases of alopecia areata have one or several small patches will regrow their hair in 6 to 12 months time with no treatment. A common accompaniment of the early stage of alopecia is the presence of many small, brownish-white scales. Total loss of the scalp hair (alopecia totalis) or all of the body hair (alopecia universalis) carries with it a very poor prognosis for eventual return of the hair. This disease occurs

most commonly in young adults and less commonly in children. The cause is unknown. Alopecia areata must be differentiated from tinea of the scalp, trichotillomania, secondary syphilis, discoid lupus erythematosus, alopecia cicatriza and folliculitis decalvans. Treatment consists of reassuring the patient that it would be exceedingly rare to lose all their hair and that lesions might enlarge come but that within 6 to 8 months time all hair will be back. So long as the fine hairs are still visible, it is not impossible to re-attain a healthy growth of hair. If nothing is done to improve the general health, the tone of the scalp and the local circulation, even this laguno disappears, the follicles will have been reabsorbed – reverted to the simple skin structure from which they originally developed (Thomson '69: 38). The new hair might come in white at first but the natural color would soon return. Corticosteroid therapy causes regrowth of hair in some of the severe cases but should be administered orally, intralesional injection or intramuscular injection of 10 mg triamcinolone parenteral suspension (0.25 ml of Kenalog 40 IM) once a week for 6 to 8 weeks, then less frequently, has been beneficial for severe, widespread cases (Sauer '85: 261, 262). **Hair transplantation** has become an accepted cosmetic procedure. Small cylindrical plugs are removed from the the scalp in a bald area, and exchanged for plugs of similar size from a well-covered area of the same scalp. The implanted, vigorously active clumps of follicles heal into their new homes, and continue to produce a strong growth of hair. With enough plugs, a considerable amount of scalp may be re-planted. The operation can be carried out under local anesthetic but can take a lot of surgical time. Trasplanted hair has been reported to flourish for at least several years.(Thomson '69: 73).

The congenital presence of completely gray or white hair (albinism) or of patches of gray hair is quite rare. Graying of the scalp hair is a slowly progressive process. Hereditary factors determine whether such grayness will begin in early or late adulthood or not at all. Patchy gray hair can develop following nerve injuries. The new hair that grows in during the healing of alopecia areata is usually white or gray. Excessive growth of hair (hypertrichosis or hirsutism) can be a psychological problem. Congenital hypertrichosis is very rare. Localized hypertrichosis is ordinarily seen in association with nevi, after removal by electrosurgery it is often necessary to remove the remaining excess long hairs by an electrosurgical method. Excessive hair growth on the face can occur quite obviously in women following administration of male hormone, corticosteroids and minoxidil (Loniten). Tumors of the ovary and adrenal can

produce hirsutism. Therapy from least expensive to most effective are bleaching the hairs, plucking the hair, depilatories, epilating waxes and electrosurgical removal. Electrolysis is not generally available in the National Health Service (Mackie '92: 136).

**Dandruff** is the presence of many small, brownish-white scales, that may be referred to as furfuraceous desquamation or pityriasis, and is often an early sign of impending baldness in men with a hereditary disposition for baldness. Dandruff is simply an excessive and visible shedding of the superficial cornified layers of the epidermis of the scalp. Evidence suggests dandruff is associated with the presence in the hair follicles of large numbers of a yeast organisms called *Pityrosporon*. The yeast is found on most scalps, but in some dandruff sufferers the numbers present are much greater than average. The only discomfort among its symptoms are a characteristic ticklish or mildly itchy sensation in the scalp, and a slight feeling of unpleasant warmth. The scales of dandruff are produced by the epithelium and indicate a significant deviation from the normal state of its condition. The presence of clumped, dead cells is the characteristic of dandruff. It is formed by the abnormally gummy nature of the scalp secretions, which bind the cells into visible scales. The secretions should normally serve to coat the hair with an oily film of sebum. In dandruff, there is a change in the nature of the secretion. Exposure of the hair (and skin) to fresh air and friction produces a clear and wholesome complexion (Thomson '69: . Anti-dandruff shampoos are available over-the-counter but most antifungal shampoos require a doctor's prescription in the UK (e.g. Nizoral shampoo). A second approach is to apply a cream containing a keratolytic – a preparation that lifts this scale away from the scalp – overnight before shampooing. The scale will build up again but, for a day or two, the shoulders will be clear of dandruff scales. At any age there is often a temporary shedding of hair after severe illness, particularly if this has been associated with high fevers. The technical term for this is telogen effluvium. Time will remedy the situation and the normal pattern of hair growth will resume. Those who are on chemotherapy for serious illnesses may experience loss of scalp hair because some, but not all, drugs used in chemotherapy, including methotrexate, affect the growing hair follicle. Once again, normal hair growth will return when the chemotherapy is stopped. In addition certain illnesses associated with parts of the body other than the skin may be associated with poor scalp hair growth, these include disorders of the thyroid gland and in some people, severe anaemia due to loss of iron (Mackie '92: 132-135). The normal functioning of the sebaceous glands produces enough greasy material to coat the hair shafts making them more effectively water-repellent and at the same time giving an improved appearance of glossiness, this can be disrupted by dandruff or an equally unpleasant disorder due to an excessive flow of sebum, known as **seborrhea**. The causes of this are frequently a combination of the intense physiological activities of adolescence and unsatisfactory nutrition. Seborrhoea occurs most commonly at puberty and in early adult life, and if there are no accompanying indications of unsatisfactory general health, the local treatments for toning the scalp are usually sufficient. Nutritional guidance is called for (Thomson '69: 47). Vitamin A (Retinol), Calcium, Phosphorus and Iron are important.

**Ringworm** of the scalp is not found in the adult, and almost always occurs before the age of puberty. Hair loss is more gradual than in alopecia areata, and the affected area does not become completely bald. The hair follicles protrude, with the appearance of gooseflesh, and around the borders of the patch are broken-off hairs. Within the patch, the skin is usually scaly and the hairs upon it may be easily pulled out. Microscopic examination shows the presence of parasitic organisms – most often fungal. In some cases, the patch looks like an abscess and is severely inflamed. The presence of the typical fungi consisting of tiny, round shining bodies and red structures (mycelia) may be the only sure diagnosis however firmly anchored hairs around the

border of the patch is a significant indication of ringworm. In the treatment of ringworm individual towels, comb, brush and soap are the rule, and under no circumstances should the patient use such articles belonging to another person. The hair and scalp should be frequently and thoroughly cleansed. Hairs which detach easily should be removed from the patch once or twice daily, followed by a soapy rinse. When **neuritis**, painful inflammation of the nerve that causes the skin to become reddened, thickened and peculiarly shiny, occurs in the scalp, the hair growth is likely to be disturbed. A common effect is the loss of pigment, so that the hair grows white, or growth ceases and the hair falls out. An alternative effect is a coarsening of the hair growth, which is less noticeable on the scalp than on other parts of the body. No local treatment is likely to improve such a condition, since the causes are systemic. The logical approach is through nutrition and other forms of treatment beneficial to the entire nervous system such as the medicinal tea valerian which is known as a strong "nervine" (Gladstar '12) and as with most natural remedies it takes about one month for every year of neglect (Thomson '69: 51-58).

**Head lice** are a species of louse with a preference for the human scalp. Their eggs are called nits. One head louse can lay very large numbers of eggs, and tends to do this on the hair shafts closest to the scalp, as the louse appears to be more comfortable at the higher temperatures found closer to the scalp. Head lice are generally transmitted from scalp to scalp by fairly prolonged, close, head contact. The lice require body warmth to survive and therefore do not last long on combs or hats. Treatment involves using an insecticide or acaricide preparation containing malathion, carbaryl or phenothrin, leaving it in contact with the hair for 12 hours, and then painstakingly combing out the dead and now harmless nits with a fine comb (Mackie '92: 132-135). **Pediculosis**, lice infestation, affects persons of all ages but usually those in the lower-income strata, because of lack of cleanliness and infrequent changes of clothing. It is also seen as a sexually transmitted disease. Three clinical entities are produced (1) infestation of the hair by the head louse *Pediculus humanus capitis*, (2) infestation of the body by *P. humanus corporis* and (3) infestation of the pubic area by the pubic louse *Phthirus pubis*. Since lice bite the skin and live on the blood, it is impossible for them to live without human contact. The readily visible oval eggs or nits are attached to hairs or to clothing fibers by the female. After the eggs hatch, the newly born lice mature within 30 days. Then the female can live for another 30 days and deposit a few eggs daily. The bite is not unusual but is seldom seen because of the secondary changes produced by the resulting intense itching. In the scalp and pubic form the nits are found on the hairs, but the lice are found only occasionally. In the body form the nits and the lice can be found after careful searching in the seams of the clothing. In the scalp for the skin is red and excoriated, with such severe secondary bacterial infection, in some cases, that the hairs become matted together in a crusty, foul-smelling "cap". Regional lymphadenopathy is common. A morbilliform rash on the body, an id reaction, is seen in longstanding cases. In the body form linear excoriations and secondary infection, seen mainly on the shoulders, the belt-line, and the buttocks, mask the primary bites. In the pubic form the secondary excoriations are again dominant and produce some matting of the hairs. This louse can also infest body, axillary, and eyelash hairs. An unusual eruption on the abdomen, the thighs and the arms, called maculae cerulae, because of the bluish, pea-sized macules, can occur in chronic cases of public pediculosis. Pediculosis must be differentiated from bacterial infection seborrheic dermatitis or dandruff, hair casts resembling nits, scabies, senile or winter itch, or pyoderma. Treatment for pediculosis capitis and pubis is lindane shampoo (Kwell or Scabene) 60.0 shampoo and comb hair thoroughly, leave on the hair for 4 minutes. Shampoo again in 3 days. For secondary scalp infections trim hair as much as possible, shampoo once a day with an antiseborrhea-type shampoo. Neosporin or other antibiotic ointment. Change and clean bedding and headwear after 24 hours of treatment. Storage of headwear for 30 days will destroy the lice and the nits.

Pediculosis corporis is treated with phenol (0.5%) in calamine lotion 120.0 applied locally for itching. Have the clothing laundered or dry cleaned. If this is impossible, dusting with 10 lindane powder will kill the parasites. Care should be taken to prevent reinfestation. Storage of clothing for 30 days will kill both nits and lice (Sauer '85: 219, 220).

There are between 6 and 12 million cases of **head lice** in the United States every year. Head lice are highly contagious and if one person in a family becomes infected, everyone in the household must be treated. Lice are the insects, nits are the eggs. Nits are harder to eliminate than lice. Dead nits are white, live nits are hair colored so they are harder to see. Nearly all lice treatments are available over-the-counter. A single application will usually kill all head lice, taking about 12 hours to clear the problem. A second application is necessary 10 days later to kill any newly hatched nits. Alcohol-based solutions are the most effective, but water-based alternatives are available for small children and eczema and asthma sufferers. Many oils, including eucalyptus, geranium, parsley, Scotch pine, rosemary, lavender, thyme and tea tree, will kill lice. The safest to use on children are tea tree and lavender. In a small bottle mix 1 tsp pure tea tree or lavender essential oil, with 5 tbsp warm water, 2 tbsp pure alcohol or vodka and 1 tsp castor oil. Shake the bottle well, then make a series of ½ in. partings in the hair. Apply the lotion over the scalp covering approximately 2 in. up the hair shaft from the roots and leave for 12 hours or overnight. Shampoo using warm water, massaging well into the scalp. Comb through the hair with a nit comb to remove dead lice and egg cases. Let hair dry naturally, heat will evaporate the active ingredients. Repeat every three days for two weeks and check regularly for any reinfestation. Swimming pool chlorine, perms and hair dyeing can reduce the effectiveness of the treatment (Davenport et al '03: 58, 59).

In general, **nails** cause fewer problems than hair, but when problems do arise in the nail or around it, there may be a lot of pain. This is particularly true if infection or bleeding develops under the nail. Like hair, nail can be thought of as modified epidermis. The finger-nails take about 6 months to grow out and toe-nails take even longer, about 2 years. The cuticle is a thin membrane that divides the nail from the skin of the nail fold, that prevents infection, dirt or debris from lodging in the narrow space between nail and nail-fold. Normal health nails need no special care other than regular trimming. Both finger and toe nails should be cut straight across and, particularly on the toes, should not be curved around the end of the digit. A curved, free nail end will encourage the development of an ingrown nail, which digs into the adjacent finger, or more often toe, and can be extremely painful. Like skin, nails react badly to immersion in strong degreasing detergents and vinyl gloves and regular use of hand cream are good practice. Common minor problems with nails are splitting, ridging and white marks. Splitting due to thin nails may be due to an inherited tendency, but may also occur if the diet is low in protein, so eat protein. Ridged nails and white marks on nails may be due to trauma to the nails. Common minor problems with nails include warts around the nails (periungual warts), paronychia, and fungal infection of the nail, which generally has spread from the adjacent skin. A rarer but potentially very important problem is the development of malignant melanoma in the nail bed – a brown or black pigmented mark under or around the nail should be checked (Mackie '92: 137, 138). Ridged nails are often associated with overworked kidneys, the overuse of tea or coffee, and the drinking of much water (Thomson '69: 49).



**Periungual warts** are common warts that involve the skin around the nail. Because the skin in this area is relatively bound down to surrounding structures, the warts can press on nerves and be painful. Untreated they may cause the nail to grow in an abnormal manner, and should be treated sooner than later. Paronychia is inflammation around the nail and is usually the result of infection in the narrow space between the nail and the nail fold; it is associated with loss of cuticle. Individuals at greatest risk are those

who have their hands in water a lot but find it difficult to use waterproof gloves. Paronychia can be recognized by the presence around the nail of a tender, often throbbing, raised red margin. Sometimes a little bead of pus can be seen or pressed out of the nail fold area. The infection may be bacterial or fungal, particularly due to *Candida*, which grows well in the moist environment around the nail, but is usually a mixture of these micro-organisms. Paronychia requires careful attention. It is necessary to try to keep the hands out of water, or the problem is likely to return. Ointments and lotions for this problem require to be coaxed and massaged carefully into the crevice between the nail and nail fold to ensure that the medication reaches its target. Once the paronychia has been cured, the cuticle should be allowed to grow back to perform its protective role. If paronychia has gone untreated for any length of time the nail itself may be ridged and damaged. This will come right in time, but will take months not weeks. **Tinea unguium** is an infection of the nails caused by the same organisms – the dermatophytes – that cause athlete's foot. The problem usually develops months after the itchy, peeling skin between the toes. The usual signs that the nails are infected are that they become crumbly, ridged and in time may become very heaped up and misshapen. This can reach the stage of causing problems with footwear. Prevention is key. Athlete's foot should be treated promptly (Mackie '92: 139) with athlete's foot crème (clotrimazole).

## 11. Hereditary disease and aging



There are many hereditary skin diseases. **Ichthyosis** is the most common one. There are a number of classifications of ichthyosis – ichthyosis vulgaris, x-linked ichthyosis vulgaris, lamellar ichthyosis (autosomal recessive), nonbullous ichthyosiform erythroderma (autosomal recessive), keratosis palmaris et plantaris, mal de Meleda, keratosis pilaris, keratosis punctate, ichthyosis hystrix, and bullous ichthyosiform erythroderma. Of the many types of ichthyosis, the autosomal dominant ichthyosis vulgaris form is the

most common. Small white scales, often in association with keratosis pilaris-type lesions, are seen. Scaling may be deep enough in some diseases. The arms and legs are most severely affected. This common form of ichthyosis is worse in the winter. In most cases there is essentially no scaling in the summertime. There is a tendency for improvement after puberty or early adult life. Xerosis or acquired ichthyosis is the most common cause of this dry skin problem in aging individuals. In young adults vitamin A deficiency, hypothyroidism, Hodgkin's disease, lymphosarcoma or carcinomatosis must be ruled out. Advise that there is no cure. Suggest an emollient soap such as Dove. Vitamin A orally appears to be beneficial for some cases. The dose should be 100 to 200 thousand units a day but for not longer than 4 or possibly 6 months at a time. Vitamin A acid (retinoic acid)(Retin-A) locally is helpful for lamellar

ichthyosis, and moderately helpful in dominant ichthyosis vulgaris. A-Hydroxy acids locally are quite effective especially for lamellar ichthyosis but also ichthyosis vulgaris and x-linked ichthyosis. A good preparation is 5% lactic acid in a hydrophilic ointment base.

**Albinism** is a congenital disorder characterized by partial or universal loss of pigment of skin, hair and choroid. Life expectancy is shortened. **Piebaldism** is a central white forelock overlying a depigmented area of the scalp. **Vitiligo** are unpigmented patches with highly pigmented borders. **Freckles** (ephelides) are small, brownish macules developing around the time of puberty that are accentuated by sunlight, they are to be differentiated from lentigine, which develop earlier (around the age of 2) are more widespread on the body and do not disappear in the winter. **Seborrheic keratoses** are transmitted as a simple autosomal dominant trait. **Keloids** are an autosomal dominant trait. **Nevi** are probably genetically transmitted. **Trichoepithelioma** are transmitted as an irregular autosomal dominant trait with partial limitation to the female sex (Sauer '85: 291-293, 296).

It had been recognized as early as the 19<sup>th</sup> century that **psoriasis** was an inherited disease, with the first analysis of the genetic basis carried out in 1931. However it was not until the establishment of the Human Genome Project during the first half of the 1990s that it became feasible to begin a systematic search for the genes determining psoriasis. In 1996, a gene map of the human genome containing 16,000 of the 50,000-100,000 genes then estimated to be present was published. Stronger HLA associations had been found in patients with an age of onset younger than 40 years, and who showed a higher frequency of affected first-degree relatives, than patients with a later onset whose HLA associations were much weaker. The strongest association observed in psoriasis was that of HLA-Cw6, an allele rarely increased in frequency in patients with other inflammatory diseases. However, only a proportion (approximately 10%) of HLA predisposed individuals go on to develop psoriasis, suggesting that inheritance of a particular HLA allele is not sufficient by itself for initiation of the disease. Several additional psoriasis genes, triggered by environmental factors, are involved. The first genome wide linkage study of psoriasis families was published in 1994 and reported a susceptibility locus on chromosome 17q25. None of the families with linkage to chromosome 17q however, showed any association with Cw6, providing the first evidence for the existence of genetic heterogeneity. Two to three years later, susceptibility loci for familial psoriasis were reported on chromosomes 4q21 and 6p. The susceptibility locus on chromosome 6 was located in the MHC region p21.3, close to the HLA-C, as predicted from the HLA association studies. This locus, named PSOR1 (psoriasis susceptibility 1), was subsequently confirmed by several research groups and found to confer significant risk (35-50%) for development of psoriasis. However, since all psoriatic patients carry Cw6, it seems more likely that the PSORS1 gene was a gene close to HLA-Cw6 rather than Cw6 itself; subsequent studies using more precise mapping methods were consistent with this assumption. The identification of 11 further linkage sites on 10 different chromosomes followed and were numbered PSORS-2-PSORS7. It has been established over the last two decades that psoriasis is a T cell mediated disease. CD4<sup>+</sup> T cells are essential for initiating and maintaining the psoriatic process, and, when removed by treatment, the disease is temporarily switched off. Both dermal CD4<sup>+</sup> T cells and epidermal CD8<sup>+</sup> T cells each consist of small numbers of dominant clones that have expanded in situ, suggesting that unidentified antigens drive the disease process, namely *Streptococcus* and *Staphylococcus*. It is likely that other components derived from yeasts (*Malassezia* and *Candida albicans*) or viruses (HIV, retroviruses, papillomaviruses) which are associated with the triggering and/or exacerbation of psoriasis. Peptidoglycan is a strong activator of innate immunity, the immediate, non-specific response to pathogens which precedes the T cell response. Innate immunity in psoriasis has

become a current focus of research as evidence is emerging that the response to pathogens dysregulated, with a marked increase in the production of anti-bacterial peptides. Overall, the findings suggest that psoriasis may be an autoimmune T cell disease, triggered by infection (Baker '08:" 92-94, 110, 111).

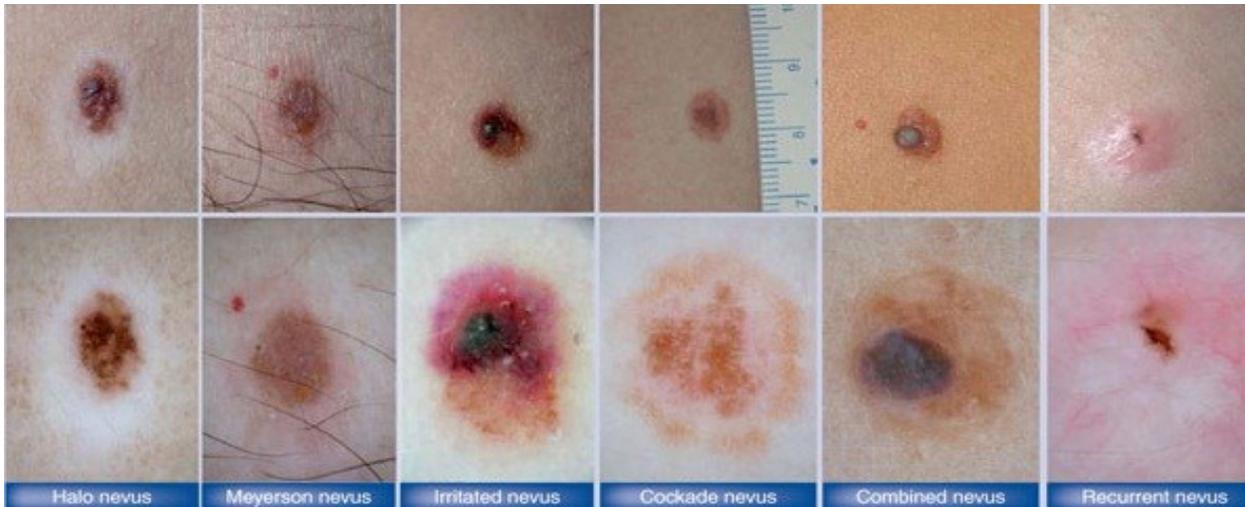


The word **birthmark** describes an abnormality either of skin's blood vessels or of the pigment-producing melanocyte cells in the skin. They are usually seen at birth but may appear within the first week or two of life. A number of minor blemishes are not actually visible at birth but are first seen at the age of 2- weeks. These will therefore not have been seen by the midwife or nurses involved with the delivery of the baby, or when the baby was checked prior to leaving the hospital. The most common type of birthmark is an abnormality of the blood vessels. These

abnormalities – **angiomas** – are very common and are present in as many as one baby in ten. Quite a large number of these angiomas first appear at the age of about 1 week. The most common type of angioma is a cavernous angioma, sometimes referred to as a **strawberry naevus** because the surface of the birthmark resembles a strawberry. This type of angioma begins as a small pinkish area anywhere on the skin surface, but most commonly on the head and neck. During the first 6 months or so of the baby's life these birthmarks tend to grow quite rapidly and become raised above the skin surface. These strawberry marks rarely grow for longer than 6 months, when they stop growing and will generally remain static for another 6 months or so. After this time they will slowly shrink and become very much paler. Thus, by the time the baby is aged around 2, a birthmark that was very obvious at 6 months is hardly visible at all and may only be seen as an area of paler, slightly wrinkled skin. There is no surgical or dermatological treatment that will give as good a final cosmetic result on the child's skin as letting nature take its course. When the strawberry mark is at its most obvious, between the ages of 6 months and one year, it can be rather fragile, and bleeding from these birthmarks is not uncommon, gentle pressure with a cotton ball stops bleeding fairly quickly (Mackie '92: 19, 20).

A second type of birthmark arising from blood vessels is called the stork mark or **capillary nevus**. This may be present in a very mild form on the nape of the neck or on the skin of the face between the eyes. A slightly more extensive form may be seen overing part of one cheek of the chin or forehead. These capillary nevi are frequently present at birth, and do not tend to grow above the level of the skin surface like the strawberry nevus. These capillary nevi do not tend to shrink spontaneously and without treatment they will remain unchanged. Until recently the best treatment for such vascular naevi was to provide a cosmetic cover-up cream. Laser treatment is effective but involves many sessions treating a small area. It is important to treat each area only once, to avoid scarring, and it is therefore essential for the patient to lie very still. Laser treatment for vascular birthmarks is being introduced in a small number of National Health Service hospitals in the UK, although it is more widely available in North America.

## Nevi



**Congenital melanocytic nevi** or moles are the other main group of birthmarks arising from the melanocytes. Most young adults have around 20 to 30 moles, usually between 2 and 4 mm in diameter, and the great majority of these first appear between the ages of 12 and 20 years. However, about one baby in a hundred is born with a congenital melanocytic naevi, or **mole**. This type of birthmark is usually present at birth, although, as with the blood vessel birthmarks, a small proportion first appear between the ages of 1 and 4 weeks. They are usually seen as a faint brown mark on any part of the body and may vary in size from about 1 cm in diameter to covering quite a large area of skin. Over the first few months of the baby's life these moles often become very much darker and occasionally there is a fine growth of downy hair. Babies born to darker-skinned parents frequently have a bluish mark present over the lower back area at birth. This is quite a normal finding in Asian babies, and is not associated with unusual hair growth; it is sometimes called a **Mongolian spot**. It usually becomes paler as the child grows and in time will disappear almost completely. Congenital melanocytic naevi or **brown moles** present at birth do not need any immediate treatment unless they start to grow or change in any way. Many specialists believe that removing the moles in later childhood, when the child is aged between 9 and 12 and can cooperate with a local anesthetic, is a good policy, to reduce the slight risk that a mole could become malignant and cancerous later in life (Mackie '92: 22, 23).



There are few problems found on the skin at birth. Of the many so-called birth marks, only the **superficial erythematous hemangiomas** at the nape of the neck (nuchal) and center of the brow (glabellar) are commonly seen at birth. Most of the glabellar hemangiomas disappear in later childhood while the nuchal ones can persist. **Port-wine type hemangiomas** may also be present at birth, but it is a rare defect. The well-known **strawberry or cavernous hemangiomas** usually are noticed at birth as only a small red spot on the skin surface and do not appear as obvious skin defects until the age of 3 or 4 weeks. Neonatal erythema is quite common but unimportant and the lesions fade without treatment in 2 to 3 days. The cause is unknown. **Mongolian spots** on the buttocks and sacral area are common. **Neonatal jaundice** is very common and can prove to be a diagnostic problem. A few growths, such as linear epidermal hamartomas are present on the skin at birth, but the more common true melanocytic nevi or "**moles**" found on the skin of almost every adult are rarely seen at birth. An exception is the congenital

**giant pigmented nevus**, which is extremely rare. Dermatitis is rare at birth, even **cradle cap** takes a few days after birth to develop. Acne and **milia** can be present at birth. The acne, as small comedones or pustules, may be related to the administration of progesterone to the pregnant mother. Other **rare dermatoses** present at birth may include several forms of ichthyosis, congenital aplasias (absence of nails, hair, glands, or areas of skin), congenital ectodermal dysplasia, incontinentia pigmenti in the blister stage, and epidermolysis bullosa (Sauer '85: 327).

**Baby skin** is thinner, less oily and more fragile than that of an adult, so it becomes irritated, sore and sunburned. Prominent sebaceous glands or whitish bumps may appear, both should disappear naturally in a few weeks. Blocked sweat ducts sometimes cause blisters. A baby's hair is usually very fine, and babies are frequently born blond and develop darker hair as they become older. A premature baby may be born with fine, long hairs – called lanugo hairs – covering the head, shoulders and back. These form in the fetus at around 20 weeks, but they are normally shed before a full-term birth. Babies are born with soft, rapidly growing nails that are almost always perfect – congenital abnormalities of the nail are very rare. Both sexes produce the hormone testosterone, which causes the sebaceous glands in hair follicles and pores to produce the natural oil known as **sebum**. When the body overproduces sebum, dead skin cells tend to clog the sebaceous glands, creating the blemishes that characterize acne. Sebaceous gland activity can also make hair greasier. Hormones also trigger the conversion of vellus hairs in the genital areas and armpits into terminal hairs – as well as the growth of facial hair and more terminal body hair in adolescent boys.



Up to 70 percent of pregnant women develop a condition called **melasma** (also called chloasma), in which the skin color of the forehead, temples and central part of the face darkens, because of an increase in estrogen in the bloodstream that usually settles down when the pregnancy ends. Mole size and activity may also increase (Devenport et al '03: 43). During pregnancy, the levels of circulating female hormones in the body are very much higher than normal. The skin is responsive to these hormones and, in general, the skin changes of pregnancy are flattering – most women feel that their skin is fresher and smoother-looking than before, and are very happy with the effect of their circulating hormones. Occasionally, in the first 3 months of pregnancy some women experience a temporary flare-up of acne. A high proportion of the hair on the scalp is in the active growing phase during pregnancy, and for this reason hair during pregnancy is often particularly thick, lustrous and healthy-looking. About 3 months after the birth much of the hair that was growing during pregnancy will switch into its normal shedding phase. For a few months the scalp hair will be a little thinner than normal, but in time the normal rhythm of hair growth and shedding will return. The pigment-producing melanocytes of the skin are mildly sensitive to female hormones. In women with darker, Hispanic or Mediterranean-type coloring, there are often quite striking changes in the skin's pigmentation during pregnancy. There is pigmentation on the mid-line of the skin of the stomach, around the nipples, and possibly around the cheeks and mouth. This 'chloasma', more descriptively, 'the mask of pregnancy' is made more striking by exposure to the sun. This pigmentation will fade after delivery of the baby but does not always disappear completely. During pregnancy many women find that their skin becomes slightly drier than usual. This will pass after delivery of the baby, but in the meantime a pleasant bath oil and possibly one of the cleansing ointments, such as emulsifying ointment BP, instead of soap for the body and a cosmetic cleansing preparation for the face can be used (Mackie '92: 57, 58).



The newborn is usually washed gently with a mild soap and then oiled daily. A skin problem can develop if the mother is too fastidious and bathes the skin excessively. This can cause dry skin (xerosis) or even a contact dermatitis. If there is a familial tendency toward atopic eczema then excess and too frequent bathing, especially in the winter, is definitely harmful. The lanolin in baby oils can also be irritating, and a switch to Vaseline Dermatology Formula Lotion or Cream. **Cradle cap** is a

yellowish, greasy, and crusted collection of vernix caseosa and shedding skin, caught around the hairs of the scalp. Non-fluorinated corticosteroid cream twice a day cuts down on inflammation and epidermal shedding and the use of a mild shampoo two or three times a week, followed by gentle removal of the scaling with a comb. Lack of daily bathing and adequate drying of the skin leads to bacterial or candida **intertrigo**. Diaper area dermatitis can be a manifestation of contact dermatitis, caused by too much bathing, or intertrigo caused by too little bathing. **Prickly heat** is a problem caused by the wrong environment, too many clothes, and/or too warm a room. One sees small, pinpoint sized vesicles or pustules localized or generalized. Treatment consists of removing the cause (fewer clothes or lower room temperature) and application of a calamine-type lotion three or four times a day. Children acquire most of the skin disease of adults, especially those that affect their parents (Sauer '85: 327-337).



**Eczema** is an inflammation of the skin that causes the sensation of itch and makes the sufferer want to scratch. An alternative name for eczema is dermatitis – the two terms mean exactly the same thing and it is not uncommon for some doctors to use the term eczema to describe the problem in babies and dermatitis in older children and adults. The two types of eczema which can affect young babies are seborrheic eczema and atopic eczema. **Seborrheic eczema** is now relatively uncommon, although 30 years ago it was a common problem in the large children hospitals in big cities. Seborrheic eczema usually affects small babies when they are less than 3 months old. It can be recognized by the presence of fairly extensive scaling on the scalp, like excessive dandruff, sometimes referred to as cradle cap. Seborrheic eczema is usually best treated by a small quantity of relatively mild topical steroid creams prescribed by a doctor. Seborrheic eczema generally clears up completely before the baby is 6 months old and is therefore only a temporary problem. **Atopic eczema** is often a more severe and persistent type of eczema than the seborrheic type. It tends to run in families and may be associated with chest problems, including asthma and hay fever. Babies with atopic eczema tend to look as if they are uncomfortable. Before their fingers are coordinated and they are able to scratch, a baby with atopic eczema will try to rub its cheek against the sheet or pillow, causing redness of the cheek's skin. Once they can coordinate their fingers, small scratch marks will appear on the face, and when the entire skin is exposed at bath-time the baby may try to rub and scratch its tummy and other parts of the body. Babies with atopic eczema are frequently irritable and tend to feed and sleep less well than other babies. Most babies who develop atopic eczema do so between the age of 6 months and 1 year. Atopic eczema is partly inherited. If one parent has a personal history of atopic eczema there is an increased risk of the child having the problem, if both parents have a history of atopic eczema the risk is further increased. Babies with atopic eczema often have a relatively dry skin for which bath oil should be used routinely. Suitable preparations include Hydromol, Alpha Keri, and Oilatum; select, non-perfumed, lanolin-free bath oil, can give rise to allergies. People with atopic eczema do not react to the cold sore virus in the normal way, and instead of lifelong immunity after one mild infection, are

prone to repeated attacks of small blisters, usually on the upper lip, and if they come into contact with someone with a cold sore, may develop quite a severe and widespread infection. While this can be treated with Acyclovir. It is important that a baby with eczema should not come into contact with anyone who has the cold sore virus (Mackie '92: 25-28).

Common **childhood skin infections** include (1) measles, caused by the measles virus, (2) german measles, caused by the rubella virus, (3) chickenpox, caused by a pox virus, and (4) scarlet fever, caused by streptococcus (Mackie '92: 31). Other common skin infections of childhood are infection with the common wart virus, infection with bacteria causing impetigo, and other rarer problems. Very few children go through childhood, without at some stage developing warts on the hands, face or feet. The Latin name for warts is verruca, and plantar warts, found on the soles of the feet, are often called verrucae. The most common lace for warts to develop is on the fingers around the finger-nails. Many children have two or three small warts in this area. These warts frequently disappear of their own accord after 3-6 months and cause no problems. During this time the child may pass the wart virus to the hands of one of his or her friends or to a brother or sister, but as hand warts are so common it is almost impossible to prevent this happening. There are a number of wart paints on the market that contain materials designed to encourage peeling of the skin and minor irritation. These wart paints have been shown in scientific studies to be of some value. They are very safe and be bought over-the-counter. It is worthwhile purchasing one of these wart paints and applying it regularly every night for a month or two to the warts before asking a doctor for more effective, but also more painful treatment – freezing with liquid nitrogen. Verrucae, or warts on the feet, tend to be more troublesome and frequently cause pain. They therefore require earlier and more vigorous treatment than hand warts. The child should be prevented from running around the house with bare feet and encouraged to wear at least socks, and preferably slippers, to stop the wart virus being shed on the carpet of the bedroom or playroom for the next barefooted child along to pick up. Spread of the war virus in the bathroom should also be avoided and the child with plantar warts should have his or her own towel and bath-mat. Children occasionally develop small, rather flat warts on the face, particularly on the cheek. These are called plane warts and although they are much smaller than the warts found on the hands and on the feet, they are unusually difficult to treat and often sit stubbornly on the skin. In time the child will develop immunity to the wart virus and the plane warts will disappear spontaneously, leaving no mark and no scarring. It is very difficult to treat plane warts without damaging the delicate facial skin, and freezing should be delayed (Mackie '92: 31, 34-38).

The most obvious effects on the skin of the sudden surge of hormones through the bloodstream between the ages of about 10 and 14 are on the sebaceous, or grease-producing, glands, and the hair. The **sebaceous glands** have lain dormant since birth but with the stimulus of hormones they suddenly become very active. These glands are found in their creates numbers on the forehead, the nose, the central part of the cheeks, and the chin. This central panel of the face will become shiny and greasy because the sebum form these very active glands is coming to the skin surface through the small openings of the pilo-sebaceous follicles, or 'pores'. If this sebum is regularly washed away with soap and water, the skin will usually remain smooth and healthy-looking, but in some teenagers the amount of sebum trying to et to the surface is so great that the opening of the follicle becomes blocked at the skin surface. This blockage quickly becomes blackened, as a result of exposure to the air and the result is a blackhead. If this is not dealt with rapidly, it can be the beginning of acne. Girls will frequently find their greasy skin is particularly troublesome in the week or so before their period is due. The best specific aid to coping with teenage skin is regular use of soap and water. Teenage skin needs the drying effect

of soap, and does not require greasy moisturizing agents or emollients. Teenage hair will become greasy and lank if not shampooed frequently. Many teenagers wish to shampoo their hair daily, and this will do no harm. Teenage skin miseries can be partly controlled, if not completely prevented, by a sensible lifestyle. A balanced diet, regular mealtimes, plenty of fresh fruit and vegetables, half-an-hour in the fresh air each day and a regular exercise program are all good for the body in general, including the skin. Late nights, stuffy discos and a diet of sweets and chips do not help anyone to look their best. A deodorant or anti-antiperspirant may be needed in the armpits (Mackie '92: 42, 43).

Studies on teenagers in the UK have suggested that it is normal rather than abnormal to have at least a mild degree of acne, which is not usually called acne at all but just thought of as a few spots at some time during the teenage years. The problem usually begins earlier with girls than with boys. Girls will find their acne problems more troublesome between the ages of 13 and 16, while for many boys the problem does not start until about 15 and goes on until the age of about 19. Some people suffer from lingering problems with acne after the teenage years, but this is the exception. Mild acne usually involves the face, and the area most commonly affected is the central panel – forehead, the nose and the chin. Many teenagers have a few blackheads in these areas. If the problem with obstructed outflow continues, the sebum trapped on the way to the surface of the epidermis may leak into the surrounding dermis. When this happens the problem changes from being just a simple blackhead to being a raised, inflamed papule or spot on the skin. Sometimes these red spots develop unsightly yellow heads. As well as involving the face, acne may involve the front of the chest and, particularly in boys, the back over the shoulder area. Blackhead extractors are sold in pharmacies but must be used with care and should always be sterilized in boiling water after use, they should not be used just before going out to meet friends, as for an hour or two after applying pressure to the skin around blackheads and spots, the skin will be inflamed and red. Treatments applied to the skin are very often based on benzoyol peroxide, which is a drying, mildly antiseptic preparation. When first used it can cause some dryness, redness and minor irritation. This is part of the treatment, and the preparation should not be stopped because this happens. After about a week the redness usually disappears, as do the blackheads.

Another approach to managing mild acne is the use of **oral antibiotics**. These are prescribed not because acne is an infection, but because, among other things, antibiotics appear to alter the movement of the white cells normally found in the blood vessels, and it is these white cells – leucocytes – that are responsible for the yellow tops of spots on the skin. By altering the way in which they move into the skin, antibiotics make inflamed spots less likely. Tetracycline antibiotics, ideally doxycycline 'the once a day antibiotic', are prescribed for the treatment of acne. However, tetracycline cannot be prescribed if there is any possibility of pregnancy, or in children under the age of 8, because it can cause yellow stain on the bones and permanent teeth. Ideally it should be taken with a glass of water half-an-hour or so before a meal, so that it can be absorbed through the lining of the stomach; if it is taken with food it may not be absorbed. Treatment applied directly to the skin usually takes a week or two to have an effect, and the usual waiting time for an oral antibiotic is 1-2 months. For acne a low dose of antibiotic is prescribed for a long period of time. Many acne sufferers have to take tetracyclines for 6, 9 or even 12 months. Fortunately, tetracyclines are safe preparations (in children over 8 as it causes permanent yellowing of developing permanent teeth) and there are no long-term side-effects (Mackie '92: 45-48). Doxycycline is also a first line treatment for pneumonia (particularly throat infections), syphilis and tuberculosis, and only needs to be taken once a day. Long term use will however cause the depletion of gut flora that must be corrected by the daily consumption of at

least 25 billion probiotic organisms daily, found in yoghurt, kefir or as a dietary supplementation capsule, to prevent antibiotic associated colitis.

For girls the use of a hormonal combination similar to that found in the **oral contraceptive pill** may well be of value in the management of acne. The hormonal combination most commonly prescribed for acne is Dianette, starting 5 days after the period has begun and continuing for 21-22 days. As with other forms of treatment for acne, there is usually a large period of 2 to 3 months before any benefit can be expected, and most should be discontinued after 9 months to a year, to be sure their own hormones are still working in the normal manner, and they have not developed any small cysts, common in those receiving hormonal therapy. An alternative treatment for acne in both sexes is a synthetic, vitamin A-like drug called Roaccutane in Europe and Accutane in the US. This has a very dramatic effect on the sebaceous glands. If small samples of skin are removed before and 4 months after oral Roaccutane and compared under microscope, it will be seen that after Roaccutane treatment the sebaceous glands have shrunk dramatically to a size similar to that found in small children before puberty. As the sebaceous glands shrink, their secretion of sebum dries up. The lips tend to dry and crack in the way which they may do when exposed to cold winter weather, and the lining of the nose may become dry, giving a permanent feeling of a stuffy nose and sometimes resulting in nose bleeds. The secretion of tears is also affected and there are complaints of dry-feeling, gritty eyes. The level of circulating fats in the blood may also become elevated, it is therefore necessary to get a blood sample checked, it is rare to have to cut treatment short because of this, but the levels return rapidly to their pretreatment state. All of these side-effects are relatively easy to put up with provided the acne sufferer has severe acne and knows the treatment is doing good. Accutane can damage an unborn child if taken by a young woman who is in the early stages of pregnancy, resulting in very serious defects of the heart, the hearing system and other organs. A standard course of Roaccutane usually lasts 4 months and the risk to an unborn child is so serious that most specialists will not prescribe Roaccutane unless the girl who wishes treatment for her acne is prepared to take the oral contraceptive for a month before starting Roaccutane, continue the oral contraceptive for the full 4 months of Roaccutane treatment and for another month after the Roaccutane course ends. Thus a 4 month course of Roaccutane involves a 6 month course of treatment with an oral contraceptive (Mackie '92: 48-50). One of the compensations of having teenage eczema is that acne will almost certainly not occur. The skin should be prevented from drying out by having a warm, not hot, daily bath with an added emollient. Baths are better for dry skin than showers. A cleansing ointment (such as emulsifying ointment BP or unguentum Merck) should be used instead of soap and creams may be prescribed (Mackie '92: 56).

Between the ages of 12 and 20 it is normal to develop a sprinkling of small, flat, brown marks on the skin surface, mostly where exposed to sunlight. These small **moles** are entirely normal. The great majority are smaller than 3-4 mm in diameter and can be covered with the blunt end of a pencil. The average young adult in North America and the UK has between 20 and 40 of these small moles scattered over his or her skin. They are entirely normal and the vast majority will remain present on the skin for around 20 years and will then slowly disappear in middle age. Older people have very few moles on their skin. Occasionally, particularly in boys, an interesting halo of white skin appears round a small mole, mostly on the back, this is called a **halo naevus**, and is nothing to worry about. The white area that is left when the mole disappears will persist for some time, often 2 or 3 years, before the normal skin color returns. During this time, the mole must be protected from sunlight. Occasionally, moles become inflamed and lumpy. This most often happens to moles on the face, particularly if the mole has one or two protruding hairs. The reason for this sudden inflammation is often that the hair follicle has

become irritated and inflamed. To remove the mole a small operation under a local anesthetic may leave a small scar (Mackie '92: 53-55).

In the middle years, the dermis begins to hold less water and fat so skin loses its "roundness" and starts to **sag**. The skin becomes less resilient because fewer elastic fibers are produced. It becomes dry in response to less sebum production, and cell renewal takes longer, so older cells remain on the skin surface longer, causing creases and wrinkles. This process is apparent in most people by their late 40s; in those who have spent time in the sun or who smoke, it becomes apparent earlier. Hair begins to turn gray, and some people start to lose their hair. The age at which this happens is genetically determined, but, like the skin, the hair is also affected by UV radiation from the sun, becoming dry and coarse after a lot of sun exposure. As the body gets older, the nails, particularly the toenails, and life starts to take its toll on the feet and nails, with the development of problems such as hard skin. As the body ages, the skin becomes increasingly thinner and more wrinkled because of loss of elasticity, collagen, moisture and fat. Exposure to UV rays speeds up this aging process, especially in Caucasian skin. In addition, the number of melanocytes in the skin gradually decrease with advancing age, making skin even more susceptible to UV damage and so also to skin cancer. With advancing years, the amount of sebum produced falls (slightly in men, significantly in women) so that skin becomes drier and less supple. The amount of collagen in the skin decreases by about 1 percent per year through adult life – more in women after menopause – causing skin to sag. Fewer fibroblasts are present in the dermis, so wounds heal more slowly. Over the age of 70, the skin is less able to regulate body heat, which is why the elderly are so much more susceptible to the effects of severe cold weather (Davenport et al '03: 34, 35).

### Aging Skin Conditions



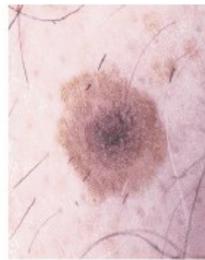
Seborrheic  
keratosis



Benign  
nevus



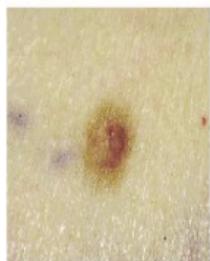
Solar  
lentigo



Dysplastic  
nevus



Actinic  
keratosis



Pigmented  
actinic keratosis



Malignant  
melanoma



Malignant  
melanoma



Basal cell  
carcinoma



Squamous  
cell carcinoma

Source: Research Gate

Some of the earliest signs of aging of the skin are the development of **hyperpigmented macular lesions** known as freckles, age spots, liver spots and lentigines. These can begin in individuals in

their 40s. They develop most commonly on the dorsum of the hands and on the face, in direct proportion to the genetically determined fair complexion of the individual and the dosage of sun gained through the earlier years of life. On the face, and to a lesser extent on the rest of the body, wrinkling of the skin also progresses with age. Diffuse hyperpigmentation of the face and hands, again in the sun-exposed areas, becomes more definite with age. Hyperpigmentation on the side of the neck, which is a combination of red and brown discoloration, seen particularly in women, is called **poikiloderma of Civatte**. **Actinic keratoses** have a predilection for sun-exposed area of the body. Seborrheic keratoses are very common and can be so black and angry looking they can be confused with malignant melanoma. Another manifestation of aging is the development of comedones on the face lateral to the orbicular area. **Pedunculated fibromas** and pedunculated seborrheic keratoses are extremely common on the neck and axilla. These can begin in the 40s and 50s. Almost every elderly individual has small, bright red capillary hemangiomas of no clinical significance. One the legs is very common to see dry skin or xerosis. As people age, they need to cut down on their frequency of bathing, especially in the winter. Winter itch is quite common on the legs and can make the patient miserable, treatment is corticosteroid ointment and less frequent bathing. Bruising occurs more frequently on aging skin. The color of the entire skin becomes pale and opaque. The hair develops varying shades, from grayness to pure white color in certain individuals. The male-pattern alopecia, which can begin in the late teens, becomes progressive through life. For the elderly patient, balding manifests as a diffuse thinning of the scalp, hair. This senile alopecia can occur in both males and females. The sebaceous glands and sweat glands become less active in older age. The mucous membranes become drier. The role of both corticosteroids and antibiotics in decreasing the number of elderly patients needing hospitalization is enormous (Sauer '85: 343-345).



From the age of about 40 onwards, skin care is mainly directed towards preventing dryness. A dry skin is a **wrinkled skin** and wrinkles are generally associated with 'aging'. The skin on the face of a healthy 60 year old shows some fine wrinkles, perhaps some deeper lines, a few broken veins on the cheeks, and some variation in the skin color. By contrast, the skin on the buttocks is usually smooth, soft and a uniform color. One of the best demonstrations of aging is a comparison of the skin of someone who has lived all their life in Northern

Europe or the northern US with that of a relative of a similar age who emigrated to Australia or to the southern part of the United States early in life – the relative who emigrated will usually look older for their years because of the weathering and aging effect of constant sunshine on the skin. Smoking is associated with wrinkles. People who had a relatively oily or greasy skin as teenagers, and who may have suffered from acne, have the compensation that as they grow older their skin will often look younger for longer because they have had a greater regular output from their sebaceous glands. Those who had perfect 'normal' skin as teenagers will usually find on the other hand that their skin is looking drier earlier. The signs that skin is becoming a little more mature are the appearance of wrinkles at the sides of and under the eyes, very often around them, and often on the neck. This is also frequently associated with a steady drying of the skin on the hands, particularly on the backs, and dryness and sometimes with fine scaling, of the shins of the lower legs, particularly during the winter months. Any part of the skin that is habitually dry, feels tight after washing or has fine scaling needs some additional replacement of moisture by a moisturizing cream (Mackie '92: 69-73).

Small cherry-red spots, very often only 1-2 mm in diameter, may develop on the trunk; several may appear at any one time. The medical name for these is **Campbell de Morgan spots**, after the individual who first described them. They are of no particular importance and are in no way any type of skin cancer or precancerous change in the skin. Unless they are causing problems they should be left alone. Also very common are the small warty, slightly scaly, brown areas a little bit raised above the skin surface that appear on covered and uncovered skin – **seborrhoeic warts**, seborrhoeic keratoses and basal cell papillomas. They are a minor and unimportant overgrowth of the more superficial part of the skin, the epidermis. Although one of the names for these little changes is a seborrhoeic wart, they are not caused by the wart virus. These little scaly lesions are usually quite easily kept under control by the regular gentle use of a loofah in the bath to remove any superficial scaling from their surface. They can be easily removed either by freezing or by the use of an electric needle. A third minor change, usually found on facial skin in older people, is the appearance of little broken blood vessels or small capillaries, usually seen on the cheeks and nose of people who have always had a high coloring. These are difficult to remove and, once developed, are best treated by a light covering of cosmetic. Women in this age range may also be concerned about a reddish brown, almost stain-like, mark on the side of the neck. The dermatological name for this is **berloque dermatitis**, and it is a result of applying perfume or toilet water to the sun-exposed skin of the neck. The sunlight and the perfume interact, and this discoloration is the result. The simple solution is to spray the perfume on to skin that is not exposed to light where it will not cause any discoloration (Mackie '92: 73-75). **Varicose veins** of the lower legs can give rise to stasis dermatitis or eczema and varicose ulcers. If varicose veins are left untreated the area of skin on the inside of the ankle area may become red or even brown in color, irritable, and itchy. This is varicose dermatitis, and is a sign that blood from the veins has leaked into the surrounding skin; a swollen vein will often be seen close to this area. If this vein is bumped and damaged, for example during a fall, it may break down completely and a stasis or varicose ulcer will result. Once formed, these are both very difficult to heal and keep healed, because the skin is already so badly damaged by the varicose veins and eczema. Many older people have chronic problems with their feet. Once **bunions**, corns and callosities have developed, the problem of finding comfortable shoes becomes even greater. Poor circulation may lead to cold feet, and the desire to warm them quickly with hot water, using a hot water bottle, or by the fire. Rapid rewarming of cold feet can cause chilblains, so try to stop the feet becoming cold by wearing warm socks and roomy shoes or winter boots (Mackie '92: 73-76, 78, 79).

### III. Oncology

#### 1. Skin cancer

**Skin cancer** is the most commonly diagnosed cancer in the US. However, the actual number of the most common types – basal cell and squamous cell (i.e., keratinocyte carcinoma or KC), also referred to as non-melanoma skin cancer – is difficult to estimate because cases are not required to be reported to cancer registries. The most recent study of KC occurrence estimated that in 2012, 5.4 million cases were diagnosed among 3.3 million people. Invasive melanoma accounts for about 1% of all skin cancer cases, but the vast majority of skin cancer deaths. In 2020, an estimated 100,350 new cases of melanoma will be diagnosed in the US and 6,850 people will die from the disease. Incidence is most common among non-Hispanic whites, who have an annual rate of 28 cases per 100,000, compared to 7 in American Indians/ Alaska Natives; 5 in Hispanics; and 1 in non-Hispanic blacks and Asians/Pacific Islanders. Incidence rates are higher in women

than in men before age 50, but by age 65, rates in men are double those in women, and by age 80 they are triple. This pattern largely reflects age and sex differences in historical occupational and recreational exposure to ultraviolet radiation, although use of indoor tanning among young women also contributes. Differences in early-detection practices and use of health care may also play a role. The overall incidence of melanoma of the skin rose rapidly over the past 30 years, but trends in the past decade vary by age. From 2007 to 2016, the rate decreased by 1.2% per year in individuals younger than 50 years of age while increasing by 2.2% per year among those ages 50 and older. Mortality trends also vary by age, with a declining trend in individuals younger than 50 years of age since the mid-1980s, but only in the past decade in older adults. Advances in treatment have accelerated declines in the past five years; from 2013 to 2017, the death rate for melanoma declined by 7.0% per year in adults younger than 50 years of age and by 5.7% per year in older adults (ACS '20: 24).

For melanoma, **major risk factors** include a personal or family history of melanoma and the presence of atypical, large, or numerous (more than 50) moles. Excess exposure to ultraviolet (UV) radiation from sunlight or the use of indoor tanning increases risk of all common types of skin cancer. Risk is also increased for people who are sun-sensitive (e.g., sunburn easily or have natural blond or red hair color) and those who have a history of excessive sun exposure (including sunburns) or skin cancer. Risk is also increased in people with a weakened immune system and certain genetic syndromes. Most skin cancer cases and deaths are caused by exposure to UV radiation, and thus potentially preventable. Exposure to intense UV radiation can be minimized by wearing protective clothing (e.g., long sleeves, a wide-brimmed hat, etc.); wearing sunglasses that block ultraviolet rays; applying broad-spectrum sunscreen that has a sun protection factor (SPF) of at least 30 to unprotected skin as directed; seeking shade; and not sunbathing or indoor tanning. Children and adolescents should be especially protected from the sun (and indoor tanning) because severe sunburns early in life may particularly increase risk of melanoma. Communities can help prevent skin cancer through educational interventions in schools and providing shade at schools, recreational sites, and occupational setting. In 2014, the US surgeon general released a Call to Action to Prevent Skin Cancer because of the growing burden of this largely preventable disease. The purpose of this initiative is to increase awareness and encourage all Americans to engage in behaviors that reduce the risk of skin cancer. The best way to detect skin cancer early is to be aware of new or changing skin spots or growths, particularly those that look unusual. Any new lesions, or a progressive change in a lesion's appearance (size, shape, or color, etc.), should be evaluated promptly by a clinician. Periodic skin examination, perhaps with the help of a partner for areas that are hard for you to see, may be helpful in identifying changes (ACS '20: 24).

**Warning signs** of all skin cancers include changes in the size, shape, or color of a mole or other skin lesion; the appearance of a new skin growth; or a sore that doesn't heal. Changes that progress over a month or more should be evaluated by a clinician. Basal cell carcinoma may appear as a growth that is flat, or as a small, raised pink or red translucent, shiny area that may bleed following minor injury. Squamous cell carcinoma may appear as a growing lump, often with a rough surface, or as a flat, reddish patch that grows slowly. The ABCDE rule outlines warning signs of the most common type of melanoma: A is for asymmetry (one half of the mole does not match the other half); B is for border irregularity (the edges are ragged, notched, or blurred); C is for color (the pigmentation is not uniform); D is for diameter greater than 6 millimeters (about the size of a pencil eraser); and E is for evolution, meaning a change in the mole's appearance over time. Not all melanomas have these signs, so be alert for any new or changing skin growths or spots.

Most early skin cancers are diagnosed and treated by **removal** and microscopic examination of the cells. Most cases of KC are cured by removing the lesion through minor surgery or other techniques (e.g., freezing). Radiation therapy and certain topical medications may be used. For melanoma, the primary growth and surrounding normal tissue are removed and sometimes a sentinel lymph node is biopsied to determine stage. More extensive lymph node surgery may be needed if the sentinel nodes contain cancer. Melanomas with deep invasion or that have spread to lymph nodes may be treated with surgery, immunotherapy, chemotherapy, and/or radiation therapy. The treatment of advanced melanoma has changed greatly in recent years, with FDA approval of several new immunotherapy and targeted drugs that can be very effective. Chemotherapy may be used but is usually much less effective than newer treatments. Almost all cases of KC can be cured, especially if the cancer is detected and treated early. Although melanoma is also highly curable when detected in its earliest stages, it is more likely than KC to spread to other parts of the body. The 5-year relative survival rate for melanoma is 92%. Eighty-four percent of cases are diagnosed at a localized stage, for which the 5-year survival rate is 99%. More than half of patients diagnosed with distant-stage disease now survive at least one year because of recent advances in treatment (ACS '20: 25).

Tumors arising from the epithelial cells of the skin are the **most common malignancies** of human beings; more than 400,000 new cases are estimated to occur annually in the United States. The most important etiologic factor is probably chronic exposure to ultraviolet radiation. Residence at equatorial latitudes, lightness of skin and hair color, blue or gray eyes, freckling, easy burning and poor tanning, and a history of outdoor occupation all indicate increased risk. Thus skin cancer is much more common in whites than in blacks, has an increasing incidence with age, and favors solar-exposed areas of skin, such as the head and neck, and the dorsa of the hands. Other risk factors include industrial exposures to tar products and ingestion of arsenic from contaminated water, medicines (Fowler's solution), or herbicides and pesticides. Skin cancer also occur as sequelae of occupation or therapeutic exposure to ionizing radiation, chronic infections, burns, trauma, and immunosuppression. They are also associated with some well-established premalignant conditions of the skin (actinic keratoses, Bowen's disease, and erythroplasia of Queyrat), as well as with certain heritable disorders (xeroderma pigmentosum, albinism and the basal cell nevus syndrome) (Wittes & Sober '90: 329). Some 10 percent of skin cancers occur in a familial setting. Most sporadic and non-familial skin cancers occur after the age of 50, although melanoma is now a leading cancer type in young adults. The highest risk is for those with a fair skin and poor tanning ability. Black skinned groups are at a much lower risk of skin cancer. Living on the north east coast of Australia (Queensland) is perhaps the biggest risk though, only to Caucasians, not Aborigine. For many skin cancers there is convincing evidence that UVB is the directly offending agent. UV damages DNA in a manner that leaves a unique chemical footprint, a simple but consequential code change in DNA that converts a nucleotide base C (cytosine ) type to a T (thymine) type. **Skin cancer** is the most prevalent form of all cancers in the U.S. and the number of cases continues to rise. Currently around 20 percent of melanomas prove fatal and yet all are potentially curable by simple surgical excision (Greaves '00: 177, 259).

**Sun exposure** is not always harmful, in fact, exposure to the sun is necessary to protect you from disease. Sunlight is a great source of vitamin D that should be embraced through moderate exposure. Four hundred IU of vitamin D is the bare minimum daily dose, that can be had by exposing the face and arms to 15 minutes of light a day, to prevent rickets and other vitamin D-deficiency diseases, but it won't give the same protection as 15-30 minutes of exposure to very

bright sunlight each day. 10,000 IU for a short time may be needed to raise depleted levels. Vitamin D deficiency can be tested with a test called 25-hydroxy-vitamin D – 25(OH)D. Sunscreens won't work if they have less than SP15 protection or if they are out of date. Only buy products with titanium dioxide or zinc oxide (Fuchs '07: 24, 26). It has been calculated that if the skin of children and teenagers were protected at all times from excessive sun exposure, then 78% of all skin cancers that develop later in life could be prevented. Over half of the sun exposure that a normal individual receives in their entire life takes place during childhood (Mackie '92: 30).

### Types of Skin Cancer



Credit. Medicinenet.com, left squamous cell carcinoma, upper right basal cell carcinoma and lower right malignant melanoma.

There are three main types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal and squamous cell cancers are less serious types and make up 95 percent of all skin cancers and are highly curable. **Melanoma**, made up of abnormal skin pigment cells called melanocytes, is the most serious form of skin cancer and causes 75 percent of all skin cancer deaths. Left untreated, it can spread to other organs and is difficult to control. Ultraviolet (UV) radiation from the sun is the number one cause of skin cancer, but UV light from tanning beds and winter sun is just as harmful. Cumulative sun exposure causes mainly basal cell and squamous cell skin cancer, while episodes of severe sunburns, usually before age 18, can cause melanoma later in life. Other less common causes are repeated X-ray exposure, scars from burns or disease and occupational exposure to certain chemicals. The risk is greatest for people who have fair or freckled skin that burns easily. **Basal cell carcinoma** may appear as a small smooth, pearly or waxy bump on the face, ears, and neck, or as a flat/red or brown colored lesion on the trunk or arms and legs. **Squamous cell carcinoma** can appear as a firm, red nodule, or as a rough, scaly flat lesion that may itch, bleed and become crusty. Both basal cell and squamous cell cancers mainly occur on areas of the skin frequently exposed to the sun, but can occur anywhere. **Melanoma** usually appears as a pigmented patch or bump, it may resemble a normal mole, but usually has a more irregular appearance. Standard treatments for non-melanoma skin

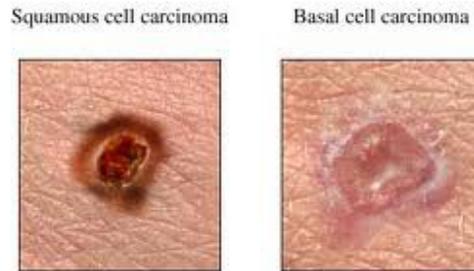
cancer (basal cell or squamous cell carcinomas) include: Mohs surgery excision of cancer and some extra tissue; electro-desiccation and curettage, cryosurgery, laser therapy and drugs (chemotherapy, biological response modifiers). The topical application of blood root seems to be the most readily available, effective treatment of squamous and basal cell carcinomas. Standard treatments of melanoma skin cancer include: wide surgical incision, sentinel lymph node mapping (for deeper lesions) to determine if the melanoma has spread to local lymph nodes for the use of drugs (chemotherapy, biological response modifiers) and radiation therapy (Mooney '07: 21-23).

The most common forms of skin cancer –basal cell carcinomas, squamous cell carcinomas and malignant melanomas – arise from the epidermis of the skin. On the other hand, mycosis fungoides which has an effect on the skin via the immune system, affects less than one in 10,000 people. The most common form of skin cancer is a **basal cell carcinoma (BCC)**. It is sometimes referred to as a rodent ulcer because the growth does not spread elsewhere in the body but very slowly nibbles away at local tissue in a rodent-like manner. BCC does not spread to other areas of the body. If left untreated, BCC can disfigure. There are about 1 million cases of BCC each year in the U.S. alone. There is no doubt that a major cause of BCCs is long-term exposure to sunlight. They are more frequently seen in people older than 50 but now younger people are developing such cancers. Treatment of these tumors depends on the type of tumor present, where it is located, its size, and the general health of the patient. The tumor can be removed by curettage and cautery, cryotherapy using liquid nitrogen, ablative laser therapy, excision of the actual growth, radiation, topical therapy with a cream such as 5-Fluorouracil can produce a good cure. 40 percent of patients develop a new BCC within 5 years of the first.

**Squamous cell carcinoma (SCC)** is the second most common type of skin cancer in the U.S. An SCC often takes the form of a lump, which may ulcerate, become crusty and bleed, and be quite painful to touch. There is a small risk of such a tumor spreading to another part of the body. It is estimated that about 1.2 million SCCs are diagnosed every year in the U.S. The main aims of treatment are the destruction of primary growth and prevention of the tumor spreading elsewhere. Surgical excision is the treatment of choice, curettage and cautery can produce a good result, and radiation can be effective. Bloodroot is effective on superficial SSC. Malignant melanoma is the most worrisome type of skin malignancy. About 54,000 melanomas are diagnosed in the United States every year. A malignant melanoma can occur spontaneously or can develop from a preexisting mole. The principle treatment for malignant melanoma remains surgical intervention. The mole is removed with a safety margin of skin around the mole to ensure that all the cancerous cells have been removed. After the mole has been removed, a patient is given a full skin check at regular for at least 5 years (Davenport et al '03: 130-132).

**Basal cell epithelioma** is the most common malignancy of the skin. Fortunately, it is not a metastasizing tumor, and the cure rate can be 100% if these lesions are treated early and adequately. There are four clinical types of basal cell epitheliomas (1) noduloulcerative, (2) pigmented, (3) fibrosin (sclerosing), and (4) superficial. The noduloulcerative basal cell epithelioma is the most common type. It begins as a small waxy nodule that enlarged slowly over the years. A central depression forms that eventually progresses into an ulcer surrounded by the pearly or waxy border. The surface of the nodular component has a few telangiectatic vessels, which are highly characteristic. The pigmented type is similar to the noduloulcerative form, with the addition of brown or black pigmentation. The fibrosing type is extremely slow growing, usually seen on the face, and consists of whitish, scarred plaque with an ill-defined border, which rarely becomes ulcerated. The superficial form may be single or multiple, usually

on the back and chest and characterized by slowly enlarging, red, scaly areas that, on careful examination, reveal a nodular border with telangiectatic vessels. A healed atrophic center may be present. Ulceration is superficial when it develops. Over 90% of the basal cell epitheliomas occur on the head and neck. Exposure to inorganic arsenic can lead to formation of superficial basal cell epitheliomas. Destructive forms of this tumor can invade cartilage, bone, blood vessels, or large areas of skin surface and result in death. Basal cell epitheliomas must be differentiated from squamous cell carcinoma and other lesions. Surgical excision is recommended.



Credit: Veteran's Today

**Squamous cell carcinoma** is a rather common skin malignancy that can arise from an actinic keratosis or leukoplakia. The grade of malignancy and metastasizing ability varies from grade I (low) to grade IV (high). Other terms for this tumor include prickle cell epithelioma and epidermoid carcinoma. Squamous cell carcinoma present as a rapidly growing nodule that soon develops a central ulcer and an indurated raised border with some surrounding redness. This type of lesion is the most malignant. The least malignant form has the clinical appearance of a warty, piled up growth, which may not ulcerate. The lesion can occur on any area of the skin and mucous membrane but most commonly on the face, particularly lower lip and ears, tongue and dorsum of the hands. The cure rate can be high when lesions are treated early. Most occur in elderly males. Squamous cell carcinoma must be differentiated from basal cell epithelioma, actinic keratosis, pseudoepitheliomatous hyperplasia and keratoacanthoma (that may disappear spontaneously) (Sauer '85: 308-310).

**Nonmelanoma skin cancers** are the most curable malignant tumors of human beings. Most tend to remain localized. Although basal cell carcinomas (BCC) are capable of metastasis only about 400 cases late in the course of inadequately controlled local disease have been reported. Squamous cell carcinoma (SCC) behaves more variably. The usual SCC arising in light-exposed areas of skin damaged by chronic ultraviolet exposure has a low incidence of metastasis. By contrast SCC in shaded parts of the anatomy are much more likely to metastasize. SCC after radiation metastasizes in about 20% to 25% of cases. There is no staging system for nonmelanoma skin cancers because metastasis is so rare. The goal of therapy ought to be the expeditious removal of all viable tumor in a manner that ensures a satisfactory cosmetic result. Surgical excision, electrodesiccation and curettage, cryotherapy and microscopically controlled "fresh-tissue" surgery are the available modalities. If the tumor is large a flap or skin graft may be necessary. **Curettage and cryotherapy** are most useful for small (<10 mm diameter) BCC that is located on flat surfaces or tumors having depth no greater than the dermis or at most the upper subcutaneous layer. It appears that **cisplatin** has antitumor activity, singly or in combination with bleomycin or doxorubicin, has produced major regression of tumor in selected cases. **Premalignant lesions** of the skin are all amenable to treatment before invasive cancer

develops. Actinic keratoses can be removed by excision, curettage or cryotherapy. **Bloodroot** desquamitive ointment is effective. For patients with multiple lesions, topical **5-fluorouracil** (5-FU) is effective, 1% to 5% 5-FU cream or gel is applied twice daily for 10 to 21 days or longer until marked erythema and crusting develop in the treated skin; the lesions are then allowed to slough and re-epithelialize. Bowen's disease may be treated in a similar fashion, however, if 5-FU is employed it must be of longer duration and under occlusion. Leukoplakia occurring in the setting of chronic tobacco usage should probably be treated with **isotretinoin** (13-cis-retinoic acid), 1 mg to mg/kg/day for 3 months significantly decreases the number and size of leukoplakia lesions in such patients. Because of a potential side-effects an experienced physician is recommended, pregnancy is an absolute contra-indication (Witte & Sober '90: 329-331).

**Malignant melanoma** comprises approximately 2.4% of newly diagnosed cancer cases in the United States and 1% of cancer deaths. The incidence of **malignant melanoma** increased considerably in the 1970s. There were an estimated 5500 deaths from this neoplasm in 1986, and melanoma is now reportedly twice as common as Hodgkin's disease. By the year 2000 it is estimated that one individual in 150 will develop a malignant melanoma. Predisposing factors include heredity, complexion (fair skin, blue eyes), ultraviolet exposure (the incidence of melanoma in the United States is increased in those states nearer the equator), and the presence of a large bathing-trunk congenital nevi. The occurrence of one malignant melanoma in a patient confers a 900-fold risk of developing a second malignant melanoma compared with the general population. First degree relatives of patients with malignant melanoma are approximately to times more likely to develop a malignant melanoma than the general population. **Dysplastic nevus syndrome** (DNS) is an autosomal-dominant disorder characterized by irregular, atypical moles (nevi) (Creagan '90: 323). Fifty percent of melanomas arise from preexisting nevi. Although melanomas make up only 1% of all skin cancers, they account for 67% of the death due to skin cancer in the United States. The best chance for a cure lies in early diagnosis and prompt, adequate surgical and chemotherapeutic treatment of the primary lesion (Sauer '85: 319). Malignant melanoma is radioresistant (Ceagan '90: 326).

There are four major types of malignant melanoma. The most common is the **superficial spreading melanoma** which develops from an in situ lesions, it grows slowly with a resulting good prognosis. **Nodular melanomas** grow quite rapidly and have a poorer prognosis. **Acral lentiginous melanoma**, occurs on the palms, soles and around the nails, is the most common type seen in black patients, ulcerates and metastasizes rapidly, so that it has the poorest prognosis. **Lentigo maligna melanoma**, the least frequent type, develops from a lentigo maligna, occurs on the exposed areas of the body in the elderly, mainly on the forearms and face, grows slowly peripherally, and has a high survival rate. The classic malignant melanoma is a black to purple nodule, but it may be flat, or predunculated, and may be pink, red, tan, brown or black. **Malignant change** in pigmentation (particularly the development of pseudopodia or areas of satellite pigmentation), erythema surrounding the lesion, induration, friability with easy bleeding tendency and ulceration around a longstanding skin lesion should arouse suspicion. The greater the depth of involvement of the growth, the worse the prognosis. Malignant melanoma must be differentiated from benign nevus, pigmented basal cell epithelioma and subungual hematoma, history of recent injury. **Rapid and adequate therapy** after diagnosis and staging involves a wide surgical excision, lymph node dissection, chemotherapy and immunotherapy (Sauer '85: 319, 320).

## Mole Chart



Any skin lesion undergoing change in the size, color or texture of a nevus or freckle, especially if a lesion bleeds or scales, is suspected of being cancerous. A critical prognostic discriminant of malignant melanoma is the **vertical extension** of the primary lesion. A level I lesion is confined to the epidermis and does not have metastatic potential, whereas a level V lesion permeates the subcutaneous fat with a grave prognosis. The thickness of the melanoma is measured from the stratum corneum to the deepest penetration of the tumor rather than the level of the invasion. Eight-year survival varies with thickness in the following manner: 99% +/- 1% (<0.85 mm); 93% +/- 2% (0.85 mm – 1.69 mm); 69% +/- (1.7 mm – 3.6 mm); and 38% +/- 6% (>3.6 mm).

**Surgical resection** is necessary. The safety of conservative margins was demonstrated in a review of 1151 patients with lesions less than 1 mm thick. Sixty-two percent had resected margins of 2 cm or less. Only 8% recurred locally, and the median survival of this group was 3 years. In another study of 118 patients, the survival of patients with lesions less than 2 mm thick was not influenced by the extent of resection and there was no apparent survival advantage for lesions 2 mm or more in thickness by increasing the margins of resection to more than 3 cm. Survival was substantially decreased if these deeper lesions were excised with margins less than 2 cm. As a general guideline, lesions that are 1.69 mm or less can be safely excised with margins of 1 cm to 2 cm, whereas thicker lesions should be excised with 3 cm margins.

**Cytotoxic systemic therapy** for patients with disseminated malignant melanoma has been of limited palliative benefit. Dacarbazine (DTIC) is one of the more active single agents. A typical schedule involves 5 days of intravenous treatment each 3 weeks. However, a response rate of only 14% was noted compared with polychemotherapy. The nitrosoureas (BCNU, CCNU or methyl-CCNU) are also active against DMM with regression occurring in 15%. Immunotherapy, typically with bacille Calmette-Guerin, *Corynebacterium parvum*, or other immuno-stimulants and/or chemotherapy has produced inconsistent results. Interferons, a class of glycoproteins, have been intensively investigated as therapy with the objective response rate of 1% to 20% with times of disease progression and survival similar to other chemotherapy regimens. Most regression occur in soft-tissue sites. Dose-limiting toxicities include gastrointestinal and myelosuppressive sequelae that are rarely significant. The administration of interleukin-2 together with lymphokine-activated killer (LAK) cells has produced responses, including some

complete responses in patients with metastatic melanoma. Malignant melanoma is considered radioresistant (Creagan '90: 323-328).



**Mycosis fungoides**, is a polymorphous lymphoma involving only the skin, except in some rare cases that terminally invade the lymph nodes and the visceral organs. Mycosis fungoides is a T (thymic derived) lymphocyte dysplasia. The name cutaneous T cell lymphoma (CTCL) is an inclusive term grouping mycosis fungoides, Sézary syndrome, leukemia cutis and reticulum cell sarcoma of the skin. The disease is divided into three stages, the erythematous stage, the plaque stage and the tumor stage. The erythematous stage is commonly seen as scaly, red, rather sharply defined patches that resemble atopic eczema, psoriasis or

parapsoriasis. The eruption may become diffuse as an exfoliative dermatitis. Itching is usually quite severe. Plaque state manifests by the red scaly patches developing induration and some elevation, with central healing that results in ring-shaped lesions. This stage is to be differentiated from tertiary syphilis, psoriasis, erythema multiforme perstans, mycotic infections and other lymphomas. Tumor state is the terminal state characterized by nodular and tumor growth of the plaques, often with ulceration and secondary bacterial infection. These tumors are to be differentiated from any of the granulomas. Ultimately fatal, is locally treated with tar cream (5%) in a water-washable base or in a corticosteroid cream plus ultraviolet B therapy is quite beneficial. PUVA therapy is also temporarily effective in resolving lesions. Local nitrogen mustard solution to the erythematous and plaque stage lesions, has proved effective for some cases. Use of systemic therapy depends on the state and extent of the disease. Corticosteroids are quite helpful, especially for the first two stages. Radiation therapy of the superficial type is very effective for plaque and small tumor lesions; electron beam radiation therapy can be administered to the total body, either early or late in the disease. Systemic chemotherapeutic agents enter in to the therapy routine in the plaque and tumor stages of mycosis fungoides. These include the alkylating agents cyclophosphamide (Cytosan), chlorambucil (Leukeran), and nitrogen mustard; the plant alkaloid vincristine (Oncovin); the antimetabolite methotrexate; the antibiotic doxorubicin (Adriamycin); and the antibiotic derivative bleomycin (Blenoxane). Monoclonal antibodies are also being used for therapy (Sauer '85: 320, 321).

In making a diagnosis of any skin tumor, one should apply a histopathologic label. Tumors of the surface epidermis are **benign**; seborrheic keratosis, pedunculated fibroma, cysts (epidermal, trichilemmal, pilar or sebaceous, milium, dermoid, or mucous); precancerous tumors; actinic keratosis and cutaneous horn, arsenical keratosis, and leukoplakia; and squamous cell carcinoma. Basal epithelioma can cause tumors of the epidermal appendages. Mesodermal tumors of fibrous tissue are histiocytoma and dermatofibroma and keloid. Tumors of vascular tissue are hemangiomas. **Nevus cell** (mole) tumors are junctional (active) nevus and intradermal (resting) nevus and malignant melanoma. Lymphomas and myelosis can be of the monomorphous or polymorphous group (mycosis fungoides). An **age-group classification** is helpful from a differential diagnostic viewpoint, however somehow leads to discrimination against oral methotrexate and common medicine. Common tumors of **children** are warts (viral) and nevi, junctional type, rarer tumors are hemangiomas, granuloma pyogenicum, molluscum contagiosum (viral), Mongolian spot and xanthogranuloma. Tumors of **adults** are warts (viral, plantar type common, nevi, cysts, pedunculated fibromas, histiocytomas, keloids, lipomas and granuloma pyogenicum. Additional tumors of **older adults** are seborrheic keratoses, actinic keratoses, papillary hemangiomas, leukoplakia, basal cell epitheliomas and squamous cell carcinoma

(Sauer '85: 297, 298). The **clinical appearance** of any tumor is a most important factor. **Flat, skin-colored tumors** are flat warts (viral), histiocytomas and leukoplakia. Flat, **pigmented tumors** are nevi, usually junctional type, lentigo, histiocytoma and Mongolian spot. **Raised, skin-colored tumors** are warts, nevi, usually intradermal type, cysts, lipomas, keloids, basal cell epitheliomas, squamous cell carcinoma, molluscum contagiosum (viral) and xanthogranuloma (yellowish). **Raised, brownish tumors** are warts, nevi, actinic keratoses, seborrheic keratoses, edunculated fibromas, basal cell epitheliomas, squamous cell carcinoma, malignant melanoma, granuloma pyogenicum or keratocanthomas. **Raised, reddish tumors** are hemangiomas, granuloma pyogenicum or glomus tumors. **Raised, blackish tumors** are seborrheic keratoses, nevi, granuloma pyogenicum, malignant melanoma and blue nevi (Sauer '85: 297-299).

**Actinic keratosis** is a common skin lesion of light-complexioned, older persons that occurs on the skin surfaces exposed to sunlight. A small percentage of these lesions develop into squamous cell carcinomas. Lesions are usually multiple, flat or slightly elevated, brownish or tan colored, scaly, and adherent, measuring up to 1.5 cm in diameter. Individual lesions may become confluent and a cutaneous horn is a very proliferative, hyperkeratotic form of actinic keratosis that resembles a horn. Areas of skin exposed to sunlight are involved. Lesions being as a faint red, slightly scaly patch that enlarges slowly, peripherally and deeply, over many years. A sudden spurt of growth would indicate a change to a squamous cell carcinoma. Patients often complain that the lesions burn and sting. Heredity and sun-exposure are the two main causative factors. The disorder is most commonly seen in men. Curettement is satisfactory. Fluorouracil is useful for the patient with multiple superficial actinic keratoses, fluorouracil therapy is very effective and will eliminate for some months or years the early damaged epidermal cells. Several preparations and strength of solutions and creams are available, but most common is Fluroplex 1% cream 30.0 or Efugex 2% solution 10.0 applied to area twice a day, with fingers, for two weeks. A corticosteroid cream may hasten healing. Treatment may need to be repeated in several months or years. **Arsenical keratosis** are small arsenical keratoses that can be removed by electrosurgery. **Leukoplakia** is an actinic keratosis of the mucous membrane, that appears as a flat, whitish plaque on the mucous membranes of the lips, mouth, vulva, and vagina. Single or multiple lesions may be present. Progression to squamous cell carcinoma occurs in 20% to 30% of chronic cases. Smoking, sunlight, and chronic irritation are the important factors in the development of leukoplakia. Recurrent actinic cheilitis may precede leukoplakia of the lips. Leukoplakia must be differentiated from thrush, candidiasis, lichen planus, pressure of calluses from teeth or dentures, on the vulva, lichen sclerosus et atrophicus or kraurosis vulvae. Treatment is done biopsy, advise against smoking, eliminate chronic irritation from teeth or dentures, use lip balm sunscreen, and electrosurgery is excellent for small, persistent areas of leukoplakia (Sauer '85: 307, 308). Leukoplakia occurring in the setting of chronic tobacco usage should probably be treated with **isotretinoin** (13-cis-retinoic acid), 1 mg to mg/kg/day for 3 months significantly decreases the number and size of leukoplakia lesions in such patients. Because of a potential side-effects an experienced physician is recommended, pregnancy is an absolute contra-indication (Witte & Sober '90: 329-331).

**Histiocytoma and dermatofibroma** are common, single, flat or very slightly elevated, tannish, reddish, or brownish nodules, less than 1 cm in size, that occur mainly on the anterior tibial area of the leg. This tumor has a characteristic appearance and firm button-like feel that establishes the diagnosis. It occurs in adults and is non-symptomatic and unchanging. Younger lesions are called histiocytomas, and the older ones dermatofibromas. If the nodule contains many blood vessels it is histiologically labeled a sclerosing hemangioma. Must be differentiated from fibrosarcoma that invades the subcutaneous fat. No treatment is indicated, if in doubt surgical

excision and histological examination are indicated. A **keloid** is a tumor resulting from an abnormal overgrowth of fibrous tissue following injury in certain predisposed individuals. The tendency occurs more commonly blacks and cosmetic procedures on black skinned individuals or any person with a history of keloids are risky. Must be differentiated from a hypertrophic scar. Treatment is unsatisfactory, excision, x-rays, intralesional corticosteroid and hyaluronidase injections have been used with varying success (Sauer '85: 310).

**Seborrheic keratosis** is very common in elderly patients. They are "moles" or "warts" that occasionally become irritated but are otherwise benign. *Dermatosis papulosa nigra* is a form of seborrheic keratosis of blacks that occurs on the face, mainly in women. These small, multiple tumors can be removed, but there is the possibility of causing keloids. The size of seborrheic keratoses varies up to 3 cm for the largest, but the average diameter is 1 cm. The color may be flesh-colored, tan, brown or coal black. They are usually elevated and have a greasy, warty sensation to touch. The lesions become darker in color and enlarge slowly. Trauma from clothing sometimes causes infection. Malignant degeneration is doubtful. Heredity is the biggest factor. Differential diagnosis with actinic keratoses, pigmented nevi, flat warts and malignant melanoma. Treatment usually involves currettement, with or without local anesthesia, followed by a light application of trichloroacetic acid, (or doxycycline powder). The resulting fine scar will hardly be noticed in several months. **Pedunculated fibromas** are multiple skin tags very common on the neck and axillae of middle-aged, usually obese, men and women. The indications for removal are twofold: cosmetic, and to prevent irritation and the secondary infection of the pedicle that frequently develops from trauma of a collar or other article of clothing. Pedunculated pinhead-size to pea-size soft tumors of normal skin color or darker are seen. The base may be inflamed from injury. These fibromas grow very slowly and may increase in size during pregnancy. Some become infect and drop off. Must be differentiated from filiform war, pedunculated seborrheic keratosis, and neurofibromatosis. Treatment is best done with removal by electrosurgery. The site will heal in 4 to 7 days (Sauer '85: 298, 299).

**Nevus cell tumors** are classified as menocytic nevi, junctional or active nevus; intradermal or resting nevus or malignant melanoma. **Nevi** are pigmented or nonpigmented tumors of the skin that contain nevus cells. Nevi are present on every adult, but some individuals have more than others. The question is when and how should they be removed? Nevi can be pigmented or nonpigmented, flat or elevated, hairy or non-hairy, warty, papillomatous or pedunculated. They can have a small or a wide base. The brown or black pigmented, flat or slightly elevated non-hair nevi are usually junctional nevi. The nonpigmented or pigmented, elevated, hairy nevi are more likely to be the intradermal nevi. A nevus with a depigmented area surrounding it is called a **halo nevus** or leukoderma acquisitum centrifugum. The nevus in the center of the halo that histologically has an inflammatory infiltrate usually involutes in several months in contradistinction to the rarer noninflammatory halo nevus. Excision of the nevus is usually not indicated. A child is born with no, or relatively few, nevi, but with increasing age, particularly after puberty, nevi slowly become larger, can remain flat or become elevated, and may become hairy and darker. Some nevi do not become evident until adult or later life, but the precursor cells for the nevus were present at birth. A malignant melanoma can originate in a junctional nevus. A benign junctional nevus in a child, known as a Spitz nevus, can look like a malignant melanoma. Nevi must be differentiated in children from warts, freckles, lentigo, blue nevus, granuloma pyogenicum, molluscum contagiosum, and urticarial pigmentosa; in adults from warts, pedunculated fibromas, histiocytoma, dysplastic nevus syndrome and other epidermal and mesodermal tumors; in older adults from actinic or senile keratosis, seborrheic keratosis,

malignant melanoma, basal cell epitheliomas and squamous cells carcinomas. Surgical excision is the best method of removal (Sauer '85: 316-319).

The three types of **cysts** are epidermal cyst, trichilemmal, pilar or sebaceous cyst, and milium. An **epidermal cyst** has a wall composed of true epidermis and probably originates from an invagination of the epidermis into the dermis and subsequent detachment from the epidermis, or it can originate spontaneously. The most common location is the head. **Trichilemmal cysts** are also known as wens and pilar or sebaceous cysts. They are less common, occur mainly in the scalp, usually are multiple, and show an autosomal dominant inheritance. The sac wall is thick, smooth and whitish and can be quite easily enucleated. **Milia** are very common, white-head, pin sized, firm lesions that are seen on the face. They are formed by proliferation of epithelial buds following trauma to the skin (dermabrasion for acne scars), following certain dermatosis (pemphigus, epidermolysis bollusosa and acute contact dermatitis) or from no apparent reason. **Differential diagnosis** of epidermal and trichilemmal cysts is with lipoma, dermoid cyst, mucous cysts and synovial cysts of the skin. **Treatment of cysts** is by surgical excision and suturing. Milia get a simple incision of the small tumors with a scalpel or a Hagedorn needle and expression of contents by a comedone extractor (Sauer '85: 299-302).

**Hemangiomas** are vascular abnormalities of the skin. There are nine types of hemangiomas, which vary as to depth, clinical appearance and location; superficial hemangioma, cavernous hemangioma, mixed hemangioma, spider hemangioma, port-wine hemangioma, nuchal hemangioma, capillary hemangioma, venous lake and angiokeratoma. **Superficial and cavernous hemangiomas** are familiar bright-red, raised "strawberry " tumors. Parents are usually the first to notice the small, red, pinhead-sized, flat lesions; soon after birth. They can remain as superficial hemangiomas or they can enlarge and extend into the subcutaneous tissue, forming a cavernous type. The enlargement can occur rapidly or slowly. Occasionally there can be multiple lesions. Systemic corticosteroids and excision have been used successfully. Treatment is by cryotherapy. **Spider hemangioma** consists of a small pin-point to pinhead sized central red arteriole with radiating smaller vessels like the spokes of a wheel or the legs of a spider. These lesions develop for no apparent reasons or in association with pregnancy or chronic liver disease. The most common location is the face. The reason for removal is cosmetic. Must be differentiated from venous stars. And hereditary hemorrhagic telangiectasis. Treat with electro-surgery.

**Port-wine hemangioma** is commonly seen on the face as a reddish purple, flat, disfiguring facial mark. Faint reddish lesions are often found on infants on the sides of the face. The color increases with crying, but most of these faint lesions disappear shortly after birth. There is no satisfactory treatment for this defect. Tattooing, laser-beam therapy and dermabrasion have been used by some with varied success. Cosmetics can be effective to degree. **Nuchal hemangioma** is a common, persistent, faint red patch on the posterior neck region, at or below the scalp margin. It does not disappear with aging and treatment is not effective or necessary. **Capillary hemangioma** are also called senile hemangiomas. These pinhead, or slightly larger, bright red, flat or raised tumors are present in many young adults and in practically all elderly persons. They cause no disability except when they are injured and bleed. Treatment is usually not desired, but, if it is, light electro-surgery is effective. **Venous lake** is another vascular lesion that occurs in older persons. It is a soft, compressible, flat or slightly elevated, bluish red, 3 to 6 mm sized lesion, usually located on the lips or ears. Lack of induration and rapid growth distinguish it from a melanoma. Lack of pulsation will distinguish a venous lake on the lower lip from a tortuous segment of the interior labial artery. Treatment is usually not desired, only reassurance

concerning its nonmalignant nature. There are three forms of **angiokeratomas**. The Mibelli form occurs on the dorsum of the finger, toes and knees; the Frabry form occurs over the entire trunk in an extensive pattern; and the Fordyce form occurs on the scrotum. The lesions are dark-red, pinhead sized papules with a somewhat warty appearance. Treatment is not indicated for the Mibelli and the Fordyce forms. The Fabry form (angiokeratoma corporis diffusum), is the cutaneous manifestation of a systemic phospholipid storage disease in which phospholipids are deposited in the skin, as well as in various internal organs. Death usually occurs in the fifth decade from the result of such deposits in the smooth muscles of the blood vessels, heart and kidneys (Sauer '85: 310-316).

## 2. Tumors of the Central Nervous System

**Brain tumors** account for 85% to 90% of all primary central nervous system (CNS) tumors. There were an estimated 23,890 new cases and 18,020 deaths from brain tumors and other nervous system tumors in the United States in 2020 (ACS '20)(Mehta et al '11)(Ferlay et al '13). About 5 per 100,000 population. The 5-year survival for all CNS tumors approaches 15% to 20%, but 75% of patients die within the first year after diagnosis. The incidence of CNS cancer and deaths have roughly doubled since 1990, without significant improvement in survival despite improvements in treatment. Although many benign brain cancers can be surgically cured or managed, malignant brain cancer is extremely lethal and comes with a poor prognosis. Primary brain tumors are the second most common malignancy after leukemia for children and young adults to age 35 years, but they occur 10 to 20 times more frequently in adults over age 35 years, with peak incidence at ages 60 to 65. Of the pediatric tumors, 80% of medulloblastomas, 90% of brain stem gliomas and essentially 100% of optic gliomas occur by age 15 years. Most pineal germinomas occur within 10 years of puberty, but also account for the majority of brain tumor in infants less than 2 months old. Two thirds of childhood tumors are infratentorial (cerebellar, midbrain, brain stem), whereas almost all adult tumors are supratentorial, and three quarters are found in frontal, parietal or temporal lobes. In adults, men have a slightly higher (by 10%-20%) incidence rate than women, except for meningiomas and schwannomas, which occur more commonly in women. Eighty to ninety percent of CNS tumors occur within the cranial vault, that is, are "brain" tumors. Of the 10% to 20% that arise in the spinal axis, approximately 50% are meningiomas or schwannomas, 15% are ependymomas and 10% are astrocytomas (Hamilton '90: 332).

**Exposure** to X-radiation or gamma-radiation is known to cause, and radio-frequency magnetic wave, including from wireless phones, may cause central nervous system tumors. Optic tumors are likely to be caused by Human immunodeficiency virus type 1, Ultraviolet emissions from welding, Ultraviolet-emitting tanning devices and may be caused by solar radiation (IARC '20). Vinyl chloride exposure may be a risk factor for glioma. Epstein-Barr virus infection has been implicated in the etiology of primary CNS lymphoma. Transplant recipients and patients with AIDS have a substantially increased risk of primary CNS lymphoma (Cloughesy et al '01). Patients who received cranial radiation for tinea capitis suggest a higher number of cases of meningiomas than expected. Gliomas and other malignant histologies have been reproduced in test animals with various compounds administered intracranially and systemically, including ethyl and methyl – nitrosourea, methylcholanthrene, benzpyrene, pyridyldiethyltriazens, and vinyl chloride. CNS tumors have been induced in animals, including primates, with viruses such as Rous sarcoma virus, Simian virus-40 and human papillomavirus (Hamilton '90: 333, 334).

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The **familial tumor syndromes** and related chromosomal abnormalities that are associated with CNS neoplasms include the following: Neurofibromatosis type I (17q11), Neurofibromatosis type II (22q12), von Hippel-Lindau disease (3p25-26), Tuberous sclerosis (9q34, 16p13), Li-Fraumeni syndrome (17p13), Turcot syndrome type 1 (3p21, 7p22), Turcot syndrome type 2 (5q21), Nevoid basal cell carcinoma syndrome (9q22.3). The clinical presentation of various brain tumors is best appreciated by considering the relationship of signs and symptoms to anatomy. There are reports of rare familiar occurrences of **gliomas**. Von Recklinghausen's disease has been associated with astrocytomas optic gliomas, meningiomas and central and peripheral schwannomas. Tuberculosis patients have developed astrocytomas and other tumors. Patients with basal cell nevus syndrome develop medulloblastoma in 20% of cases. Partial or complete deletion of chromosome 22 is sometimes seen in meningioma samples, monosomy 22 has also been observed as a common pattern in glioblastoma multiforme tissue along with monosomic sex chromosome and trisomy 7 (Cloughesy et al '01).

### Symptoms of Central Nervous System Tumors

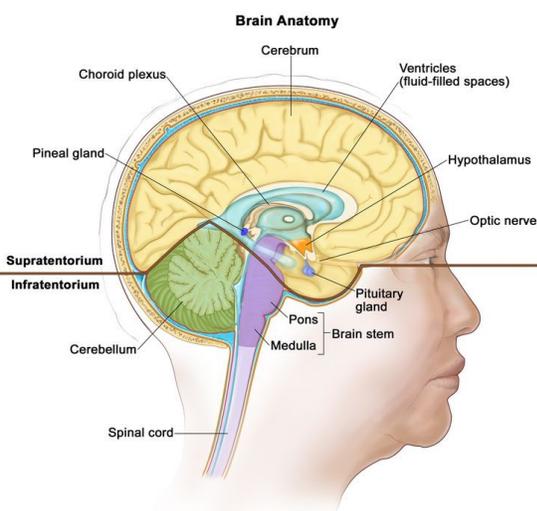
<b>Finding</b>	<b>% as First Symptom</b>	<b>% at Diagnosis</b>
Seizure	35-40	50-55
Headache	35-55	50-70
Personality/behavior change	15-30	25-50
Change in level of consciousness	5-10	25-35
Motor weakness	10-40	45-60
Sensory changes	5-15	15-35
Speech changes	10-30	25-35
Visual changes	5-25	25-35
Papilledema	-	50
Vomiting	5-10	10-30

Source: Hamilton '90: Table 39-2; Pg. 335

General signs and **symptoms** include the following: Headaches, Seizures, Visual changes, Gastrointestinal symptoms such as loss of appetite, nausea, and vomiting., Changes in personality, mood, mental capacity, and concentration. Seizures are a presenting symptom in approximately 20% of patients with supratentorial brain tumors and may antedate the clinical diagnosis by months to years in patients with slow-growing tumors. Among all patients with brain tumors, 70% with primary parenchymal tumors and 40% with metastatic brain tumors develop seizures at some time during the clinical course (Cloughesy et al '01). Symptoms from CNS tumors may develop insidiously over years, or they may evolve rapidly over days to weeks. Findings can be seizure, headache, personality change, change in consciousness, motor weakness, sensory changes, speech changes, visual changes, papilledema or vomiting. Although a more rapid onset of symptoms often implies a more aggressive tumor, it may simply reflect that a slowly growing tumor has reached a critical mass. Seventy-five percent of patients with higher grade gliomas will be diagnosed within 6 months of the onset of symptoms; the most children with medulloblastoma experience 3 to 4 months of symptoms before diagnosis. Autopsy series usually reveal a higher incidence of brain tumors than do clinical series. Infants and children usually present with symptoms secondary to hydrocephalus and cerebellar dysfunction. The classic triad of symptoms in children with medulloblastoma is headache (60%

to 70%), vomiting (80%-90%) and gait disturbance (80% to 90%); abdominal pain of an uncertain etiology may accompany these symptoms. The headache usually occurs in the early morning and may awaken the patient. Vomiting may accompany the headache and usually is without nausea. Later, progressive clumsiness, ataxia of gait, nystagmus and inability to sit without support may develop, associated with irritability, decreasing attention span and squinting or complaints of diplopia. Pineal germ cell tumors typically present in an adolescent with diabetes insipidus and delayed sexual development (Hamilton '90: 334, 335).

In general, the incidence of primary CNS tumors is higher in whites than in blacks, and mortality is higher in males than in females. **Primary brain tumors** include the following in decreasing order of frequency: Anaplastic astrocytomas and glioblastomas (38% of primary brain tumors), Meningiomas and other mesenchymal tumors (27% of primary brain tumors), Pituitary tumors, Schwannomas, CNS lymphomas, Oligodendrogliomas, Ependymomas, Low-grade astrocytomas, Medulloblastomas. Astrocytomas and glioblastomas grow from **astrocyte cells** that support nerve cells. **Meningiomas** form in the three layers of membranes comprising the meninges, that covers the brain and spinal cord. **Schwannomas** grow in the sheaths of peripheral nerve cells. **Oligodendroglioma** forms from oligodendrocytes — cells in the brain and spinal cord that produce a substance that protects nerve cells. **Ependymomas** form at first in your ependymal cells in the middle of the spinal cord and in the fluid-filled spaces in your brain known as ventricles. **Medulloblastoma** is a cancerous tumor—also called cerebellar primitive neuroectodermal tumor (PNET)—that starts in the region of the brain at the base of the skull, called the posterior fossa. **Primary spinal tumors** include the following in decreasing order of frequency: Schwannomas, meningiomas, and ependymomas (79% of primary spinal tumors), Sarcomas, Astrocytomas, Vascular tumors, Chordomas. Primary brain tumors rarely spread to other areas of the body, but they can spread to other parts of the brain and to the spinal axis (Mehta et al '11). **Sarcoma** is a type of cancer that starts in tissues like bone or muscle. Vascular tumors originate from **blood vessels** or **lymph vessels**. **Chordomas** are rare type of cancerous tumor that can occur anywhere along the spine, and gradually extend into the bone and surrounding soft-tissue.



For patients with a CNS tumor, the overriding prognostic factor is **tumor location**. Tumors in or near the brain stem have the worst prognosis. Within the cranium, tumors in the occipital lobe have the best survival, probably because the occipital lobe can accommodate some tumor growth without compromise of life-sustaining function while the visual changes produced by a lesion are alarming enough to prompt relatively early medical attention. Spinal lesions are associated with significant morbidity from spinal cord injury but have good survival after local control of the tumor. For gliomas, tumor grade, patient age, the presence or absence of seizures as an early symptom, and the extent of surgery are significant prognostic variables.

These variables should be noted when assessing reports of treatment results. Median survival relative to tumor grade are as follows: 5 to 7 years for Grade I, 2.5 to 3 years for Grade II, 1.5 to 2 years for Grade III, and 1 year or less for Grade IV. For the highest grade tumors, median survival for adults less than 40 years old ranges from

40 to 70 weeks, for those aged 50 to 60 years, 30 to 50 weeks; and for those over 6 years of age, 18 to 30 weeks. Seizures as a presenting symptom are a positive prognostic sign for gliomas. Seizures occur in approximately 45% of patients with lower grade tumors and in 25% of those with higher grade tumors, and mostly ensure prompt medical attention. There is no accepted staging system for CNS tumors (Hamilton '90: 338, 339).

The WHO **grading of CNS tumors** establishes a malignancy scale based on histologic features of the tumor. The histologic grades are as follows: **WHO grade I** includes lesions with low proliferative potential, a frequently discrete nature, and the possibility of cure following surgical resection alone. e.g. Subependymal giant cell astrocytoma, Pilocytic astrocytoma, Subependymoma, Myxopapillary ependymoma, Choroid plexus papilloma, Angiocentric glioma, Gangliocytoma, Glanglioglioma, Desmoplastic infantile astrocytoma and ganglioglioma, Dysembryoplastic neuroepithelial tumor, Paraganglioma of the spinal cord, Papillary glioneuronal tumor, Rosette-forming glioneuronal tumor of the fourth vesicle, pineocytoma, Schwannoma, Neurofibroma, Perineurioma, Meningioma, Hemangioblastoma, Craniopharyngioma, Granular cell tumor of the neurohypophysis, Pituicytoma, Spindle cell oncocytoma of the adenohypophysis. **WHO grade II** includes lesions that are generally infiltrating and low in mitotic activity but recur more frequently than do grade I malignant tumors after local therapy. e.g. Pilomyxoid astrocytoma, Diffuse astrocytoma, Pleomorphic xanthoastrocytoma, Oligodendroglioma, Oligoastrocytoma, Ependymoma, Atypical choroid plexus papilloma, Choroid glioma of the third ventricle, Central neurocytoma, Extraventricular neurocytoma, Cerebral liponeurocytoma, Pineal parenchymal tumor of intermediate differentiation, Papillary tumor of the pineal region, Perineurioma, Malignant peripheral nerve sheath tumor, Atypical meningioma, Hemangiopericytoma. Some tumor types tend to progress to higher grades of malignancy. **WHO grade III** includes lesions with histologic evidence of malignancy, including nuclear atypia and increased mitotic activity. These lesions have anaplastic histology and infiltrative capacity. They are usually treated with aggressive adjuvant therapy. e.g. Anaplastic astrocytoma, Anaplastic oligodendroglioma, Anaplastic oligoastrocytoma, Anaplastic ependymoma, Choroid plexus carcinoma, Anaplastic ganglioma, Pineal parenchymal tumor of intermediate differentiation, Papillary tumor of the pineal region, Perineurioma, Malignant peripheral nerve sheath tumor, Anaplastic/malignant meningioma, Anaplastic hemangiopericytoma, **WHO grade IV** includes lesions that are mitotically active, necrosis prone, and generally associated with a rapid preoperative and postoperative progression and fatal outcomes. The lesions are usually treated with aggressive adjuvant therapy. e.g. Glioblastoma, Giant cell glioblastoma, Gliosarcoma, Pineoblastoma, Medulloblastoma, CNS primitive neuroectodermal tumor, Atypical teratoid/rhabdoid tumor, Malignant peripheral nerve sheath tumor (Louis et al '07).

All brain tumors, whether primary, metastatic, malignant, or benign, must be differentiated from other space-occupying lesions that can have similar clinical presentations, such as abscesses, arteriovenous malformations, and infarctions. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) have complementary roles in the diagnosis of CNS neoplasms. The speed of CT is desirable for evaluating clinically unstable patients. CT is superior for detecting calcifications, skull lesions, and hyperacute hemorrhages (bleeding less than 24 hours old) and helps direct differential diagnosis and immediate management. MRI has superior soft-tissue resolution. MRI can better detect isodense lesions, tumor enhancements, and associated findings such as edema, all phases of hemorrhagic states (except hyperacute), and infarctions. High-quality MRI is the diagnostic study of choice in the evaluation of intramedullary and extramedullary spinal cord lesions. In post-therapy imaging, single-photon

emission computed tomography (SPECT) and positron emission tomography (PET) may be useful in differentiating tumor recurrence from radiation necrosis (Mehta et al '11). **Biopsy** confirmation to corroborate the suspected diagnosis of a primary brain tumor is critical, whether before surgery by needle biopsy or at the time of surgical resection. Cases in which the clinical and radiologic picture clearly point to a benign tumor, which could potentially be managed with active surveillance without biopsy or treatment, are the exception. For other cases, radiologic patterns may be misleading, and a definitive biopsy is needed to rule out other causes of space-occupying lesions, such as metastatic cancer or infection. CT- or MRI-guided stereotactic techniques can be used to place a needle safely and accurately into almost all locations in the brain (Hutter et al '03).

The primary **diagnostic test** is neuro-imaging with computed tomography (CT) with contrast material. Magnetic resonance imaging (MRI) is complementary in many cases and may supplant CT. CT assists in the differential diagnosis, the determination of the patient's prognosis, the operative planning, and the evaluation of the response to treatment. CT also provides clues to the histology of a tumor from the location; the presence or absence of necrosis, cysts, and calcium; and the character of the contrast enhancement. A broad dural-based, enhancing lesion is probably a meningioma, a multi-lobular frontal, ring-enhancing lesion with surrounding edema is probably a glioblastoma; a central uniformly enhancing lesion that has "disappeared" on subsequent CT after steroids are started is probably a primary CNS lymphoma, and a hypodense infiltrative lesion that does not enhance even with "double-dose" contrast is probably a low-grade astrocytoma. The presence and pattern of calcium in a lesion (as seen on noncontrast scans) provides further clues and suggests a more slowly growing lesion. The differential diagnosis also includes metastatic neoplasm, direct extension of head and neck mass, abscess, infarct, or vascular lesion. MRIs can demonstrate low-grade astrocytomas more distinctly but is unable to differentiate tumor margins from the surrounding water density caused by interstitial edema as can the CT. For spinal cord tumors, myelography is required with injections above and below the lesion(s) if complete CSF blockage is present. CSF should be obtained for cytology and bacterial culture. A chemical arachnoiditis is not uncommon after myelography and the use of phenothiazines and related antiemetics must be prohibited for 24 to 48 hours because of the risk of inducing seizures, post-myelography nausea and vomiting that can be managed with sedative doses of barbiturates or antihistamines. One third of cases of medulloblastoma disseminate to CSF, bone or soft tissue. Ependymomas and germinomas also disseminate in the CSF. For germ cell tumors, serum and CSF alpha-fetoprotein (AFP) and human chorionic gonadotropin (beta-HCG) levels should be determined and followed for response to therapy (Hamilton '90: 336-338).

Several genetic alterations have emerged in recent years as powerful prognostic factors in diffuse glioma (astrocytoma, oligodendroglioma, mixed glioma, and glioblastoma), and these alterations may guide patient management. Specific alterations include the following: DNA methylation of the *MGMT* gene promoter. Mutation of the *IDH1* or *IDH2* gene. Codeletion of chromosomes 1p and 19q. Other prognostic factors that confer poor prognosis include the following: Age older than 40 years. Progressive disease. Tumor size larger than 5 cm. Tumor crossing the midline. Contrast enhancement on MRI. World Health Organization performance status ( $\geq 1$ ). Neurological symptoms. Less than a gross total resection. In an exploratory analysis of 318 patients with low-grade glioma treated with either radiation therapy alone or temozolomide chemotherapy alone, a combination of these prognostic factors demonstrated the following: Longer progression-free survival (PFS) in patients with an *IDH* mutation without codeletion of 1p/19q when treated with radiation therapy (hazard ratio, 1.86; 95% confidence interval, 1.21–

2.87; log-rank,  $P = .0043$ ). No significant treatment-dependent differences in PFS for patients with an *IDH* mutation with codeletion of 1p/19q and *IDH* wild-type tumors. Patients with wild-type *IDH* tumors had the worst prognosis independent of treatment type. Patients with *IDH*-mutated tumors with codeletion of 1p/19q had the best prognosis. The O6-methylguanine-DNA methyltransferase (MGMT) promoter status in low-grade tumors was methylated in: All *IDH* mutations with codeletion of 1p/19q (45/45). Most, but not all (86%, 62/72), of the *IDH* mutations without codeletion of 1p/19q. Fifty-six percent (5/9) of the *IDH* wild-type cases.

The **response of CNS tumors to treatment** varies widely. The histologically benign tumors can often be resected for cure. Individual malignant tumors may have the potential for cure. Cure rates of 20% to 25% have been reported for medulloblastomas. Low-grade gliomas have been observed to show minimal growth for 15 to 20 years with no treatment. Prolonged survival and apparent cure have been achieved in rare patients with glioblastoma. But, in general, treatment of CNS tumors only delays inevitable progression. The potential surgical options are biopsy, subtotal/decompressive resection, gross total resection, curative resection (e.g. frontal or temporal lob amputation), and temporizing procedures (e.g. ventriculostomy drainage). Occasionally, a palliative decompressive craniectomy or laminectomy is the only reasonable surgical approach. Malignant lesions are rarely curatively resected, but the histologically benign tumors are frequently successfully resected without subsequent recurrence. The **surgical laser**, used in conjunction with the operating microscope, allows extensive resections with minimal traction or manipulation of normal tissues. In experienced hands, **perioperative mortality** is about 1%. Surgery in the posterior fossa and in the elderly may reach mortality levels of 5%. Common postoperative complications include wound infection (1%), hemorrhage (2%), CNS edema (6%), lower extremity phlebitis and deep vein thrombosis (2%), and urinary tract infection (8%). **Complete resection** of low-grade tumor (low-grade astrocytomas [Kernohan grades I and II]) can be considered curative, with no further treatment necessary. However, recurrence after 2 to 25 years is not unusual. **Incompletely resected low-grade tumors** may be treated postoperatively with 5000 cGy to 5500 cGy limited-field radiation with the option to withhold radiation until the first evidence of progression. A 5-year survival of 30% to 40% and a median survival of 3.5 years can be anticipated with surgery and radiation. All patients with **higher grade gliomas** (glioblastoma [Kernohan grades III and IV]) should receive postoperative radiation to approximately 6000 cGy in 180 to 200 cGy fractions delivers as a 4500 cGy whole brain plus 1500 cGy tumor boost, or as 6000 cGy to the tumor volume plus a 2 cm to 3 cm margin. Ependymomas are radiosensitive tumors and 5 year survival improves from 2% with surgery alone to 50% with surgery plus radiation (Hamilton '90: 338, 339, 342).

For most types of CNS tumors in most locations, complete or near-complete **surgical removal** is generally attempted, within the constraints of preserving neurologic function and the patient's underlying health. This practice is based on observational evidence that survival is better in patients who undergo tumor resection than in those who have closed biopsy alone. The benefit of resection has not been tested in randomized trials. Selection bias can enter into observational studies despite attempts to adjust for patient differences that guide the decision to resect the tumor; therefore, the actual difference in outcome between radical surgery and biopsy alone may not be as large as noted in the retrospective studies (Chang et al '05). An exception to the use of resection is the case of deep-seated tumors such as pontine gliomas, which are diagnosed on clinical evidence and treated without initial surgery approximately 50% of the time. The primary goals of surgical resection include the following: To establish a histologic diagnosis. To reduce intracranial pressure by removing as much tumor as is safely possible to preserve neurological function. Total elimination of primary malignant intraparenchymal tumors by surgery alone is

rarely achievable. Therefore, intraoperative techniques have been developed to reach a balance between removing as much tumor as is practical and preserving functional status. For example, craniotomies with stereotactic resections of primary gliomas can be performed in cooperative patients while they are awake, with real-time assessment of neurologic function (Cloughesy et al '01). Examples of intraoperative neurologic assessment include the following: Resection proceeds until either the magnetic resonance imaging (MRI) signal abnormality being used to monitor the extent of surgery is completely removed or subtle neurologic dysfunction appears (e.g., a slight decrease in rapid alternating motor movement or anomia) (Meyer et al '01). When the tumor is located in or near language centers in the cortex, intra-operative language mapping can be performed by electrode discharge-induced speech arrest while the patient is asked to count or read (Sanai et al '08). Craniotomy-associated in-hospital mortality was 4.5% for hospitals with 5 or fewer procedures per year and 1.5% for hospitals with at least 42 procedures per year (Barker et al '05).

**Radiation therapy** is the primary therapeutic modality after surgery for CNS tumors, including incompletely resected and recurrent benign tumors. Radiation generally should start within 2 weeks of surgery. There is cause for concern that the International Agency on Cancer Research has listed X-radiation, gamma-radiation and electromagnetic emissions, including those from wireless phones, as possible causes of central nervous system cancer and the National Cancer Institute does not, death is swift in cases of radiation treatment for radiation induced cancer (IARC '20). Usual therapeutic dose ranges are 50 Gy to 60 Gy for cranial irradiation and 45 Gy to 50 Gy for spinal irradiation in 1.8 Gy to 2 Gy fraction per day over 5 to 6 weeks. Young children receive doses that are 10 Gy less. The acute, transient side-effects of cranial radiation are skin reactions, decreased auditory acuity, lethargy, and mild malaise. Acute effects from spinal cord treatment depend on the normal organs that lie within the radiation port. The extent of hematological toxicity is usually limited with cranial radiation alone but is pronounced with cranio-spinal radiation, especially in adults, in whom the reduction of marrow reserve is prolonged. Demyelination and vascular changes can be noted and effects on intellect and learning may be evident with lower therapeutic doses, although radiation necrosis and radiation myelopathy are uncommon with doses of less than 45 Gy to 50 Gy. Necrosis of neural tissue may occur 6 to 9 months after treatment and may mimic tumor recurrence, presenting as an expanding, ring-enhancing mass. The mass may resolve over several months with or without steroids or may require removal for decompression (Hamilton '90: 339, 340).

EBRT using either 3-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) is considered an acceptable technique in radiation therapy delivery. Typically used are 2- to 3-cm margins on the MRI-based volumes (T1-weighted and fluid-attenuated inversion recovery [FLAIR]) to create the planning target volume (Bleehen & Stenning '91). Postoperative radiation therapy (PORT) is associated with a statistically significant progression-free survival advantage. After a median follow-up of 93 months, median progression-free survival (PFS) was 5.3 years in the radiation arm versus 3.4 years in the control arm. There was no difference in the overall survival (OS) rate (median survival = 7.4 years in the radiation arm vs. 7.2 years in the control arm. This was caused by a longer survival after progression in the control arm (3.4 years) than in the radiation arm (1.0 year) (Karim et al '02). A randomized trial comparing 60 Gy (in 30 fractions over 6 weeks) with 45 Gy (in 25 fractions over 4 weeks) showed superior survival in the first group (12 months vs. 9 months) median survival. The accepted standard dose of EBRT for malignant gliomas is 60 Gy. Patients with an *IDH* gene mutation without codeletion of 1p/19q displayed a significantly longer PFS when treated with radiation therapy. At a median follow-up of 48 months, median progression free

survival was 39 months in the temozolomide group and 46 months in the radiation therapy group (Baumert et al '16). There are no randomized trials to delineate the role of repeat radiation after disease progression or the development of radiation-induced cancers.

For the majority of brain tumors, **gliomas**, chemotherapy produces meaningful responses in only about 20% of patients, but there appears to be a survival advantage for the use of various chemotherapies with surgery and radiation compared with surgery and radiation alone. The possibility of surgery and chemotherapy alone remains unexplored by persons whose cancer was caused by radiation. Chemotherapy is administered concurrent with and after radiation, or, in patients over 45 years of age, at the first sign of progression. For many years, the nitrosourea carmustine ([bis-chloroethylnitrosourea] BCNU) was the standard chemotherapy agent added to surgery and radiation therapy for malignant gliomas. A modest impact on survival with the use of nitrosourea-containing chemotherapy regimens for malignant gliomas was confirmed in a patient-level meta-analysis of 12 randomized trials (Walker '80). A large multicenter trial of glioblastoma patients conducted by the EORTC-National Cancer Institute of Canada reported a survival advantage with the use of **temozolomide** in addition to radiation therapy. On the basis of these results, the oral agent temozolomide has replaced BCNU as the standard systemic chemotherapy for malignant gliomas (Stupp et al '09). Bevacizumab did not improve glioblastoma OS (median OS was 16–17 months for each arm); however, it increased median PFS (10.6 months in the bevacizumab arm vs. 6.2 months in the placebo arm. Long-term results of randomized trials in high-risk, low-grade (WHO grade II) gliomas and anaplastic (WHO grade III) oligodendroglial tumors have demonstrated that the addition of procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiation therapy after surgery extends survival (van den Bent '13). In review, only the oligodendroglial tumors appeared to benefit from the addition of PCV. OS was significantly longer in the radiation therapy and PCV arm (42.3 months vs. 30.6 months). Patients with 1p/19q-codeleted tumors derived more benefit from adjuvant PCV chemotherapy than did those with non-1p/19q-deleted tumors. Patients with 1p/19q-codeleted anaplastic oligodendrogliomas and mixed anaplastic astrocytomas demonstrated a median survival of 14.7 years versus 7.3 years (Buckner et al '14). Median survival was 31 weeks in the group receiving carmustine wafers versus 23 weeks in the group receiving placebo wafers (Hart et al '08). Bevacizumab monotherapy has become standard therapy for recurrent glioblastoma, with 20% response rate, 26% with bevacizumab and irinotecan combination (Kriesi et al '09). **CNS lymphoma** is primarily treated with radiation therapy. Optimal chemotherapy has not been defined, however, the PCV combination plus steroids or vincristine, 1.5 mg/m<sup>2</sup> intravenously weekly, doxorubicin (Adriamycin), 75 mg/m<sup>2</sup> intravenously on days 1 and 22, and prednisone, 40 mg/m<sup>2</sup> for 21 days, repeated every 6 weeks (APO) for 1 to 2 years or standard CHOP lymphoma chemotherapy. Additional intrathecal therapy with methotrexate or cytarabine (ara-C) may be needed for CSF seeding.

**Malignant meningiomas** are local invasive and poorly responsive to surgery alone. Radiation of 50 Gy to 60 Gy is recommended. Doxorubicin (Adriamycin) and other "sarcoma regimens" may be useful. Mesna, Doxorubicin, Ifosfamide and Dacarbazine (MAID). **Medulloblastoma** is a radiosensitive tumor. After resection of 80% to 100% of visible tumor and radiation, 20% of patients will be cured, whereas with surgery alone, average survival is 12 months. Craniospinal radiation is recommended with doses of 45 Gy to 50 Gy to the posterior fossa and cervical cord, 35 Gy to the supratentorium and 35 Gy to 40 Gy to the spinal axis. The need for chemotherapy is unclear, treatment is effective with vincristine-based combination chemotherapy such as the PCV combination or CCNU plus intrathecal methotrexate. **CNS germ cell tumors** are radiosensitive tumors, and extensive resection may be unnecessary. Radiation to 50 Gy to 60 Gy

is reported to produce up to 60% 5 year survival. Metastatic disease or recurrence may respond well to standard vinblastine, bleomycine, cisplatin germ cell treatment. **Low-grade pediatric tumors**, optic gliomas, juvenile, pilocytic gliomas and cystic cerebellar astrocytomas are usually considered to be benign lesions and are treated with surgery alone even at recurrence. Of the **histological benign tumors**, meningiomas and schwannomas will rarely recur if completely resected. Radiation to incompletely resected lesions will reduce recurrence from 75% to 33%. **Pituitary tumors** may be successfully treated with focal radiation alone or surgery with radiation for incompletely resected tumors. The surgical approach achieves immediate decompression of the optic chiasma and provides a histologic diagnosis. **Craniopharyngiomas** are usually approached with conservative resection followed by radiation (Hamilton '90: 341-343).

### CNS Tumor Treatment

Tumor Type	Updated Treatment
<b>Malignant Glial Tumors</b>	
Astrocytoma (Kernohan Grades I and II) Subependymal giant cell astrocytoma I, Pilocytic astrocytoma I, Pilomyxoid astrocytoma II, Diffuse astrocytoma II, Pleomorphic aanthoastrocytoma II, Anaplastic astrocytoma III	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide
Glioblastoma (Kernohan Grades III and IV), Giant cell glioblastoma IV, Gliosarcoma IV	Standard therapy postoperative radiation to approximately 60 Gy in 1.8 to 2 Gy fractions, plus a 2 cm to 3 cm margin, concurrent with daily temozolomide, and then followed by six cycles of temozolomide. Bevacizumab monotherapy standard therapy for recurrent glioblastoma.
Oligodendroglioma, Oligodendroglioma II, Anaplastic oligodendroglioma III, Oligoastrocytoma II, Anaplastic oligoastrocytoma III	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide. Procarbazine, lomustine, and vincristine (PCV).
Ependymoma, Subependymoma I, Myxopapillary ep[ependymoma I, ependymoma II, Anaplastic ependymoma III,	Radiosensitive tumors. 5 year survival improves from 2% with surgery alone to 50% with surgery plus radiation 60 Gy.
<b>Adult Nonglial Malignant Tumors</b>	
Primary CNS lymphoma (microglioma)	Dexamethasone, 10 mg initially, and 4 mg every 6 hours orally or intravenously. For spinal cord compression doses equivalent to dexamethasone, 50 mg per day PCV combination plus steroids or vincristine, 1.5 mg/m <sup>2</sup> intravenously weekly, doxorubicin (Adriamycin), 75 mg/m <sup>2</sup> intravenously on days 1 and 22, and prednisone, 40 mg/m <sup>2</sup> for 21 days, repeated every 6 weeks (APO) for 1 to 2 years or standard CHOP lymphoma chemotherapy.
Choroid plexus tumors, Choroid	Complete resection curative. Incompletely resected

plexus papilloma I, Atypical choroid plexus papilloma, Choroid plexus carcinoma	tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
Neuroepithelial tumors, Angiocentric glioma I, Chordoid glioma of the third ventricle II	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
Neuronal and mixed neuronal-glial tumors, Gangliocytoma I, Ganglioglioma I, Anaplastic ganglioma III, Desmoplastic infantile astrocytoma and ganglioglioma I, Dysembryoplastic neuroepithelial tumor I, Central neurocytoma II, Extraventricular neurocytoma II, Cerebellar liponeurocytoma II, Paraganglioma of the spina cord I, Papillary glioneuronal tumor I, Rosette-forming Glioneural tumor of the fourth ventricle.	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
Pineal Tumors, Pineocytoma I, Pineal parenchymal tumor of intermediate differentiation II & III, Pneuoblastoma IV, Papillary tumor of the pineal region II & III	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
Embryonal tumors, Medulloblastoma IV, CNS primitive neuroectodermal tumor IV, Atypical teratoid/rhaboid tumor IV	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
Tumors of the cranial and paraspinal nerves, Schwannoma I, Neurofibroma I, Perineurioma I, II & III, Malignant peripheral nerve sheath tumor II, III & IV	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
Meningioma, Meningioma I, Atypical meningioma II, Anaplastic/malignant meningioma III, Hemangiopericytoma II, Anaplastic hemangiopericytoma III, Hemangioblastoma I	Poorly responsive to surgery alone. Radiation of 50 Gy to 60 Gy.
Tumors of the sellar region, Craniopharyngioma I, Granular cell tumor of the neurohypophysis I, Pituicytoma I, Spindle cell oncocyoma of the adenohypophysis I	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
<b>Malignancies of Childhood</b>	
Diffuse Astrocytic tumors, Diffuse astrocytoma, IDH-mutant and IDH-wildtype, Anaplastic astrocytoma, IDH-mutant and IDH-wildtype, Glioblastoma, IDH-mutant and IDH-	Resection. Given the long-term side effects associated with radiation therapy, postoperative chemotherapy may be initially recommended. The most widely used regimens to treat tumor progression or symptomatic nonresectable, low-grade

wildtype, Diffuse midline glioma, H3K27M-mutant. Other Astrocytic tumors, Pilocytic astrocytoma, Subependymal giant cell astrocytoma, Pleomorphic astrocytoma, Anaplastic pleomorphic xanthoastrocytoma. Gliomas, Angiocentric glioma, Astroblastoma	gliomas are the following options, including carboplatin and vincristine (CV); thioguanine, procarbazine, lomustine, and vincristine (TPCV); vinblastine alone; temozolomide alone; or temozolomide in combination with carboplatin and vincristine.
Ependymal tumors: Subependymoma, Myxopapillary ependymoma, Ependymoma, Ependymoma, RELA fusion-positive, Anaplastic ependymoma	All patients undergo surgery to remove the tumor. Post-surgical treatment is radiation therapy consisting of 54 Gy to 59.4 Gy to the tumor bed for children aged 3 years and older. The use of radiation therapy (54 Gy) has been extended to patients as young as 1 year, with similar EFS and OS rates when compared with older children. For completely resected tumors, the 7-year EFS was 76.9%, without radiation the 5-year PFS rate was 61.4%. Near-total resection 5-year PFS rate was 68.5%. 5-year PFS rate was 25% for patients with subtotal resection, in whom a second surgery was not feasible, and 50% for patients in whom a second surgery resulted in a gross-total resection. Chemotherapy is used in patients with residual tumor in to attempt to achieve a state of no evidence of disease before the patients undergo radiation therapy
Neuronal and mixed neuronal-glioma tumors, Dysembryoplastic neuroepithelial tumor, Ganglioglioma, Desmoplastic infantile astrocytoma and ganglioma, Papillary glioneuronal tumor, Rosette-forming glioneuronal tumor, Diffuse leptomeningeal glioneuronal tumor, Extraventricular neurocytoma, Cerebella liponeurocytoma, Paraganglioma	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
Pineal tumors, Pineoblastoma,	Complete resection curative. Incompletely resected tumors irradiated with 50Gy to 55Gy. Oral Temozolomide.
Embryonal tumors, Medulloblastoma, WNT-activated, Medulloblastoma, SHH-activated and TP53-mutant, Medulloblastoma, SHH activated and TP53-wildtype, Medulloblastoma, non-WNT/non-SHH group 3, Medulloblastoma, non-WNT/non-SHH group 4, Medulloblastoma, classic, Medulloblastoma desmoplastic/nodular, Medulloblastoma with extensive	Complete surgical resection of the tumor is the optimal treatment. Craniospinal radiation of 45 Gy to 50 Gy to the posterior fossa and cervical cord, 35 Gy to the supratentorium and 35 Gy to 40 Gy to the spinal axis. Vincristine-based combination chemotherapy such as the PCV combination. Recurrent CNS embryonal tumors can respond to chemotherapeutic agents used singularly or in combination, including cyclophosphamide, cisplatin, carboplatin, lomustine, etoposide, topotecan, temozolomide, and antiangiogenic metronomic

modularity, Medulloblastoma, large cell/anaplastic, Embryonal tumor with multilayered rosettes C19MC-altered, Medulloepithelioma, CNS neuroblastoma, CNS ganglioneuroblastoma, Atypical teratoid/rhaboid tumor, CNS embryonal tumor with rhaboid features	therapy. The use of vismodegib is limited to skeletally mature children
Germinoma (pineal), Embryonal carcinoma, Yolk sac tumor, Choriocarcinoma, Mature teratoma, Immature teratoma, Teratoma with malignant transformation, Mixed germ cell tumor,	Germ cell tumors are radiosensitive; resection may be unnecessary. The dose of craniospinal irradiation is (24 Gy) followed by a boost to the primary site (40–45 Gy) resulting in 5-year overall survival rates of higher than 90%. Chemotherapy agents such as cyclophosphamide, bleomycin, ifosfamide, etoposide, cisplatin, and carboplatin are highly active in CNS germinomas. The use of chemotherapy before radiation therapy has increased survival rates
Sellar tumors, Adamanthomatous craniopharyngioma, Papillary craniopharyngioma	
Brain stem glioma	Complete resection curative. Incompletely resected tumors irradiated with 40Gy to 45Gy. Carboplatin and vincristine (CV) or thioguanine, procarbazine, lomustine, and vincristine (TPCV).
Low-grade tumors: optic glioma, cystic cerebellar astrocytoma, juvenile pilocytic astrocytoma	Benign lesions treated with surgery alone even at recurrence.
<b>Histologically Benign Tumors</b>	
Meningioma	Rarely recur if completely resected. Radiation to incompletely resected lesions.
Schwannoma (acoustic neuroma)	Rarely recur if completely resected. Radiation to incompletely resected lesions.
Pituitary adenoma	Focal radiation alone or surgery with radiation for incompletely resected tumors.
Craniopharyngioma	Resection followed by radiation.

Source: Hamilton '90: Table 39-1; Pg. 333, National Cancer Institute 2020

Primary brain tumors are a diverse group of diseases that together constitute the most common solid tumor of childhood. The Central Brain Tumor Registry of the United States (CBTRUS) estimates that approximately 4,300 U.S. children are diagnosed each year (Ostrom et al '13). Between 1975 and 2010, **childhood cancer** mortality decreased by more than 50% (Smith et al '14). While more than 70% of children diagnosed with brain tumors will survive for more than 5 years after diagnosis, survival rates are wide-ranging depending on tumor type and stage. Long-term sequelae related both to the effects of the tumor and its treatment are common. Debilitating effects on growth and neurologic development have frequently been observed after radiation therapy, especially in younger children. Secondary tumors have increasingly been diagnosed in long-term survivors. The dose and volume of radiation therapy appropriate for specific tumor types continues to be refined, and techniques for its administration (e.g., more conformal targeted-field design and protons) have evolved to mitigate the potential for adverse effects. In

addition, the role of chemotherapy in allowing a delay or reduction in the administration of radiation therapy is under study, and preliminary results suggest that chemotherapy can be used to delay, limit, and sometimes obviate, the need for radiation therapy in children with benign and malignant lesions (Smith et al '10).

**Astrocytomas** are many grades. Diffuse Astrocytic tumors, Diffuse astrocytoma, IDH-mutant II and IDH-wildtype, Anaplastic astrocytoma, IDH-mutant III and IDH-wildtype, Glioblastoma, IDH-mutant and IDH-wildtype IV, Diffuse midline glioma, H3K27M-mutant IV. Other Astrocytic tumors, Pilocytic astrocytoma I, Subependymal giant cell astrocytoma I, Pleomorphic xanthoastrocytoma II, Anaplastic pleomorphic xanthoastrocytoma III. Gliomas, Angiocentric glioma I, Choitoid glioma of the third ventricle II, Astroblastoma (uncertain) (Louis et al '07). Molecular subtypes of pediatric glioblastoma multiforme show prognostic significance. Patients whose tumors have histone K27M mutations have the poorest prognosis, with 3-year survival rates below 5%. In the thalamus, wild-type high-grade gliomas have a somewhat better prognosis than do those harboring an H3.3 mutation. For high-grade gliomas in the thalamus, patients with H3 wild-type tumors have a somewhat better prognosis (2-year overall survival [OS], 71%) than do patients who harbor H3 K27M mutations (2-year OS, 13%)(Karreman et al '18). Surgical resection is the primary treatment for childhood low-grade astrocytoma. Patients with gross-total resection had 8-year PFS rates exceeding 90% and OS rates of 99%. By comparison, approximately one-half of patients with any degree of residual tumor (as assessed by operative report and by postoperative imaging) showed disease progression by 8 years, although OS rates exceeded 90% (Wisoff et al '11). Given the long-term side effects associated with radiation therapy, postoperative chemotherapy may be initially recommended. The most widely used regimens to treat tumor progression or symptomatic nonresectable, low-grade gliomas are the following: Carboplatin with or without vincristine. Numerous options can be considered, including carboplatin and vincristine (CV); thioguanine, procarbazine, lomustine, and vincristine (TPCV); vinblastine alone; temozolomide alone; or temozolomide in combination with carboplatin and vincristine. Oral temozolomide was equal to nitrosurea combinations with fewer side-effects (Ater et al '12). The radiation therapy dose to the tumor bed is usually at least 54 Gy. Despite such therapy, overall survival (OS) rates remain poor. Similarly poor survival is seen in children with spinal cord primaries and children with thalamic high-grade gliomas (i.e., diffuse midline gliomas, H3 K27M-mutant tumors) treated with radiation therapy (Fouladi et al '03).

Primary CNS **Germ Cell Tumors** GCTs are a heterogeneous group of neoplasms that are more common in Japan and other Asian countries than in North America and Europe. In North America, they account for approximately 4% of all primary brain tumors, with a peak incidence from age 10 years to age 19 years and a male predominance in a pineal location (Ostrom '17). The dose of craniospinal irradiation is (24 Gy) followed by a boost to the primary site (40–45 Gy) resulting in 5-year overall survival rates of higher than 90%. Chemotherapy agents such as cyclophosphamide, ifosfamide, etoposide, cisplatin, and carboplatin are highly active in CNS germinomas. Patients receiving chemotherapy agents that require hyperhydration (e.g., cyclophosphamide, ifosfamide, and cisplatin) are often quite challenging to manage because of the possibility of diabetes insipidus in patients with primary tumors of the suprasellar region (Afzal '10). An international group of investigators has explored a chemotherapy-only approach primarily for younger children. The investigators were able to achieve a complete response in 84% of patients with germinomas treated with chemotherapy alone. Fifty percent of these patients suffered tumor relapse or progression; many recurrences were local, local plus ventricular, and ventricular alone and/or with leptomeningeal dissemination throughout the CNS,

which required additional therapy, including radiation. Subsequent studies have continued to support the need for radiation therapy after chemotherapy (Balmaceda et al '96). The prognosis for children with central nervous system (CNS) nongerminomatous germ cell tumors (NGGCTs) is that 10-year overall survival (OS) for NGGCTs ranges between 70% and 80%. Anticancer agents that have been used include carboplatin, etoposide, bleomycin, ifosfamide, and vinblastine in different combinations. The use of chemotherapy before radiation therapy has increased survival rates (Robertson et al '97).

**CNS atypical teratoid/rhabdoid tumor (AT/RT)** is a rare, clinically aggressive tumor that most often affects children aged 3 years and younger but can occur in older children and adults. Approximately one-half of AT/RTs arise in the posterior fossa. Treatment including radiation and intrathecal chemotherapy the reported 2-year progression-free survival rate was 53%, and the overall survival rate was 70% (Chi et al '09). Radiation therapy appears to have a positive impact on survival for AT/RT patients, with a 6-year overall survival (OS) rate of 66%. Radiation therapy was either focal (54 Gy) or craniospinal (36 Gy, plus primary boost), depending on the child's age and extent of disease at diagnosis. Radiation alone was better for children under age 3 (Bartelheim et al '16). The activity of tazemetostat in children with AT/RT is under clinical evaluation (Italiano et al '18).

**Embryonal tumors** (medulloblastoma and non-medulloblastoma) are a collection of biologically heterogeneous lesions, that share the tendency to disseminate throughout the nervous system via cerebrospinal fluid (CSF) pathways. They comprise 20% to 25% of primary CNS tumors arising in children. Five-year overall survival (OS) in children with equivocal findings (80%) was not different from 5-year OS in patients who had normal MRI findings (84.8%) (Pomeroy et al '02). CSF analysis is conventionally done 14 to 21 days after surgery. As many as 10% of patients will have evidence of free-floating tumor cells in the CSF without clear evidence of leptomeningeal disease on MRI scan (Bennet et al '17). Complete surgical resection of the tumor is the optimal treatment. Postoperatively, children may have significant neurologic deficits caused by preoperative tumor-related brain injury, hydrocephalus, or surgery-related brain injury. Radiation therapy to the primary tumor site is usually in the range of 54 Gy to 55.8 Gy. In most instances, this is given with a margin of 1 cm to 2 cm around the primary tumor site. Chemotherapy, usually given during and after radiation therapy, is a standard component of treatment for older children with medulloblastoma and other embryonal tumors. Chemotherapy can be used to delay and sometimes obviate the need for radiation therapy in 20% to 40% of children younger than 3 to 4 years with nondisseminated medulloblastoma (Packer et al '06). A multiagent chemotherapy regimen that included high-dose intravenous and intraventricular methotrexate has been used with 5 year EFS better than 90%. A variety of chemotherapeutic regimens have been successfully used, including the combination of cisplatin, lomustine, and vincristine or the combination of cisplatin, cyclophosphamide, and vincristine. In addition, postradiation high-dose cyclophosphamide supported by peripheral stem cell rescue, but with reduced cumulative doses of vincristine and cisplatin, has resulted in similar survival rates Oyharcabal-Bourden et al '05). Recurrent CNS embryonal tumors can respond to chemotherapeutic agents used singularly or in combination, including cyclophosphamide, cisplatin, carboplatin, lomustine, etoposide, topotecan, temozolomide, and antiangiogenic metronomic therapy (Abe et al '06). The use of vismodegib is limited to skeletally mature children (Robinson et al '17).

**Ependymomas** arise from ependymal cells that line the ventricles and passageways in the brain and the center of the spinal cord. Complete resection and postoperative radiation have relatively

favorable survival rates that are in the range of 80% at 5 years (Louis et al '16). Typically, all patients undergo surgery to remove the tumor. The standard post-surgical treatment for these patients has been radiation therapy consisting of 54 Gy to 59.4 Gy to the tumor bed for children aged 3 years and older. The use of radiation therapy (54 Gy) has been extended to patients as young as 1 year, resulting in similar EFS and OS rates when compared with children older than 3 years. For completely resected tumors, the 7-year EFS was 76.9%, without radiation the 5-year PFS rate was 61.4%. Near-total resection 5-year PFS rate was 68.5%. 5-year PFS rate was 25% for patients with subtotal resection, in whom a second surgery was not feasible, and 50% for patients in whom a second surgery resulted in a gross-total resection. Chemotherapy is used in patients with residual tumor in to attempt to achieve a state of no evidence of disease before the patients undergo radiation therapy (Indelicato et al '18).

The treatment of newly diagnosed **craniopharyngiomas** may include a combination of surgery, radiation therapy, cyst drainage, and/or intracystic interferon-alpha. Regardless of treatment given, the 5-year and 10-year survival rates exceed 90%. 50 Gy to 54 Gy, in 1.8-Gy fractions, restricting the optic chiasm dose to 54 Gy. Intra-cavitary instillation of radioactive phosphorus P 32 (32P), bleomycin, or interferon-alpha, for those with cystic recurrences (Yang '10). Subcutaneous peginterferon alpha-2b to manage cystic recurrences can result in durable responses (Yeung '12). Children with **brain stem gliomas** were prescribed carboplatin and vincristine (CV) or thioguanine, procarbazine, lomustine, and vincristine (TPCV). The 5-year event-free survival (EFS) and overall survival (OS) rates for all brain stem glioma patients were 45% ± 3.2% and 86% ± 2.2%, respectively. The 5-year event free survival (EFS) rates were 39% ± 4% for CV and 52% ± 5% for TPCV (Ater '12).

Dexamethasone, mannitol, and furosemide are used to treat the **peritumoral edema** associated with brain tumors. The use of anticonvulsants is mandatory for patients with seizures (Cloughesy et al '01). Pseudo ephedrine causes brain shrinkage, cognitive difficulties and should not be used to clear sinuses. Except in the treatment of CNS lymphoma, **steroid administration** has no cytologic effect on brain tumors, but by reducing tissue edema, steroids make a major impact on symptoms and may be life-saving. Doses equivalent to dexamethasone, 10 mg initially, and 4 mg every 6 hours orally or intravenously, are given. For impending spinal cord compression doses equivalent to dexamethasone, 50 mg per day, are recommended. Steroids may influence CT scans. Reduction of steroids can begin 7 to 14 days. Patients who receive steroids for longer than 4 to 6 weeks should be considered to have a suppressed pituitary-adrenal axis and should be advised that for up tot 1 year after stopping steroids, replacement therapy should be given in the even of serious illness or surgery. Approximately half of patients will have **seizures** as part of their presenting symptomatology. They are usually successfully managed with phenytoin 300 mg to 400 mg daily in single or divided doses, and/or phenobarbital 90 mg to 180 mg daily. Post-operatively most patients receive seizure medication for 6 to 12 months, at which time, if they have been seizure free, medication withdrawal can be considered (Hamilton '90: 341, 342). Methicillin resistant *Staphylococcus aureus* (MRSA) lesions are highly suspected in the development of spinal and brain cancer as well as non-carcinogenic back pain and stroke. Toxic shock syndrome from MRSA lesion exposure to *Streptococcus* spp. is so excruciating, there is no telling what sort of tissue damage might proliferate. MRSA and toxic shock syndrome is best treated with an **Epsom salt bath**.

### 3. Lung cancer

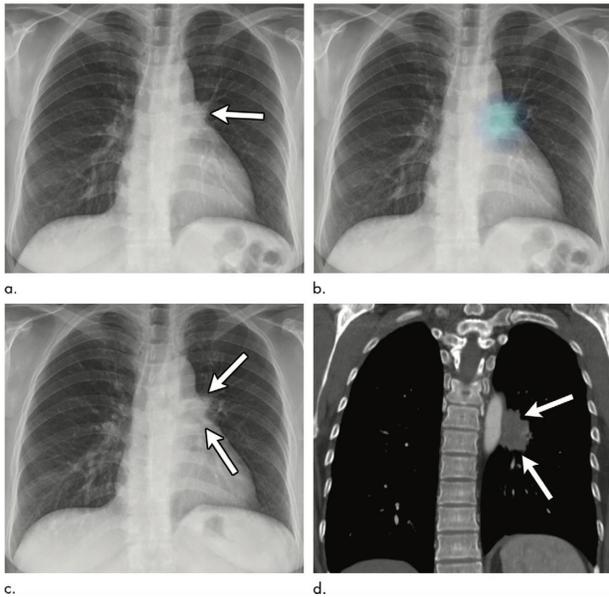
**Lung cancer** is the most common fatal neoplasm in the United States in both women and men. It has replaced tuberculosis as the major pulmonary cause of death. Approximately 150,000 new cases were diagnosed in 1988. In 2020, an estimated 228,820 new cases of lung cancer will be diagnosed in the US and 135,720 people will die from the disease. As a percentage of general population to estimate risk, the incidence rate has been declining since the mid-1980s in men, but only since the mid-2000s in women because of gender differences in historical patterns of smoking uptake and cessation. The incidence rate decreased from 2007 to 2016 by almost 3% per year in men and by 1.5% per year in women. The lung cancer death rate has declined by 51% since 1990 in men and by 26% since 2002 in women due to reductions in smoking, with the pace accelerating in recent years; from 2008 to 2017, the rate decreased by about 4% per year in men and 3% per year in women (ACS '20: 18). **Pre-diagnostic treatment** and concurrent treatment of precancerous and secondary pulmonary conditions should be emphasized to improve lung cancer care. Ampicillin (Principen) treats pneumonia. Pneumovax should be administered to the pulmonary patient to avoid many strains. A dab of hydrocortisone crème to the chest cures the cough and hard pulmonary nodules of aspergillosis that elaborates carcinogenic aflatoxin. Hydrocortisone crème, and essential oils of eucalyptus, lavender and peppermint help cure coronavirus and mold allergies without the Cushing's disease side-effect of prolonged corticosteroid use. Prednisone should be more widely used in lung cancer chemotherapy regimes because it is widely effective at treating all sorts of pulmonary and epithelial diseases.

The patient with **bronchogenic carcinoma** is generally past age 35. Only 3% of cases are diagnosed in patients before 35 years of age. Cough is the commonest symptom. Either the onset or a change in the nature of a chronic cough is the most common symptom. Hemoptysis is a particularly suggestive sign and should never be ignored, particularly in patients over 35 with a history of smoking. Vague nonpleuretic chest pain added to a worsening cough and hemoptysis is a common triad seen in these diseases. Dyspnea may occur, secondary either to an obstruction of an airway or to lymphatic spread of the tumor. Recurrent pneumonia may be the first evidence of the presence of endobronchial obstructive lesion. All pneumonias should be subjected to radiographs at intervals of 6 weeks to 2 months to document complete clearing. If an infiltrate persists, increases in size, does not fully resolve on serial radiographs or recurs in the same location, further diagnostic steps should be taken. Persistent infiltrate with evidence of volume loss is particularly worrisome. Weight loss and anorexia may be initial symptoms and most often signify extensive disease on diagnosis. A variety of symptoms may be caused by extension of the tumor within the thorax. Most of these signal advanced disease. Chest pain may be the result of pleural or rib involvement. Hoarseness is a sign of recurrent laryngeal nerve involvement. Extension to the autonomic nervous system can produce Horner's syndrome: ptosis, miosis, and anhidrosis on the affected side. Brachial plexus invasion, causing arm pain and paresthesias and often accompanied by Horner's syndrome, is referred to as Pancoast's syndrome. Blockage of the superior vena cava produces facial suffusion, edema and mental changes. Distant metastases to bone, brain, and liver often produce symptoms that prompt the first visit to the physician. Paraneoplastic syndromes frequently occur with lung cancer and occasionally produce the initial symptoms.

Pulmonary tumors produce a variety of **endocrinopathies**. Hypercalcemia may be caused by parathyroid hormone-like peptides, osteoclast-activating factor, or bony metastases. Inappropriate secretion of antidiuretic hormone (SIADH) may be produced particularly by small cell carcinomas and may cause hyponatremia. ACTH is commonly produced by lung cancers

but rarely cause full-blown Cushing's syndrome. More common is hypokalemia, based on an excess of secondary mineralocorticoid. Some hormones act to stimulate growth of tumor cells. Less understood are the neuromuscular paraneoplastic syndromes, which include Eaton-Lambert syndrome, myopathies, neuropathies, cerebellar degeneration, and dementia. One of these endocrinopathies is found in 5% to 10% of patients with bronchogenic carcinoma. Digital clubbing and hypertrophic pulmonary osteoarthropathy can occur together, but clubbing alone is more common. Hypertrophic pulmonary osteoarthropathy is manifested by periosteal elevation over the long bones, particularly the tibia and radius. This is frequently painful. Hypertrophic osteoarthropathy can also occur with nonmalignant intrathoracic processes such as lung abscess, bronchiectasis, chronic interstitial pneumonitis, bacterial endocarditis or cyanotic heart disease. It rarely occurs with extrathoracic processes such as ulcerative colitis, cirrhosis and thyroiditis. Migratory thrombophlebitis, often in unusual sites and resistant to treatment, is seen in lung cancer as in various other malignancies, but is not common. Thrombocytosis, thrombocytopenic purpura, fibrinolysis, hemolysis and red cell aplasia have also been described (Miller & Johnston '89: 321-322).

The **solitary pulmonary nodule** (SPN) is defined in radiographic terms as an opacity on the chest radiograph that is single, is rough to ovoid, is less than 6 cm in diameter, (large nodules are usually called chest masses, has distinct margins (is surrounded by aerated lung parenchyma and therefore not abutting chest wall, diaphragm, or mediastinum), and may or may not contain calcium obvious on the plain radiograph. The vast majority of SPNs do not cause symptoms or signs. Rare symptoms include hemoptysis, cough, clubbing and endocrinopathy. Up to a third have vague or nonspecific chest pain. About one third of SPNs in patients who have undergone operation are malignant (bronchogenic carcinoma, solitary metastasis, or bronchial adenoma). However, by selection of patient populations, the malignant percentage has varied from as low as 3% to as high as 80%. The overwhelming number of benign SPNs are granulomas caused by tuberculosis, histoplasmosis, or coccidioidomycosis; however, hamartoma cysts, and a host of rare benign neoplasms and other lesions have been reported. The crux of patient management involves removing primary malignant tumors and adenomas after carefully excluding all evidence of extrathoracic metastases. Some 25% to 50% of patients with "localized" bronchogenic carcinoma (appearing as SPNs) have 5 year cures. Most patients with benign lesions do not need an operation. The chance of an SPN being a primary bronchogenic carcinoma in patients less than 35 years of age is about 1%. Previous chest radiographs are extremely helpful because the growth rate of primary bronchogenic carcinoma is well known, with the average doubling time for most cell types being 4 to 7 months. More important, almost all of primary malignant bronchogenic SPNs double in volume within 1 to 16 months. If the nodule has not doubled in volume, within 16 months the lesion is not malignant. SPNs that double in volume within 30 days are almost always inflammatory. Calcification almost always indicates a benign lesion. The patient's smoking history is statistically very helpful. Oat cell, squamous cell and undifferentiated bronchogenic carcinomas are all highly related to cigarette smoking and rarely occur in nonsmokers. Adenocarcinoma, bronchial adenoma, and alveolar cell carcinoma are not closely related to smoking. Overall, nonsmoking patients with SPNs have about a 9:1 chance of having a benign disease (Neff & Perry '89: 312-314).



In the majority of cases of lung cancer, the **chest radiograph** is abnormal at the time of diagnosis. A common radiographic abnormality is the solitary pulmonary nodule, by definition less than 3 cm in diameter and completely surrounded by lung tissue. Larger lesions are termed masses. The importance of solitary pulmonary nodule is that it represents the most curable group of lung tumors with a 5-year survival rate of 70% to 90% if metastases are absent. Lung tumors, particularly squamous cell carcinomas, may cavitate. Therefore cavitory lesions should be considered potentially neoplastic. Lung abscesses can be due to underlying neoplasm, particularly in smokers. Pneumonitis that fails to resolve over 6 to 8 weeks may be a manifestation of a tumor. Atelectasis is highly suggestive of a

malignant endobronchial obstruction. Alveolar infiltrates may represent bronchioloalveolar carcinoma, and interstitial markings with Kerley B lines can be caused by lymphangitic spread of a tumor, either primary (in the lung) or metastatic. Dense, central, concentric or "popcorn" calcification seen on plain radiographs or conventional tomography is a reliable sign that a nodule is benign. Lesions that double in volume in less than 30 days are most often inflammatory. The most reliable sign of a benign tumor is lack of growth over a 2 year period. Dense, central, concentric, or "popcorn" calcification seen on plain radiographs of conventional tomography is a reliable sign that a nodule is benign. However, lesions containing only a fleck of calcification may represent scar carcinomas growing near an old calcified lesion. Malignant tumors are not common in patients under 35. Sputum cytology is noninvasive and is easily performed. Approximately two thirds of central lesions and one third of peripheral lesions can be diagnosed by this means, but the exact cell type is difficult to determine (Miller & Johnston '89: 323-326).

### Staging System for Lung Cancer

#### PRIMARY TUMOR (T)

TX	Tumor either proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically or cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i>
T1	Tumor 3 cm or less in greatest diameter, surrounded by lung or visceral pleura and without invasion proximal to a lobar bronchus.
T2	Tumor more than 3 cm in greatest diameter or a tumor of any size that either invades visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilum. The proximal extent must be within a bronchus or at least 2 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung, and there must be no pleural effusion.
T3	Tumor of any size with direct extension into adjacent structures such as parietal pleura or chest wall, diaphragm, or the mediastinum and its contents; a tumor involving a

main bronchus less than 2 cm distal to the carina; any tumor associated with atelectasis obstructive pneumonitis of the an entire lung ;or a pleural effusion.

#### NODAL INVOLVEMENT (N)

- NX Minimal requirements to assess regional nodes cannot be met
- N0 No evidence of involvement of regional lymph nodes
- N1 Metastasis to lymph nodes in peribronchial or ipsilateral hilar region including direct extension
- N2 Metastasis to lymph nodes in the mediastinum

#### DISTANT METASIS (M)

- MX Minimum requirement to assess presence of distant metastasis cannot be met
- M0 No evidence of distant metastasis
- M1 Distant metastasis present

#### STAGE GROUPING

Occult Stage: TX, N0, M0

Stage I: Tis, N0, M0 (carcinoma *in situ*)

T1, N0, M0

T1, N1,, M0

T2, N0, M0

Stage II: T2, N1, M0

Stage III: T3 with any N or M

N2 with any T or M

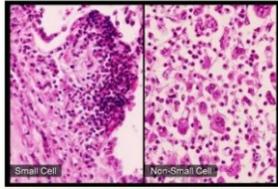
M1 with any T or N

Source: Idhe '89: 191 Table 25-1

The **four major lung cancer cell types** (adenocarcinoma, squamous, large cell and small cell) theoretically originate from a common stem cell. Adenocarcinoma of the lung is characterized by gland formation and intracellular mucin. Although incidence varies between series, this cell type appears to be increasing in frequency and is probably the most common, accounting or approximately 40% of cases. Squamous cell carcinoma is characterized by intracellular bridges and keratin synthesis, often with typical keratin "pear" formations, and currently accounts for about 30% of al lung cancer. Small cell lung cancer (formerly oat cell carcinoma) accounts for 20% of lung cancers. A characteristic chromosomal abnormality, has been identified in the majority of small cell lung cancers. Bomesin, or gastrin-releasing peptide, has been shown to have a high correlation to increased expression of the c-myc oncogene. Less common primary malignant tumors of the lung include large cell carcinoma and bronchioloalveolar cell carcinoma (a subset of adenocarcinoma) which accounts for 5% to 8% of lung cancers. The most consistent abnormality in involving oncogenes in non-small cell lung cancer is a mutation of the Ki-ras oncogene that gives it the ability to transform rodent fibroblasts. Rare cell types include giant cell carcinoma, clear cell carcinoma, and pulmonary blastoma, which account for less than 2% of lung cancers. Bronchial adenomas and carcinoid tumors are classified as benign lung tumors, although they have a rare but significant tendency to metastasize (Miller & Johnston '89: 319-321).

## Types of Lung Cancer

- Non-small cell carcinoma (NSCC) (87%)
  - Adenocarcinoma (38%)
  - Squamous cell (20%)
  - Large cell (5%)
- **Small cell carcinoma (13%)**



If a lesion is associated with a pleural effusion, **thoracentesis with cytology** and possibly **needle pleural biopsy** is a logical early step in workup. Negative cytologic results in sputum or pleural fluid do not definitely exclude malignancy. More invasive techniques for diagnosis include flexible fiberoptic bronchoscopy and transthoracic needle biopsy. **Flexible fiberoptic bronchoscopy** with transbronchial biopsy has several advantage over the transthoracic needle biopsy. It is a low-morbidity procedure: mortality is less than 0.05% and risk of pneumothorax is less than 1%.

The diagnostic yield ranges from 50% to 90%, depending on the location of the lesion. Furthermore, **endobronchial biopsies** should be obtained at potential surgical margins of the bronchial tree to rule out submucosal spread of tumor. Transthoracic needle biopsy has the advantage of a higher yield (approximately 90% to 95% accuracy) than bronchoscopy. However, the risk of pneumothorax is between 20% and 30% and one third of these require chest tube insertion. An aspiration technique is most commonly used and yields tissue for cytology and microbiologic testing only. Identification of cell type of tumors is not as accurate as with tissue biopsies. False identification of cancers as benign lesions occurs and can delay therapy (Miller & Johnston '89: 326-328).

## Lung Cancer Treatment

Type of Lung Cancer	Treatment
Non Small Cell Lung Cancer	<p>Surgery is potentially the most curative therapeutic option. Hypofractionated radiation therapy 60 Gy to 70 Gy delivered over 3 to 4 weeks with 2.4 Gy to 4.0 Gy per day. Standard treatment options for patients with newly diagnosed stage IV, relapsed, and recurrent disease include the following:</p> <ol style="list-style-type: none"> <li>1. Cytotoxic combination chemotherapy with platinum (cisplatin or carboplatin) and paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, protein-bound paclitaxel, or pemetrexed.</li> <li>2. Combination chemotherapy with monoclonal antibodies: Bevacizumab. Cetuximab. Nectinumab.</li> <li>3. Maintenance therapy after first-line chemotherapy (for patients with stable or responding disease after four cycles of platinum-based combination chemotherapy). Maintenance therapy following first-line chemotherapy. Pemetrexed following first-line platinum-based combination chemotherapy. Maintenance erlotinib following platinum-based doublet chemotherapy.</li> <li>4. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) (for patients with EGFR mutations). Osimertinib. Dacomitinib. Gefitinib. Erlotinib. Afatinib.</li> <li>5. Anaplastic lymphoma kinase (ALK) inhibitors (for patients with ALK translocations): Alectinib. Crizotinib. Ceritinib. Brigatinib. Lorlatinib.</li> <li>6. BRAF V600E and MEK inhibitors (for patients with BRAF V600E mutations). Dabrafenib and trametinib.</li> <li>7. ROS1 inhibitors (for patients with ROS1 rearrangements): Entrectinib. Crizotinib.</li> <li>8. Neurotrophic tyrosine kinase (NTRK) inhibitors (for patients with NTRK</li> </ol>

	fusions): Larotrectinib. Entrectinib. 9. Immune checkpoint inhibitors with or without chemotherapy: Pembrolizumab plus chemotherapy. Pembrolizumab alone. 10. Everolimus (for patients with unresectable, locally advanced or metastatic, progressive, well-differentiated, nonfunctional, neuroendocrine tumors). 11. Local therapies and special considerations: Endobronchial laser therapy and/or brachytherapy (for obstructing lesions). External-beam radiation therapy (EBRT) (primarily for palliation of local symptomatic tumor growth). Treatment of second primary tumor. Treatment of brain metastases.
Squamous	Docetaxel and Cisplatin (DP). Vinorelbine.
Adenocarcinoma	Bevacizumab, paclitaxel and carboplatin. Cisplatin and Pemetrexed. Pemetrexed and Carboplatin (PC). Vinorelbine. Pembrolizumab plus carboplatin and pemetrexed. Dabrafenib for <i>BRAF</i> V600E mutations.
Large Cell	Bevacizumab, paclitaxel and carboplatin. Cisplatin and Pemetrexed. Pemetrexed and Carboplatin (PC). Vinorelbine. Pembrolizumab to carboplatin plus pemetrexed. Pembrolizumab.
Small Cell Lung Cancer	Chemotherapy and radiation therapy have been shown to improve survival for patients with small cell lung cancer (SCLC). Surgery is not effective at preventing metastatic recurrence. Platinum and etoposide is the most widely used standard chemotherapeutic regimen. Standard treatment is considered to be Etoposide + cisplatin or Etoposide + carboplatin. Cisplatin + irinotecan was equal. Standard-dose PCI (25 Gy in 10 fractions). Topotecan is a standard chemotherapy for recurrent SCLC. PD-L1 inhibitors, atezolizumab and durvalumab, demonstrated prolongation of overall survival.

Source: National Cancer Institute. PDQ for Health Professionals. Non Small Cell Lung Cancer 2020 and Small Cell Lung Cancer 2020

**Non small cell lung cancer (NSCLC)** - squamous (epidermoid) carcinoma, adenocarcinoma and large cell carcinoma of the lung comprise approximately 75% of all cases of lung cancer in the United States. Squamous cell carcinoma is most clearly related to cigarette smoking, and possibly candidiasis. Adenocarcinoma is more common in women and is the most frequent type of lung cancer in nonsmokers. Squamous cancer usually presents as a central endobronchial lesion, and regional lymph nodes are the most common site of metastatic disease.

Adenocarcinoma more often arises in the periphery of the lung and relatively infrequently invades the pleural space, causing a pleural effusion. Distant metastases at diagnosis are common. The 5-year survival of all patients with NSCLC is only approximately 10% and there has been no marked improvement over the past few decades. The five year survival with distant metastatic NSCLC is less than 1%. Pathologically confirmed stages I and II are surgically resectable. Stage III includes extrapleural invasion. Patients are divided into three groups of approximately equal size: patients with tumor confined to the lung and hilar nodes that can be surgically resected; those with more advanced locoregional disease that is managed with radiotherapy, surgery, or both, and a third group with distant metastases who are treated with palliative irradiation or sometimes with chemotherapy. There is no evidence that different cell types of NSCLC differ in their responsiveness to chemotherapy. There is no proven role for postoperative adjuvant immunotherapy, radiotherapy or chemotherapy after complete surgical resection. Radiotherapy may reduce local occurrence of Stage II tumors, but no survival benefit

is noted. Following complete resection of Stage I NSCLC, 5 year survival is 40% to 50%, in Stage II patients it is 15% to 30% (Ihde, '89: 189, 193). Surgical therapy is offered as the best chance for cure in non-small cell carcinoma of the lung. For patients with non-small cell lung cancer who are not surgical candidates radiation therapy can be effective, particularly for palliation of symptoms of bronchial obstruction, bone pain, superior vena cava syndrome, or spinal cord compression. Radiotherapy has occasionally been curative, but most patients suited for cure by radiation are also surgical candidates and receive surgery. Potentially curative doses of radiation will cause loss of pulmonary function, which is often comparable to loss from resection (Miller & Johnston '89: 328, 332).

NSCLC is any type of epithelial lung cancer other than small cell lung cancer (SCLC). The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, but there are several other types that occur less frequently, and all types can occur in unusual histologic variants. NSCLCs are relatively insensitive to chemotherapy and radiation therapy compared with SCLC. Patients with resectable disease may be cured by surgery or surgery followed by chemotherapy. Local control can be achieved with radiation therapy in a large number of patients with unresectable disease, but cure is seen only in a small number of patients. Patients with locally advanced unresectable disease may achieve long-term survival with radiation therapy combined with chemotherapy. Patients with advanced metastatic disease may achieve improved survival and palliation of symptoms with chemotherapy, targeted agents, and other supportive measures. Epidermoid or Squamous cell carcinoma usually starts near a central bronchus. Adenocarcinoma and bronchioloalveolar carcinoma usually originate in peripheral lung tissue. Large cell carcinoma is another common histology (Sayer et al '04). There is a high risks of second tumors in long-term survivors, including rates of 10% for second lung cancers and 20% for all second cancers (Johnson et al '98).

WHO/IASLC Histologic Classification of NSCLC. 1. **Squamous cell carcinoma:** Papillary. Clear cell. Small cell. Basaloid. Adenocarcinoma. Acinar. Papillary. Bronchioloalveolar carcinoma. Nonmucinous. Mucinous. Mixed mucinous and nonmucinous or indeterminate cell type. Solid adenocarcinoma with mucin. 2. **Adenocarcinoma** with mixed subtypes. Variants: Well-differentiated fetal adenocarcinoma. Mucinous (colloid) adenocarcinoma. Mucinous cystadenocarcinoma. Signet ring adenocarcinoma. Clear cell adenocarcinoma. 3. **Large cell carcinoma:** Large cell neuroendocrine carcinoma (LCNEC). Combined LCNEC. Basaloid carcinoma. Lymphoepithelioma-like carcinoma. Clear cell carcinoma. Large cell carcinoma with rhabdoid phenotype. 4. **Adenosquamous carcinoma.** 5. **Carcinomas with pleomorphic, sarcomatoid,** or sarcomatous elements: Carcinomas with spindle and/or giant cells. Spindle cell carcinoma. Giant cell carcinoma. Carcinosarcoma. Pulmonary blastoma. 6. **Carcinoid tumor:** Typical carcinoid. Atypical carcinoid. 7. **Carcinomas of salivary gland:** Mucoepidermoid carcinoma. Adenoid cystic carcinoma. 8. Unclassified carcinoma (Travis et al '99).

**Surgery** is potentially the most curative therapeutic option for this disease. Postoperative chemotherapy may provide an additional benefit to patients with resected NSCLC. Radiation therapy combined with chemotherapy can produce a cure in a small number of patients and can provide palliation in most patients. Prophylactic cranial irradiation may reduce the incidence of brain metastases, but there is no evidence of a survival benefit and the effect of prophylactic cranial irradiation on quality of life is not known. In patients with advanced-stage disease, chemotherapy or epidermal growth factor receptor (EGFR) kinase inhibitors offer modest improvements in median survival, although overall survival is poor. Endobronchial therapies that preserve lung function include photodynamic therapy, electrocautery, cryotherapy, and Nd-

YAG laser therapy (Jeremy et al '07). **Lobectomy**, pneumonectomy, segmentectomy or wedge resection and sleeve resection may be indicated by the surgeon's intraoperative findings. The chosen procedure will remove all of the tumor with adequate margins of resection and maximum conservation of normal lung tissue. Postoperative mortality of 3% for lobectomy and 5% to 8% for pneumonectomy can be anticipated. The five year survival rate following complete resection of Stage I NSCLC is 40% to 50% and for Stage II 15% to 30%. Surgeons must take precautions that they do not remove too much parenchymal tissue to cause respiratory insufficiency. The predicted postoperative FEV<sub>1</sub> should exceed 800 ml. Loss of pulmonary function is roughly proportional to the percentage of total lung resected. The five year survival rate by clinical stage is as follows I (45-50%), II (25-30%), IIIa (15-20%), IIIb (5%), IV (2%). Patients with stage I, II, or IIA disease are usually assigned surgical therapy, whereas those in stages IIIb and IV are generally not believed to be candidates for curative surgery. Metastasis to contralateral mediastinal or hilar nodes places a patient in a nonsurgical category. Direct chest wall extension and selected instances of mediastinal invasion in the absence of mediastinal nodal metastasis are potentially surgically curable. **Cervical mediastinoscopy** is a minor procedure that is usually performed under general anesthesia. A small incision is made in the suprasternal notch, and the pretracheal space is entered. An instrument similar to a laryngoscope is inserted and advanced into the middle mediastinum. Paratracheal, high parabrachial and subcarinal lymph nodes can be routinely sampled. Since the trachea lies posterior to the aortic arch and main pulmonary arteries, the surgeon does not have access to the anterior and superior mediastinum. Mediastinoscopy carries a less than 2% complication rate and changes the clinical staging in 30% of lung cancer patients. It is the most important factor in increasing the resectability rate to well over 90% in patients undergoing exploratory thoracotomy (Miller & Johnston '89: 328-331).

**Radiotherapy** alone is the usual treatment given to most patients with advanced regional NSCLC with a 5 year survival of only 5% to 10%. Irradiation is not begun in patients with poor performance status, malignant pleural effusion or bulky tumors and poor pulmonary function, or those with early progressive tumor or distant metastases. Potentially curative radiotherapy is customarily administered to a total dose of 55 Gy to 60 Gy (5500-6000 rad/cGy) in continuous fractionation using megavoltage equipment. In the 40 Gy to 60 Gy range, increasing tumor dose is associated with a higher rate of complete response and decreased frequency of local recurrence, but no definitive improvement in survival due to the high probability of occult distant metastases at the time of irradiation. The role of chemotherapy has yet to be established. Chest irradiation provides the best available palliation for symptoms due to locoregional NSCLC, and it is especially effective in ameliorating pain, hemoptysis, superior vena cava obstruction, and pneumonitis distal to an incompletely obstructed bronchus. Atelectasis and vocal cord paralysis are less often relieved. Surgical resection is integrated into the management of some intrathoracic Stage III NSCLC with advanced primary tumors and absence of mediastinal node involvement with a 5 year survival as high as 20% to 35%. Bulky peripheral tumors that directly invade adjacent structures with no or only hilar nodal metastases can be resected with curative intent. Patients with only parietal pleural (not chest wall) involvement and those without nodal metastases have a better prognosis. Empiric preoperative irradiation is sometimes given to improve the likelihood of resectability. Postoperative irradiation is often administered and reduces the rate of local recurrence, but survival benefit has not been conclusively shown. Prospects for prolonged survival are dismal in patients with distant metastatic NSCLC. Median survival of fully ambulatory patients is 6 months and is only 1 to 2 months for bedridden patients. Five-year survival is less than 1%. Since there is no convincing evidence that any form of therapy improves survival in this setting, palliation of symptoms is the most important goal in management of Stage III M1 disease. Radiotherapy plays a major role in this regard. Single-

agent chemotherapy of NSCLS yields only 5% to 20% response rates and does not affect survival. Recently, combination chemotherapy regimens have produced higher response rates (20% to 40%) in patients with good performance status, but complete responses are uncommon, but complete responses of 2 years' duration have been documented. Outside a clinical trial setting, individual patients may be offered a published chemotherapy regimen provided that the patients (1) is of good performance status, (2) has evaluable tumor lesions so that response to treatment can be assessed and therapy stopped if it proves ineffective, and (3) understands the limitations of chemotherapy but still wants treatment (Ihde '89: 192-194). **Hypofractionated radiation therapy** involves the delivery of a slightly higher dose of radiation therapy per day (e.g., 2.4–4.0 Gy) over a shorter period of time compared with conventionally fractionated radiation therapy. Multiple prospective phase I/II trials have demonstrated that hypofractionated radiation therapy to a dose of 60 Gy to 70 Gy delivered over 3 to 4 weeks with 2.4 Gy to 4.0 Gy per day resulted in a low incidence of moderate to severe toxicity, 2-year OS of 50% to 60%, and 2-year tumor local control of 80% to 90%. There is an 18% relative increase in the risk of death for patients who received PORT compared with surgery alone (Bradley et al '05).

**Chemotherapy** for non-small cell carcinoma is disappointing. Response rates vary from 10% to 40%. Cure is not expected, and prolongation of life has been demonstrated only when chemotherapy is used as an adjuvant to resection. Chemotherapy for small cell lung cancer is effective, achieving an 80% initial response rate and increasing mean survival from 13 weeks to 13 months. It has been reported that up to 5% are potentially cured. Disease limited to the thorax and supraclavicular nodes is termed "limited and has a better prognosis than "extensive" disease., such as extrathoracic metastases. A recent series describes a 20% 4-year survival in optimally treated "limited" small cell lung cancer. Brain metastases are so common that prophylactic cranial irradiation is often recommended for patients with limited disease who achieve complete intrapulmonary responses to chemotherapy. Recurrence at the site of the primary pulmonary tumor occurs frequently and may be a major reason for failure of current regimen. Trials comparing radiotherapy with surgery for local control of primary disease are under way (Miller & Johnston '89: 332).

**Standard treatment** options for patients with newly diagnosed stage IV, relapsed, and recurrent disease include the following: 1. Cytotoxic combination chemotherapy with platinum (cisplatin or carboplatin) and paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, protein-bound paclitaxel, or pemetrexed. 2. Combination chemotherapy with monoclonal antibodies: Bevacizumab. Cetuximab. Necitumumab. 3. Maintenance therapy after first-line chemotherapy (for patients with stable or responding disease after four cycles of platinum-based combination chemotherapy). Maintenance therapy following first-line chemotherapy. Pemetrexed following first-line platinum-based combination chemotherapy. Maintenance erlotinib following platinum-based doublet chemotherapy. 4. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) (for patients with EGFR mutations). Osimertinib. Dacomitinib. Gefitinib. Erlotinib. Afatinib. 5. Anaplastic lymphoma kinase (ALK) inhibitors (for patients with ALK translocations): Alectinib. Crizotinib. Ceritinib. Brigatinib. Lorlatinib. 6. BRAF V600E and MEK inhibitors (for patients with BRAF V600E mutations). Dabrafenib and trametinib. 7. ROS1 inhibitors (for patients with ROS1 rearrangements): Entrectinib. Crizotinib. 8. Neurotrophic tyrosine kinase (NTRK) inhibitors (for patients with NTRK fusions): Larotrectinib. Entrectinib. 9. Immune checkpoint inhibitors with or without chemotherapy: Pembrolizumab plus chemotherapy. Pembrolizumab alone. 10. Everolimus (for patients with unresectable, locally advanced or metastatic, progressive, well-differentiated, nonfunctional, neuroendocrine tumors). 11. Local therapies and special considerations: Endobronchial laser therapy and/or brachytherapy

(for obstructing lesions). External-beam radiation therapy (EBRT) (primarily for palliation of local symptomatic tumor growth). Treatment of second primary tumor. Treatment of brain metastases.

The preponderance of evidence indicates that postoperative **cisplatin** combination chemotherapy provides a significant survival advantage to patients with resected stage II NSCLC. Preoperative chemotherapy may also provide survival benefit. Postoperative cisplatin-based chemotherapy in combination with vinorelbine (PORT '05). Preoperative chemotherapy provided an absolute benefit in survival of 6% across all stages of disease, from 14% to 20% at 5 years. The use of chemotherapy has produced objective responses and small improvement in survival for patients with metastatic disease. Patients with squamous histology benefited from docetaxel, and those with nonsquamous histologies appeared to benefit more from pemetrexed. Commonly utilized regimens include cisplatin/etoposide (EP5050) and weekly carboplatin/paclitaxel. Cisplatin-based combinations plus radiation therapy resulted in a 10% reduction in the risk of death compared with radiation therapy alone (Weick et al '91). Combination chemotherapy for the lungs have been described as Carboplatin and Etoposide (CE). Cisplatin and Pemetrexed. Docetaxel and Capecitabine (DC). Docetaxel and Cisplatin. Etoposide and Cisplatin (GC). Irinotecan and Carboplatin (IC). Irinotecan and Cisplatin (IP). Paclitaxel and Carboplatin (PC or TC). Pemetrexed and Carboplatin (PC). Vinorelbine and Cisplatin (VC)(Solimando & Waddell '12)

Patients who were treated with vinorelbine had a 1-year survival rate of 32%, compared with 14% for those who were treated with supportive care alone. Response rates were 25% in the cisplatin-plus-gemcitabine arm and 16% in the carboplatin-plus-paclitaxel arm; median survival times were 6.8 months in the cisplatin-plus-gemcitabine arm and 6.1 months in the carboplatin-plus-paclitaxel arm; 1-year survival rates were 25% in the cisplatin-plus-gemcitabine arm and 19% in the carboplatin-plus-paclitaxel arm (Tester et al '04). Randomized controlled trials of patients with stage IV disease and good PS have shown that cisplatin-based chemotherapy improves survival and palliates disease-related symptoms. Patients with nonsquamous cell histology, good PS, no history of hemoptysis or other bleeding, or recent history of cardiovascular events may benefit from the addition of **bevacizumab** to paclitaxel and carboplatin. In one randomized study patients received paclitaxel and carboplatin alone, and 434 patients received paclitaxel and carboplatin plus bevacizumab. Median survival was 12.3 months in the group assigned to chemotherapy plus bevacizumab, as compared with 10.3 months in the chemotherapy-alone group (Sandler et al '06).

Patients with tumors harboring sensitizing mutations in exons 19 or 21 of *EGFR*, particularly those from East Asia, never smokers, and those with adenocarcinoma may benefit from epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as an alternative to first- or second-line chemotherapy (Yang et al '15). **Osimertinib** was approved by the FDA for first-line treatment of *EGFR*-mutant NSCLC (exon 19 deletion or L858R). PFS, the primary endpoint, was significantly longer with osimertinib, 18.9 months vs. 10.2 months with gefitinib or erlotinib. The objective response was 71% with osimertinib versus 31% with platinum therapy (Soria et al '18). **Dacomitinib**, a second-generation, irreversible EGFR TKI, administered orally at a dose of 45 mg per day with gefitinib administered orally at a dose of 250 mg per day, as first-line therapy in patients with newly diagnosed advanced NSCLC harboring the following EGFR mutations: exon 19 deletion or exon 21 L858R substitution mutations, as detected by an FDA-approved test. Median PFS was 14.7 months in the dacomitinib group and 9.2 months in the gefitinib group (Wu et al '17).

Patients with tumors harboring *LK* translocations, *ROS1* rearrangements, or *NTRK* fusions may benefit from anaplastic lymphoma kinase (ALK), ROS1, or neurotrophic tyrosine kinase (NTRK) inhibitors as an alternative to first- or second-line chemotherapy. *ROS1* rearrangements occur in approximately 1% of patients with NSCLC. Crizotinib and entrectinib are approved by the FDA for use in patients with NSCLC and *ROS1* rearrangements, with the latter appearing to have greater activity against intracranial disease. Entrectinib has received FDA approval for treatment of patients with metastatic NSCLC whose tumors are *ROS1*-positive, regardless of the number of previous systemic therapies. The objective response rate in 53 efficacy-evaluable patients was 77%. Six percent of patients had a complete response and 72% had a partial response. **Crizotinib** was approved for patients with metastatic NSCLC whose tumors are *ROS1*-positive, regardless of the number of previous systemic therapies. The overall response rate was 72%. Six percent of patients had a complete response, 66% had a partial response, and 18% had stable disease as their best response. Patients with *ALK*-translocated locally advanced or metastatic NSCLC who had disease progression after crizotinib treatment were randomly assigned to receive 90 mg **brigatinib** every day (n = 112; 109 treated) or 180 mg brigatinib every day with a 7-day lead-in at 90 mg every day. The objective response rate was 45% for patients who received the 90 mg dose and 54% for patients who received the 180 mg dose. **Lorlatinib** 100 mg once daily continuously in 21-day cycles had an objective response of 90.0% and intracranial response of 66.7% in previously untreated patients (Hida et al '17).

Somatic gene fusions in *NTRK* occur across a range of solid tumors including in fewer than 0.5% of NSCLC tumors. The objective response rate was 75% and 73% of these responses lasted at least 6 months. Treatment was well tolerated with 93% of adverse events being grade 1 to 2. The FDA has approved **larotrectinib** for the treatment of patients who have locally advanced or metastatic tumors that harbor an *NTRK* gene fusion without a known acquired resistance mutation, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment. **Entrectinib** has received accelerated FDA approval for the treatment of solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, are metastatic, have progressed after treatment, have no satisfactory alternative therapy, or for cases in which surgical resection is likely to result in severe morbidity. The objective response rate in 54 patients was 57%. Seven percent of patients had a complete response and 50% had a partial response. The 12-month event-free survival was 68.4% for the **alectinib** group compared with 48.7% for the crizotinib group. 250 mg of crizotinib orally twice a day or the combination of pemetrexed and cisplatin or carboplatin for up to six cycles. Crizotinib is superior to chemotherapy in prolonging PFS 10.9 months vs. 7.0 months. Median PFS was 16.6 months in the **ceritinib** group and 8.1 months in the chemotherapy group - cisplatin or carboplatin and pemetrexed) every 3 weeks for four cycles, followed by maintenance pemetrexed (Peters et al '17).

Patients with tumors expressing PD-L1 (>50% by immunohistochemistry) have improved survival with **pembrolizumab**. The addition of pembrolizumab to carboplatin plus pemetrexed chemotherapy for nonsquamous advanced lung cancer improves survival irrespective of PD-L1 expression. Second-line systemic therapy with nivolumab, docetaxel, pemetrexed, or pembrolizumab for PD-L1-positive tumors also improves survival in patients with good PS (who have not received the same or a similar agent in the first-line setting). Pembrolizumab is a humanized monoclonal antibody that inhibits the interaction between the programmed death protein 1 (PD-1) coinhibitory immune checkpoint expressed on tumor cells and infiltrating immune cells and its ligands, PD-L1 and PD-L2. Pembrolizumab plus chemotherapy is

effective. The median OS for patients who received pembrolizumab alone was 30 months versus 14.2 months for patients who received chemotherapy. Pembrolizumab in combination with pemetrexed and carboplatin received FDA approval as first-line treatment of patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression. Pembrolizumab also received approval as a first-line monotherapy for patients with NSCLC whose tumors express PD-L1 ( $\geq 50\%$  staining as determined by a test approved by the FDA). Patients with adenocarcinoma may benefit from pemetrexed and bevacizumab, as well as from combination chemotherapy with pembrolizumab (Garassino et al '20). **Durvalumab** is a selective human IgG1 monoclonal antibody that blocks programmed death-ligand 1 (PD-L1) binding to programmed death 1 (PD-1) and CD80, allowing T cells to recognize and kill tumor cells. The median PFS was 16.8 months with durvalumab versus 5.6 months with placebo (Antonio et al '17).

Patients with unresectable, locally advanced or metastatic, well-differentiated, nonfunctional, neuroendocrine tumors benefit from the mammalian target of rapamycin (mTOR) inhibitor – everolimus. **Everolimus** is used for patients with unresectable, locally advanced or metastatic, progressive, well-differentiated, nonfunctional, neuroendocrine tumors. Everolimus, an oral mTOR inhibitor, is clinically active against advanced pancreatic and nonpancreatic neuroendocrine tumors. Median PFS was 11.0 months in the everolimus arm and 3.9 months in the placebo group (Yao et al '16). *BRAF* V600E mutations occur in 1% to 2% of lung adenocarcinomas. Patients were treated with **dabrafenib** (a BRAF inhibitor) 150 mg twice a day and trametinib (a MEK inhibitor) 2 mg every day overall response rate was 64%. Six percent of patients had a complete response, and 58% of patients had a partial response. The combination of dabrafenib and trametinib received approval in the treatment of patients with NSCLC whose tumors harbor *BRAF* V600E mutations as detected by an FDA-approved test (Planchard et al '17).

**Small cell lung cancer (SCLC)**, sometimes called oat cell carcinoma, differs from other types of cancer and the response to therapy so it is treated differently. Compared with other types of lung cancer, SCLC has a rapid clinical course with shorter duration of symptoms prior to diagnosis and median survival in the absence of treatment of 2 months for disseminated and 4 months for localized disease. Almost 70% of patients will have distant metastases in autopsies performed within 30 days of putatively curative surgical resection, and are rarely cured with the localized therapeutic modalities of surgery or radiotherapy. SCLC exhibits features of neuroendocrine or APUD (amine precursor uptake and decarboxylation) differentiation, including neurosecretory granules on electron micrographs, production of various polypeptide hormones both in vitro and in vivo, and much higher frequency of such paraneoplastic syndromes as ectopic Cushing's syndrome and inappropriate secretion of antidiuretic hormone than occurs in other types of lung cancer. Most importantly, patients with SCLC are markedly more responsive to chemotherapy than are patients afflicted with other lung cancer cell types. Effective combination therapy has led to four- to fivefold improvement in median survival compared to untreated patients and a small fraction apparently enjoying a long-term cure (Ihde '89: 195).

**Without treatment**, SCLC has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2 to 4 months. About 10% of the total population of SCLC patients remains free of disease during the 2 years from the start of therapy, which is the time period during which most relapses occur. Even these patients, however, are at risk of dying from lung cancer (both small and non-small cell types). The overall survival at 5 years is 5% to 10% (Johnson et al '90). At the time of diagnosis, approximately 30% of patients with SCLC will have tumors confined to the hemithorax of origin, the mediastinum, or the

supraclavicular lymph nodes. These patients are designated as having limited-stage disease (LD). Patients with tumors that have spread beyond the supraclavicular areas are said to have extensive-stage disease (ED) (Govindan et al '06). An important prognostic factor for SCLC is the extent of disease. Patients with LD have a better prognosis than patients with ED. For patients with LD, median survival of 16 to 24 months and 5-year survivals of 14% with current forms of treatment have been reported (Jänne et al '02). Patients diagnosed with LD who smoke should be encouraged to stop smoking before undergoing combined-modality therapy because continued smoking may compromise survival. Chemotherapy combined with thoracic radiation therapy (TRT) is considered the standard of care. Adding TRT increases absolute survival by approximately 5% over chemotherapy alone (Slotman et al '15).

Staging is not important for SCLC treatment. However assessing the extent of tumor dissemination is useful to establish a prognosis. Common sites of distant metastases in SCLC are the liver, bone, bone marrow, brain, lymph nodes and subcutaneous tissue, for which imaging studies are commonly performed. SCLC is now described by WHO with only one variant, SCLC combined, when at least 10% of the tumor bulk is made of an associated non-small cell component (Brambilla et al '01). Several staging systems have been proposed for small cell lung cancer (SCLC). These staging systems include the following: American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) (Lung et al '01). The 8th edition of the AJCC Cancer Staging Manual recommends the use of the TNM to classify SCLC. Veterans Administration Lung Study Group (VALG). International Association for the Study of Lung Cancer (IASLC) (Shepherd et al '07).

Chemotherapy and radiation therapy have been shown to improve survival for patients with small cell lung cancer (SCLC). The **combination** of platinum and etoposide is the most widely used standard chemotherapeutic regimen (Amarosena et al '08). SCLC is highly radiosensitive and thoracic radiation therapy improves survival of patients with LD and ED tumors (Pignon et al '92). In patients who receive chemotherapy with radiation therapy, there is no improvement in survival with the addition of surgery (Chandra et al '06). Patients who have achieved a complete remission can be considered for administration of PCI. Patients whose cancer can be controlled outside the brain have a 60% actuarial risk of developing central nervous system (CNS) metastases within 2 to 3 years after starting treatment. Most of these patients relapse only in their brain, and nearly all of those who relapse in their CNS die of their cranial metastases (Le Péchoux et al '09). Chemotherapy for patients with extensive-stage disease (ED) SCLC is commonly given as a two-drug combination of **platinum and etoposide** in doses associated with at least moderate toxic effects (as in limited-stage [LD] SCLC) (Okamoto et al '07). Cisplatin is associated with significant toxic effects and requires fluid hydration, which can be problematic in patients with cardiovascular disease. Carboplatin is active in SCLC, is dosed according to renal function, and is associated with less nonhematological toxic effects. Standard treatment is considered to be Etoposide + cisplatin or Etoposide + carboplatin. Of the other regimes only Cisplatin + irinotecan was equal (Guo et al '11). Doses and schedules used in current programs yield overall response rates of 50% to 80% and complete response rates of 0% to 30% in patients with ED. Intracranial metastases from small cell carcinoma may respond to chemotherapy as readily as metastases in other organs (Pujol et al '00).

The risk of developing CNS metastases can be reduced by more than 50% with the administration of PCI. The 3-year OS was improved from 15% to 21% with PCI. Standard-dose PCI (25 Gy in 10 fractions) was as effective as and less toxic than higher doses of brain radiation (Le Péchoux et al '09). **Radiation therapy** to sites of metastatic disease unlikely to be

immediately palliated by chemotherapy, especially brain, epidural, and bone metastases, is a standard treatment option for patients with ED SCLC. Brain metastases are treated with whole-brain radiation therapy. Chest radiation therapy is sometimes given for superior vena cava syndrome, but chemotherapy alone, with radiation reserved for non-responding patients, is appropriate initial treatment. 2-year OS was 13% in the thoracic radiation group versus 3% in the control group. Thoracic radiation therapy resulted in 6-month PFS of 24% in the thoracic radiation group versus 7% in the control group. Intra-thoracic recurrences, both isolated (19.8% vs. 46.0%) and in combination with recurrences at other sites (43.7% vs. 79.8%), were reduced by approximately 50%. The cumulative risk of brain metastases within 1 year was 14.6% in the radiation group and 40.4% in the control group (Slotman et al '15).

**Topotecan** is a standard chemotherapy for recurrent SCLC. Oral topotecan (2.3 mg/m<sup>2</sup>/day for 5 days every 21 days) or intravenous topotecan (1.5 mg/m<sup>2</sup>/day for 5 days every 21 days). Confirmed response rates were 18.3% and 21.9%, respectively (Eckart et al '07) (Goto et al '16). For patients with recurrent small-cell lung cancer, **immune checkpoint modulation** with anti-programmed death-ligand 1 (anti-PD-L1) antibodies may lead to durable responses either as single agents or in combination with cytotoxic T lymphocyte antigen-4 (anti-CTLA-4). Studies have evaluated the role of immune checkpoint inhibitors (programmed cell death-1 or programmed death-ligand 1 (PD-L1) inhibitors) in frontline treatment of patients with extensive-stage SCLC. Two PD-L1 inhibitors, atezolizumab and durvalumab, demonstrated prolongation of overall survival (OS) when combined with platinum and etoposide, compared with the same combination chemotherapy regimen alone. The median OS was 12.3 months in the **atezolizumab** group and 10.3 months in the placebo group. 1 The median OS was 13.0 months in the **durvalumab** plus platinum-etoposide group versus 10.3 months in the platinum-etoposide group. Given the paucity of treatment options and dismal prognosis for these patients, options to be considered include **nivolumab** with or without ipilimumab for PD-L1 unselected patients or pembrolizumab for patients with PD-L1-positive disease. An objective response was achieved in ten (10%) of 98 patients receiving nivolumab at 3 mg/kg; one (33%) of three patients receiving nivolumab at 1 mg/kg plus ipilimumab at 1 mg/kg; 14 (23%) of 61 receiving nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg; and ten (19%) of 54 receiving nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg (Antonia et al '16).

**Cigarette smoking** is by far the most important risk factor for lung cancer, with approximately 80% of lung cancer deaths in the US still caused by smoking. Risk increases with both quantity and duration of smoking. Cigar and pipe smoking also increase risk. Exposure to radon gas, which is released from soil and can accumulate in indoor air, is the second-leading cause of lung cancer in the US. Other risk factors include exposure to secondhand smoke, asbestos (particularly among smokers), certain metals (chromium, cadmium, arsenic), some organic chemicals, radiation, air pollution, and diesel exhaust. Specific occupational exposures that increase risk include rubber manufacturing, paving, roofing, painting, and chimney sweeping. In a large US clinical trial, screening with low-dose spiral computed tomography (LDCT) reduced lung cancer mortality by about 20% compared to standard chest x-ray among current or former (quit within 15 years) heavy smokers (at least a pack a day for 30 years). More favorable outcomes were recently reported by two European trials. The American Cancer Society recommends annual lung cancer screening for current or former heavy smokers ages 55 to 74 years who are in relatively good health and have undergone evidence-based smoking-cessation counseling (current smokers) and a process of informed shared decision making with a clinician that included a description of the potential benefits and harms of screening (ACS '20: 18).

**Symptoms**, which usually do not appear until the cancer is advanced, include persistent cough, sputum streaked with blood, chest pain, a hoarse voice, worsening shortness of breath, and recurrent pneumonia or bronchitis. Appropriate treatment for lung cancer is based on whether the tumor is small cell (13%) or non-small cell (84%), as well as the stage and molecular characteristics. For early-stage non-small cell lung cancer, surgery is the usual treatment, sometimes with chemotherapy, alone or in combination with radiation therapy. Advanced-stage non-small cell lung cancer is usually treated with chemotherapy and/or targeted drugs or immunotherapy. Early-stage small cell lung cancer is usually treated with chemotherapy, alone or combined with radiation. People with advanced small cell lung cancer might be treated with chemotherapy with or without immunotherapy; a large percentage of patients on this regimen briefly experience remission, although the cancer often returns. The 5-year relative **survival** rate for lung cancer is 19% overall (16% for men and 23% for women); 24% for non-small cell; and 6% for small cell tumors. Only 16% of lung cancers are diagnosed at a localized stage, for which the 5-year survival rate is 57% (ACS '20: 19).

Increasing age is the most important risk factor for most cancers. Other risk factors for lung cancer include the following: History of or current tobacco use: cigarettes, pipes, and cigars (Alberg et al '07). Exposure to cancer-causing substances in secondhand smoke (Anderson et al '03). Occupational exposure to asbestos, arsenic, chromium, beryllium, nickel, and other agents (Straif et al '09). Radiation exposure from any of the following: Radiation therapy to the breast or chest (Friedman et al '10). Radon exposure in the home or workplace (Gray et al '09). Medical imaging tests, such as computed tomography (CT) scans (Berrington de González et al '90). Atomic bomb radiation (Shimizu et al '90). Living in an area with air pollution (Katanoda et al '11). Family history of lung cancer (Lissouska et al '10). Human immunodeficiency virus infection (Shiels et al '09). Beta carotene supplements in heavy smokers (Omenn et al '96). Exposure to **radon daughters**, which emit radioactive gas, may act synergistically with cigarette smoke to yield a risk 50 to 100 times greater than that of the normal population. Exposure to radon occurs near uranium mining operations in the western United States and also when homes are built on or near hard rock formations. A variety of other environmental and occupational factors that increase lung cancer risk have been identified. These include **exposure** to arsenic, nickel, chromium, chloromethyl ethers, hydrocarbons, and mustard gas. Disease that causes lung scarring, such as pulmonary tuberculosis or interstitial fibrosis, may predispose to "scar carcinomas" usually peripheral adenocarcinomas of bronchioloalveolar cell carcinomas (Miller & Johnston '89: 319-321). The ever present danger of *Aspergillus niger* mold contamination of tobacco products must not be overlooked. Hard, precancerous, pulmonary lung nodules and coughing caused by **pulmonary aspergillosis** are swiftly cured with a dab of hydrocortisone crème to the chest.

The Interagency for Cancer Research implicates the Acheson process, occupational exposures associated, with, Aluminum production, Arsenic and inorganic arsenic compounds, Asbestos (all forms), Beryllium and beryllium compounds, Bis (chloromethyl) ether; chloromethyl methyl ether (technical grade), Cadmium and cadmium compounds, Chromium (VI) compounds, Coal, indoor emissions from household combustion, Coal gassification, Coal-tar pitch, Coke production, Engine exhaust, diesel, Haematite mining (underground), Iron and steel founding, MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture), Nickel compounds, Opium (consumption of), Outdoor air pollution, Painting, Particulate matter in outdoor air pollution, Plutonium, Radon-222 and its decay products, Rubber production industry, Silica dust, crystalline, Soot, Sulfur mustard, Tobacco smoke, secondhand, Tobacco smoking, Welding fumes, X-radiation, gamma-radiation of being carcinogens. The IACR suspects Acid mists,

strong inorganic, Art glass, glass containers and pressed ware (manufacture of), Benzene, Biomass fuel primarily wood), indoor emissions from household combustion of, Bitumens occupational exposure to oxidized bitumens and their emissions during roofing, Carbon electrode manufacture, alpha-Chlorinated toluenes and benzoyl chloride (combined exposures), Cobalt metal with tungsten carbide, Creosotes, Diazinon, Fibrous silicon carbide, Frying, emissions from high temperature, Hydrazine, Insecticides, non-arsenical, occupational exposures in spraying and application, Printing processes, 2,3,7,8-Tetrachlorodibenzo-para-dioxin of being carcinogenic (IARC '20).

The single most important risk factor for the development of lung cancer is **smoking**. For smokers, the risk for lung cancer is on average tenfold higher than in lifetime nonsmokers (defined as a person who has smoked <100 cigarettes in his or her lifetime). The risk increases with the quantity of cigarettes, duration of smoking, and starting age. Smoking cessation results in a decrease in precancerous lesions and a reduction in the risk of developing lung cancer. Former smokers continue to have an elevated risk of lung cancer for years after quitting. The twentieth-century **lung cancer epidemic** was hugely facilitated by the invention of cigarette-making machines in the 1880s, and the wholesale provision of free cigarettes to hundreds of thousands of soldiers in two world wars. The lung of a 'pack a day' smoker for 40 years will have been the repository for 7 to 8 kilograms of tar. Around one in ten of those who smoke 15 to 25 cigarettes a day will have lung cancer by age 75 years. Heavy smokers (more than 25 a day) suffer this fate at a higher rate. For every 20 lung cancer patients in the USA or Europe who smoke, there will be, on average, one non-smoker with a similar diagnosis. Only a minority of smokers develop lung cancer. For every 1000 young men adopting a life time habit of smoking, on average, one will be murdered, six will die in road traffic accidents and 250 are said to die of tobacco-related deaths including lung cancer. Madame Jeanne Calment who died, not of cancer, at the age of 122 years, thanks her parents for escaping the penalty of a lifelong habit of smoking. George Burns at 98 years of age still smoked 10 cigars a day. During the 1970s Xuan Wei county in southern China had one of the highest rates of lung cancer in the whole of China. What was odd was that the mortality rate for women was as high as that of men, despite the fact that less than 0.1 percent of women smoked cigarettes, compared with almost 50 percent of men. The explanation was almost certainly the burning indoors of smoky coal, as opposed to smokeless coal or wood (Greaves '00: 135-137).

In the first half of the twentieth century, **lung cancer**, formerly considered to be a very rare disease, began to be increasingly diagnosed and many doctors and scientists in both the USA and Europe, and particularly in Nazi Germany voiced their suspicion that cigarette smoking might be the cause. But it took until 1950 for epidemiologists to provide persuasive evidence for the strong association between tobacco smoking and lung cancer risk. Certain brands of cigarettes have for over a hundred years enjoyed the accolade of royal warrant or appointment to serve His or Her Majesty. The present Queen's father died of lung cancer and both his father and grandfather died of tobacco-induced lung diseases. Finally, at the turn of the century, the Queen's Warrant Officers have revoked their support for Benson and Hedges brand. But the Queen's mother will continue to provide one to John Player brands (Greaves '00: 129, 131, 256).

The incidence of lung cancer began to increase sharply in men about 1940 and in women about 1960. Cigarette smoking became a widespread habit for men around 1920, but it took twenty years for this behavior to be reflected in the incidence of lung cancer. Similarly, cigarette smoking among women only became really popular and acceptable during World War II. The more one smokes and the longer one smokes, the greater is the chance that at some point a single

cell (or one of its descendants) in one's lungs is going to accumulate enough defects in their genes to cause uncontrolled cellular growth (Friedberg '92: 69-70). Twenty-two percent of the U.S. population smoked in 2003, down from 24 percent in 1998. Deaths from mesothelioma, linked to asbestos exposure of workers in engineering and building industries in the 1960s and 1970s, are still increasing and are not expected to peak until the year 2020. Uncontrolled use of asbestos remains common outside of Europe and the USA. Countries in South East Asia have been the major importers of asbestos (Greaves '00: 262).

Currently between two and four million adults a year die of **smoking-related diseases** worldwide. Some 40 percent of these have lung cancers. Other causes of death include cancers of the mouth, pharynx and larynx, and obstructive lung disease. Cigarette smoking is also rumored to increase the risk of cancers of the pancreas, kidney and bladder. Cancers of the lung bronchi (squamous cell carcinomas) are decreasing but the previously rare adenocarcinomas of the lung are increasing substantially amongst smokers, and especially in women. These tumors arise from the deeper branch ends of the lung tree (the alveoli), and the most plausible explanation for their increase is that smokers have adopted the habit of inhaling more deeply to obtain their nicotine fix from milder cigarettes. The long latency of lung cancer due to smoking may have helped disguise the lethal connection with lung cancer for the first half of the twentieth-century, but as recently as 1994 Chief Executives of seven major cigarette manufacturers could testify under oath before the USA Government House Health and Environment Committee, that they did not believe that nicotine was addictive or that cigarette smoking caused lung cancer. One third of the world's smokers are Chinese, tobacco is their largest industrial source of tax revenue. It is calculated that one third of young Chinese men smoking now will die of a tobacco related illness during the first half of the twenty-first century, providing an accumulative death toll of around 100 million. On a worldwide scale, the annual death rate will increase to 10 million a year by 2030 and half of these individuals will be only 35 to 70 years of age. Products of metabolized benzo(a)pyrene and nitrosamines, one of the most potent carcinogens in tobacco tar, have been shown to physically associate with selective regions of the p53 gene which is a hot spot for mutation in lung cancers (Greaves '00: 132-134).

**Second-hand smoke** can increase the frequency of asthma and bronchitis. In May 2003 in the British Medical Journal a study titled Environmental Tobacco Smoke and Tobacco-Related Mortality in Prospective Study of Californians 1960-98. 35,561 individuals who were never smokers, but had a smoking spouse were studied. The main finding was exposure to environmental tobacco smoke was not significantly associated with the death rate from coronary heart disease, lung cancer or chronic obstructive pulmonary disease in men or women. Cigarette causes many problems for smokers and some problems for non-smokers, especially children and those with asthma or bronchitis, but, it has not been shown persuasively to cause either lung cancer or heart attacks. It is claimed that passive smoking increases the risk of coronary heart disease and heart attacks by 25 percent, lung cancer by 17 to 22 percent, causing 3,000 lung cancer cases a year out of a total of about 170,000 cases each year (Louria '07: 16, 17).

One of 13 cigarette smokers develops bronchogenic carcinoma; smoking cessation results in a gradual normalization of risk over a period of 10 to 20 years. The shocking rise in incidence of lung cancer in the twentieth century has suggested that environmental or behavioral factors are responsible. Tobacco smoke, particularly from cigarettes, is the major factor for this precipitous disease. Cigarette smokers have at least a 10 times greater risk of developing lung cancer than do nonsmokers. Smokers with chronic obstructive lung disease are more likely to develop lung cancer than those without obstructive lung disease. Maintaining close contact with an active

cigarette smoker, may be responsible for up to 5% of all lung cancer. Asbestos exposure is a potent risk factor for bronchogenic carcinoma, as well as **mesothelioma**. Pulmonary aspergillosis, precancerous, hard pulmonary nodules and coughing, caused by *Aspergillus niger* mold infection, that produces carcinogenic aflatoxin, from handling and smoking contaminated tobacco products, is treated with with a dab of hydrocortisone crème to the chest. Asbestos exposure and cigarette smoking act synergistically; an asbestos worker who smokes has a 50-100-fold increased chance of developing lung cancer. Whether asbestos exposure alone can be regarded as a cause of lung cancer has not been determined. The greatest hazard resulting from asbestos is that it is linked to smoking exposure in causing an increased risk of bronchogenic cancer. The risk is almost totally confined to those who are also exposed to cigarette smoke. Smokers who have been exposed to asbestos have approximately a 12-fold greater risk of developing bronchogenic cancer than do non-asbestos-exposed nonsmokers. Those who have been exposed to both have a 50-fold to 90-fold increase. It is estimated that between 2% and 2.5% of the 150,000 lung cancer cases that occurred in 1988 in the United States may have been asbestos-related (Mitchell '89: 340-344).

A history of asbestos exposure is reported in about 70% to 80% of all cases of mesothelioma (Ruffie et al '89). Histologically, these tumors are composed of spindle cells (sarcomatoid) or epithelial elements, or both (biphasic). Desmoplastic mesothelioma, consisting of bland tumor cells between dense bands of stroma, is a subtype of sarcomatoid mesothelioma. The epithelioid form is occasionally confused with lung adenocarcinoma or metastatic carcinomas. Epithelioid tumors account for approximately 60% of mesothelioma diagnoses (Travis et al '04). Attempts to diagnose by cytology or needle biopsy of the pleura are often unsuccessful. It can be especially difficult to differentiate mesothelioma from adenocarcinoma in small tissue specimens. Thoracoscopy can be valuable in obtaining adequate tissue specimens for diagnostic purposes (Boutin et al '93). Examination of the gross tumor at surgery and use of special stains or electron microscopy can often help to determine diagnosis. Pancytokeratin stains are positive in nearly all mesotheliomas. Particularly useful immunohistochemical stains for the differential diagnosis of epithelioid mesothelioma include cytokeratin 5 and 6, calretinin, WT-1, and D2-40. Calretinin and D2-40 positivity in combination with pancytokeratin positivity is most useful to distinguish sarcomatoid mesothelioma from sarcoma and other histologies (Travis et al '04). The AJCC has designated staging by TNM (tumor, node, metastasis) classification to define malignant mesothelioma. Cancers staged using the AJCC cancer staging system include classifications for diffuse malignant pleural mesotheliomas but do not include localized malignant pleural mesotheliomas or other primary tumors of the pleura (Amin et al '17).

Standard treatment for all but localized mesothelioma is generally not curative. Extrapleural pneumonectomy in selected patients with early-stage disease may improve recurrence-free survival, but its impact on OS is unknown (Rusch et al '91). Pleurectomy and decortication can provide palliative relief from symptomatic effusions, discomfort caused by tumor burden, and pain caused by invasive tumor. Trimodality therapy refers to a combination of chemotherapy, definitive surgery, and radiation therapy. Operative mortality from pleurectomy with decortication is less than 2%, while mortality from extrapleural pneumonectomy has ranged from 6% to 30% (Sugarbaker et al '93). Several single-arm, phase II studies have demonstrated prolonged survival times (compared with historic controls) for selected patients who received adjuvant radiation therapy after definitive surgery (Batirel et al '05). The use of radiation therapy in pleural mesothelioma has also been shown to alleviate pain in the majority of patients treated; however, the duration of symptom control is short-lived (Bisset et al '91). Other single-arm, phase II studies investigated neoadjuvant chemotherapy (mainly with platinum and pemetrexed

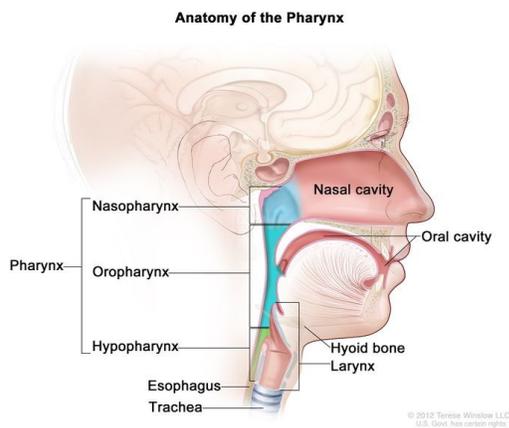
or gemcitabine) followed by definitive surgery followed by adjuvant radiation (Krug et al '09). These studies have also shown prolonged survival compared with historical controls.

First-line combination chemotherapy with cisplatin, pemetrexed, and bevacizumab showed improved survival compared with single-agent cisplatin. Median survival was 12.1 months in the pemetrexed-plus-cisplatin arm compared with 9.3 months in the cisplatin-alone arm. Median time-to-progression was significantly longer in the pemetrexed-plus-cisplatin arm (5.7 months vs. 3.9 months) (Zalcman et al '06). A study compared cisplatin alone or with the combination of raltitrexed, a thymidine synthase inhibitor. The response rate for cisplatin alone was 13.6%, while the response rate in the combination arm was 23.6%. Median overall survival (OS) was 8.8 months for single-agent cisplatin compared with 11.4 months in the combination arm, and the 1-year survival rate was 40% versus 46%. Patients randomly allocated to receive intravenous pemetrexed plus cisplatin (PC) with or without bevacizumab (PCB) had a significantly longer OS with PCB (median, 18.8 months); than with PC (median 16.1 months) (van Meerbeek et al '05). Intracavitary therapy. Intrapleural or intraperitoneal administration of chemotherapeutic agents (e.g., cisplatin, mitomycin, and cytarabine) has been reported to produce transient reduction in the size of tumor masses and temporary control of effusions in small clinical studies (Markman et al '92). A multi-institutional registry study evaluated cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for diffuse, malignant, peritoneal mesothelioma. Among 401 patients, 187 (46%) had complete or near-complete cytoreduction, and 372 (92%) received HIPEC. Of the HIPEC patients, 311 (83%) received cisplatin and doxorubicin. The median follow-up period was 33 months (range, 1–235 months). Grade 3 to 4 complications were seen in 127 (31%) of the 401 patients, and 9 patients (2%) died perioperatively. The mean length of hospital stay was 22 days (standard deviation, 15 days). The overall median survival was 53 months (1–235 months), and 3- and 5-year survival rates were 60% and 47% (Yan et al '09).

#### **4. Oropharyngeal, head and neck cancers**

In 2020, an estimated 53,260 new cases of **cancer of the oral cavity and pharynx** (throat) will be diagnosed in the US and 10,750 people will die from the disease. Smoking or being infected with human papillomavirus (HPV) can increase the risk of oropharyngeal cancer. Incidence rates are more than twice as high in men as in women. From 2007 to 2016, incidence rates decreased by 1% to 2% per year among black men and women but increased annually by about 1% among non-Hispanic white men and women. These increases are largely driven by rising rates for a subset of cancers associated with human papillomavirus (HPV) infection that arise in the oropharynx (part of the throat behind the oral cavity, including the back one-third of the tongue, soft palate, and tonsils). The death rate for cancers of the oral cavity and pharynx continued its long decline during 2008-2017 among blacks (by about 2% per year), but increased by 0.7% per year among whites, mostly reflecting an uptick for subsites associated with HPV. **Symptoms** may include an ulcer in the throat or mouth that bleeds easily and does not heal; a persistent red or white patch, lump, or thickening in the throat or mouth; ear pain; a neck mass; or coughing up blood. Difficulty chewing, swallowing, or moving the tongue or jaw are often late symptoms. Surgery and/or radiation therapy are standard treatments; chemotherapy is often added for high-risk or advanced disease. **Chemotherapy** or targeted therapy may be combined with radiation as initial treatment in some cases. Immunotherapy is a newer option for advanced or recurrent cancer. The 5-year relative survival rate for cancers of the oral cavity and pharynx overall is 65% but is much lower in blacks (48%) than in whites (67%). Studies indicate better

survival for patients with HPV-associated cancer. Only 29% of cases are diagnosed at a local stage, for which 5-year survival is 84% (ACS '20: 20).



Known **risk factors** include any form of tobacco use and alcohol consumption, with a synergistic relationship conferring a 30-fold increased risk for individuals who both smoke and drink heavily. HPV infection of the mouth and throat, especially HPV type 16, believed to be transmitted through sexual contact, also increases risk. HPV vaccines have primarily been evaluated against genital diseases but will likely prevent most HPV-associated oral cancers as well. Unfortunately, immunization rates are much lower than for other disease-preventing vaccines, with only 51% of adolescents ages 13 to 17 years (49% of boys and 54% of girls) up to date with HPV

vaccination in 2018 (ACS '20: 20). Native American women suffer high rates of **nasal cancer**, probably initiating in epithelia burned and contaminated by hot ashes blown back from a cooking fire. In 1761 in London, John Hill – doctor, botanist, and playwright – published a one-shilling pamphlet cautioning against the immoderate use of tobacco snuff. He described several cases of fatal polypuses of the nose or nasal carcinoma in men who were heavy, long-term users of snuff, and he proffered the following advice, "no man should venture upon snuff, who is not sure that he is not so far liable to cancer: and no man can be sure of that". At the beginning of the 20<sup>th</sup> century, an American clinician, Dr. R. Abe, provided compelling evidence that oral cancer was linked to tobacco exposure. The **oral cavity** is also the hot spot for cancers associated with some of the more exotic smoking styles developed in India and other parts of South East Asia. It is estimated that over 200 million people currently chew betel quid which is a mixture of betel leaf, areca nut, slaked lime, and usually, tobacco. Lethal lesions of the oral cavity are described in Indian medical texts from around 600 B.C. For **pipe smokers**, the lower lip appears to be more at risk than the upper, and it may be that the damage elicited by heat exacerbates the impact of tobacco carcinogens. For the traditional high tar **cigarette**, and particularly with inhalation, the major bronchial tracts incur the highest insult and consequent cancer rate (squamous bronchial carcinoma).

Although the **skin of the head and neck** region accounts for approximately 10% of the body surface area, most cutaneous tumors occur in this area. Benign lesions: **Nevi**, that develop soon after birth but may appear at any time in life, they reach their maximum size within a few years and do not continue to enlarge. Approximately 15% of **giant congenital pigmented nevi** give rise to malignant melanoma. Treatment consists of total removal. A blue nevus is a benign lesion that rarely becomes larger than 2 to 6 mm in diameter, it persists through life and has no malignant potential. A **seborrheic keratosis** is a light brown to black, greasy appearing, sharply demarcated papule or plaque. These are benign lesions that do not require treatment. Malignant lesions: **Actinic keratosis** is discrete, slightly scaling, pink macules and papules. They form on sun-exposed areas and are considered precancerous. Treatment consists of cryotherapy, trichloroacetic acid and topical imiquimod. **Basal cell carcinoma** is the most common skin cancer. More than 95% occur on the head and neck. Basal cell carcinomas tend to be slow growing and have a low incidence of metastasis, less than 0.1%. these cancers are easily treated by surgical excision with minimal margins. **Squamous cell carcinomas** also arise from keratinocytes. Metastatic potential is variable. Incidence of metastasis is 8% de novo squamous

cell carcinoma, and between 20% to 30% in squamous cell carcinoma arising in scars, chronic ulcers, and burn and radiation therapy sites. Management is total local excision with a resultant high cure rate. **Melanoma** consists of three types: nodular, superficial spreading and lentigo malignant melanoma, depending on the the depth of the invasion. Once the diagnosis of melanoma is made, a wide and deep excision is warranted. In the management of neoplasms of the skin, the two primary options are surgical treatment and radiation therapy. Topical agents such as fluorouracil and imiquimod are also effective. A mole chart is a useful clinical tool for following lesions (Tran, Turk & Baldwin '04: 355, 356, 359, 360, 361).

**Squamous cell carcinoma** is the sixth most prevalent cancer and constitutes more than 90% of cancers arising in the upper aerodigestive tract. Approximately 5% of all malignant tumors among men and 2% among women arise in the head and neck. More than 50,000 new cases of head and neck cancer occur each year in the United States, and there are more than 15,000 deaths annually. Worldwide, squamous cell carcinoma of the head and neck affects more than 500,000 people annually. Other tumors that arise in the head and neck region include major and minor salivary gland neoplasms, cervical nodal lymphoma, pharyngeal lymphoma arising from Waldeyer's ring or other extranodal nonlymphoid sites and undifferentiated tumors. Approximately 80% to 90% of head and neck cancers may be attributed to exposure to chemical carcinogens such as alcohol and tobacco, which act synergistically. Other common carcinogenic factors include poor dental hygiene, tobacco chewing, betel nut chewing, glossitis (tongue cancer factor), woodworking (nasal and sinus cancer factor). Radiation exposure may likewise predispose a patient to a variety of carcinomas or sarcomas in the head and neck. Viral carcinogens have been implicated, particularly the Epstein-Barr virus in nasopharyngeal carcinoma. Premalignant oral lesions are characterized by thick, whitish plaques (leukoplakia). Approximately 12,000 new cases of laryngeal cancer are diagnosed annually and there are almost 4,000 deaths (Tran & Har-El '04: 305, 307, 310).

Diagnostic procedure is that the medical doctor or dentist does a complete exam of the mouth and neck and looks under the tongue and down the throat with a small, long-handled mirror to check for abnormal areas. A procedure that combines the pictures from a positron emission tomography (PET) scan and a computed tomography (CT) scan. The PET and CT scans are done at the same time with the same machine. The combined scans give more detailed pictures of areas inside the body than either scan gives by itself. A PET-CT scan may be used to help diagnose disease, such as cancer, plan treatment, or find out how well treatment is working. Nuclear magnetic resonance imaging (NMRI) may be useful. A fine-needle biopsy is usually done to remove a sample of tissue using a thin needle. If cancer is found an HPV test is conducted. Oropharyngeal tumors related to HPV infection have a better prognosis and are less likely to recur than tumors not linked to HPV infection. Patients with oropharyngeal cancer have an increased risk of another cancer in the head or neck. This risk is increased in patients who continue to smoke or drink alcohol after treatment.

It is estimated that every year in the U.S., more than 2,370 new cases of HPV related **oropharyngeal cancers** are diagnosed in women and about 9,356 are diagnosed in men; they are most common in white men. There are about 15 different HPV types that are established causes of cancer. The most common are HPV 16 and 18, accounting for about 70% of cervical cancers and oral infection. The Johns Hopkins School of Medicine estimates that 20 million people in the U.S. currently have HPV infection, and one in 49 people will contract a new HPV infection each year. Physicians recommend the HPV vaccine for both young boys and girls, to prevention infection from the disease (Sifferlin '13). Being infected with Epstein-Barr virus (EBV)

increases the risk of nasopharyngeal cancer about 33 times higher than people who do not have EBV infection (NCI '19). Other than HPV and EBV, the major cause of head and neck cancer is tobacco, and the relative risk increases with number of cigarettes smoked per day. Alcohol produces a synergistic effect and greatly increases the risk of throat cancer when mixed with tobacco. Other known agents associated with head and neck cancer include cigars and pipe tobacco, - lip and oral cavity; chewing tobacco – oral cavity; betel nut (mixed with tobacco and lime) – buccal mucosa and floor of mouth; syphilis – tongue; nickel exposure – nasal cavity and paranasal sinus; woodworking – nasopharyngeal; prolonged sun exposure – lip; Plummer-Vinson syndrome – hypopharyngeal and esophageal cancers. 95% of all head and neck carcinomas are of the squamous cell type, classified as well differentiated, moderately well-differentiated, poorly differentiated, or undifferentiated. Spread is predominantly local or to regional nodes. Late dissemination occurs to lung, liver or bone. Metastases are more common from nasopharyngeal or hypopharyngeal primaries (Jacobs '89: 212).

### Staging System for Head and Neck Cancers

#### Primary Tumor (T)

T-0 Carcinoma in situ

For each of the head and neck regions the definition of the T classification varies.

Oral Cavity (lip, buccal mucosa, alveolar ridge, retromolar trigone, floor of mouth, hard palate and anterior two third so the tongue)

Oropharynx (soft palate, uvula, tonsillar pillar, tonsillar fossa, tonsil, base tongue and pharyngeal wall)

T1 Greatest diameter <2 cm

T2 Greatest diameter 2 cm to 4 cm

T3 Greatest diameter >4 cm

T4 Diameter > 4 cm with deep invasion (oral cavity – to antrum, pterygoids, base of tongue, skin of neck; oropharynx – to bone, soft tissues of neck, root of tongue)

Hypopharynx (pyriform sinus, postcricoid area, and posterior hypopharyngeal wall)

Supraglottic larynx (false cords, arytenoids, epiglottis, aryepiglottic folds)

T1 Tumor confined to site of origin

T2 Extension of tumor to adjacent region without fixation of hemilarynx or vocal cords

T3 Extension of tumor to adjacent region with fixation of hemilarynx or vocal cords

T4 Massive tumor invading bone, cartilage or soft tissues of neck, or extending beyond larynx for supraglottic or glottis cancers

#### Nasopharynx

T1 Tumor confined to one site of nasopharynx or no tumor visible (positive biopsy)

T2 Tumor involving two sites

T3 Extension of tumor into nasal cavity or oropharynx

T4 Tumor invasion of skull or cranial nerve involvement

#### Cervical Nodes (N)

N0 No clinically positive node

N1 Single clinically proven homolateral node < 3 cm in diameter

N2 Single clinically positive homolateral node > 3 cm but not more than 6 cm in diameter or multiple clinically positive homolateral nodes, none of which is more than 6 cm in diameter

N2a Single clinically positive homolateral node > 3 cm but not more than 6 cm in diameter

N2b	Multiple clinically positive homolateral nodes, none of which is more than 6 cm in diameter
N3	Massive homolateral node(s), bilateral nodes, or contralateral node(s).
N3a	Clinically positive homolateral node(s), one > 6 cm in diameter
N3b	Bilateral clinically positive nodes
N3c	Contralateral clinically positive node(s) only

#### Distant Metastasis

MX	Not assessed
M0	No (known) distant metastasis
M1	Distant metastasis present

#### Stage Grouping

Stage I:	T1, N0, M0
Stage II:	T2, N0, M0
Stage III:	T2, N0, M0 T1 or T2 or T3, N1, M0
Stage IV:	T4, N0 or N1, M0 Any T, N2 or N3, M0 Any T, Any N, M1

Source: (Jacobs '89: 214, 215)

**Proper staging** is crucial for planning appropriate treatment and prognosis. Precise localization of the primary tumor and assessment of regional spread are key. Since metastases are rare at presentation, a limited metastatic evaluation is advised. Biopsies should be of full thickness and should be obtained from the non-necrotic portion of the tumor, areas at the edge of the tumor, and adjacent normal mucosa. Open biopsy of the neck node is contraindicated if one suspects squamous cell cancer. Needle biopsies are useful for unknown primaries presenting in the neck or salivary glands and for thyroid cancers. False-negatives are a novice pathological mistake. Computed tomography (CT) and magnetic resonance imaging (MRI) are complementary for evaluation of the nasopharynx, sinuses, oral cavity and oropharynx. CT is superior for evaluating hypopharyngeal and laryngeal lesions, bony erosions of the base of the skull and metastatic adenopathy. For cancers of the nose, paranasal sinuses and nasopharynx, sinus series and/or sinus CT tomography are necessary to evaluate the extent of disease and potential bony destruction. Patients with cancers of the pyriform sinus, posterior pharynx, or postcricoid area should have a barium swallow if esophagoscopy was not performed in order to rule out esophageal extension or second primaries. Prior to treatment, a chest film may reveal underlying pulmonary disease or metastatic spread. A complete blood count (CBC) and chemistry profile, including liver function tests, are part of the initial evaluation. Epstein-Barr virus (EBV) antibody titers (IgA and IgG anti-EBV viral capsid antigen and early antigen) are increased in patients with nasopharyngeal cancer, and the level correlates with disease activity (Jacobs '89: 212, 213). About 60% of oropharyngeal cancers — cancers of the throat, tonsils and the base of tongue — are related to HPV. Patients should undergo a thorough dental evaluation prior to treatment, and nonsalvagable teeth should be extracted. Post-irradiation extractions are associated with increased risk of osteoradionecrosis. Fluoride treatments should be prescribed. Patients with head and neck cancer are often nutritionally deficient because they have difficulty eating animal products, bread and protein. The patient should be brought into positive nitrogen balance to reduce postoperative complications and improve tolerance to radiotherapy and/or chemotherapy (Jacobs '89: 214).

**Surgery** (removing the cancer in an operation) is a common treatment of all stages of oropharyngeal cancer. Surgery may include the following: Wide local excision: Removal of the cancer and some of the healthy tissue around it. If cancer has spread into bone, surgery may include removal of the involved bone tissue. Neck dissection: Removal of lymph nodes and other tissues in the neck. This is done when cancer may have spread from the lip and oral cavity. Plastic surgery: An operation that restores or improves the appearance of parts of the body. Dental implants, a skin graft, or other plastic surgery may be needed to repair parts of the mouth, throat, or neck after removal of large tumors (NCI '19). The extent of surgical resection is dictated by the extent of tumor at staging. The primary lesions should be widely excised leaving negative margins. Primary closure of the surgical defect is preferable, but local or regional skin flaps should be utilized when required. In the oral cavity a composite resection includes the primary, part of the mandible (if necessary) and cervical nodes. For patients in whom tumor approaches, but does not grossly involve, adjacent bone, a partial mandibulectomy may be performed. Gross bone invasion demands segmental mandibular resection, the extent of which depends on the degree of clinical involvement. In the oropharynx, if the lesion is below the level of the arytenoids, a total laryngectomy is recommended because of aspiration. In the supraglottic larynx a supraglottic laryngectomy can be performed if the cancer is confined to the supraglottic region and the forced expiratory volume (FEV) is more than 60%. A total laryngectomy should be done if (1) tumor extends to the commissures, arytenoids, thyroid cartilage, or glottis, (2) there is impaired mobility or fixation of vocal cords. In the larynx, hemilaryngectomy is appropriate to T<sub>1-2</sub> failures of radiation. For patients with known neck disease, a standard radical neck dissection should be performed. This includes the superficial and deep cervical fascia with its enclosed lymph nodes, the sternocleidomastoid and omohyoid muscles, the internal and external jugular veins, the spinal accessory nerve, and the submaxillary gland. For patients with cancers of the oral cavity, oropharynx, and supraglottic larynx in whom surgical management of the neck is chosen, a functional neck dissection should be performed. This leaves the sternocleidomastoid, the internal jugular vein and the spinal accessory nerve intact. In addition to the post-operative problems with postoperative infections and bleeding the long term problems include the following (1) cosmetic deformities, (2) speech impediment, (3) aspiration pneumonia and (4) shoulder droop and pain resulting from accessory nerve dysfunction following neck dissection (Jacobs '89: 216).

**Radiotherapy** for head and neck cancer is usually done with either teletherapy, brachytherapy or hyperthermia. In **teletherapy**, treatment with a linear accelerator (4-6 MeV energy) is preferred. Cobalt-60 units are acceptable if they operate at 80 SSD (source-to-skin distance). A combination of lateral opposed fields, anterior and lateral wedged fields, or isocentric multiple fields is used for the primary tumor site. A single anterior field with a midline block can be used to treat the neck, and lower neck fields should match the primary field at the skin. The accepted dose rate is 180 cGy to 200 cGy per day. The dose to tumor volume for primary treatment is approximately 6600 cGy to 7000 cGy in 6 to 7 weeks. The dose to a tumor bed following resection is 5500 cGy in 5 to 5 ½ weeks for negative margins, 6000 cGy for close margins and 6600 cGy-7000 cGy for positive margins. The maximum dose to the spinal cord should be no more than 4000 cGy when 200 cGy fractions are used. Postoperative radiation should not begin until postoperative healing is satisfactory (about 2 weeks). In **brachytherapy** interstitial implantation of radioactive sources is a means of obtaining high localized radiation dose to the tumor bed while minimizing normal tissue injury. The most commonly used permanent implant source is iodine. The most commonly used removable brachytherapy source is Iridium seeds. The dose rate for removable implants is between 40 cGy to 100 cGy per hour. In previously untreated patients, the total dose of iodine for 1 year is approximately 15,000 cGy. Removable

interstitial doses, when used as a booster after 5500 cGy external beam, should be limited to 25000 cGy to 4000 cGy. In hyperthermia ultrasound is used to heat tumors to 44°C. The toxic effects of radiotherapy include (1) xerostomia and loss of taste, (2) mucositis may delay treatment, (3) otitis media should be managed with decongestants but may require tube placement, (4) osteoradionecrosis of the mandible can often be prevented by appropriate preradiation dental extractions. Treatment is with antibiotics (penicillin) but in severe cases, hyperbaric oxygen and /or resection may be required, (5) laryngeal edema may follow radiation to the larynx, and a small percentage of patients may develop cartilage necrosis or a compromised airway. Conservative treatment includes antibiotics and/or steroids. Persistent edema following radiation is suspicious of tumor recurrence, (6) Lhermitte's syndrome, which is characterized by electric sensations in the spine, arms or legs or neck flexion, requires no treatment and (7) rarely hypothyroidism, heralded by an elevation of thyroid-stimulating hormone (Jacobs '89: 217, 218).

Chemotherapy can only rarely cure a patient with recurrent disease. The most active single agents for recurrent disease is cisplatin. **Cisplatin** is an effective drug whose major route of excretion is renal, and its use should be limited to patients with a creatinine clearance that is more than 50 ml/minute. The standard dose is 100 mg/m<sup>2</sup> every 3 weeks. Because of nephrotoxicity, a 24-hour infusion or mannitol diuresis is recommended. Typical standing orders are 12 hours prior to administration of cisplatin, prehydrate with 2 liters dextrose, 5%, in 0.5 normal saline plus 20 meq of potassium chloride. Three hours prior to administration of cisplatin, increase to 300 ml/hour. Just prior to administration of cisplatin, manitol, 12.5 g by rapid intravenous injection, followed by cisplatin (100 mg/m<sup>2</sup>) in saline to a concentration of 1 mg/ml is infused over 30 minutes. Follow this with a continuous infusion of mannitol 10g/hour for 6 hours, with concurrent dextrose, 5% in 0.5 normal saline plus 20 meq potassium chloride per liter at 200 ml/hour for 6 hours. Toxicities include nephrotoxicity, mild myelosuppression, moderately severe nausea and vomiting, hypomagnesemia, ototoxicity, and neurotoxicity. Response rates in excess of 15% for recurrent disease have been reported with several other drugs, including bleomycin, 5-fluorouracil (5-FU), Adriamycin, cyclophosphamide, and hydroxyurea. Drugs Approved for Head and Neck Cancer: Bleomycin Sulfate, Cetuximab, Docetaxel, Erbitux (Cetuximab), Hydrea (Hydroxyurea), Hydroxyurea, Keytruda (Pembrolizumab), Methotrexate Sodium, Nivolumab, Opdivo (Nivolumab), Pembrolizumab, Taxotere (Docetaxel), Trexall (Methotrexate Sodium).

Multiple combinations have been reported for recurrent head and neck cancer with complete and overall response rates higher than those of single agents, however there is no evidence that combination chemotherapy prolongs survival compared with single agent chemotherapy. The commonly used regimen of Cisplatin, 50 mg/m<sup>2</sup> on day 6, methotrexate, 40 mg/m<sup>2</sup> on days 1 and 15; Bleomycin 10 mg on days 1, 8, 15; had a response rate of 61%. It has been improved upon with Cisplatin, 100 mg/m<sup>2</sup> on day 1; 5-FU, 1000 mg/m<sup>2</sup> for 4 days, with a response rate is 70%. **TPF** is standard treatment for locally advanced oropharyngeal cancers. T = Docetaxel (Taxotere), P = Cisplatin (Platinol) and F = Fluorouracil. TPF is used to treat: Gastric (stomach) cancer that is advanced and Squamous cell carcinoma of the head and neck that is locally advanced. **Cetuximab** is a type of monoclonal antibody that works by binding to a protein on the surface of the cancer cells and stops the cells from growing and dividing. It is used in the treatment of recurrent and metastatic oropharyngeal cancer. Pembrolizumab and nivolumab are types of PD-1 inhibitors being studied in the treatment of oropharyngeal cancer (NCI '20).

**Chemotherapy** has been used prior to surgery in attempts to reduce tumor size and to decrease local or distal recurrence. When using chemotherapy in this manner, the optimal response is obtained after two to three cycles of chemotherapy. Reported response rates vary from 70% to 90% overall with 20% to 50% complete responses. Cure for squamous cancers of the head and neck is measured in terms of 5-year survival, although most relapses occur in the first 3 years following therapy. Follow-up should include a thorough head and neck examination every 1 to 2 months for the first year, with progressively longer intervals up to five years. A chest film should be obtained early. Approximate cure rates are for (1) oral tongue, T1, T2 – 70%-85%, T3, T4- 30%-40%; (2) floor of mouth, T1, T2-70%, T3, T4-45%; (3) tonsil, T1, T2-60%-75%, T3, T4-20%-35%; (4) pyriform sinus, T3, T4-25%; (5) glottis larynx, T1, T2-80%-90%, T3, T4-75%; (6) supraglottic larynx, T1, T2,-70%-85%, T3, T4-25%-40%; (7) base or tongue, T1, T2-50%-60% , T3, T4-20%-30%, and (8) nasopharynx, T1, T2-70%-75%, T3-55%, T4-<10% (Jacobs '89: 219, 220).

**Cancers of the salivary gland** account or less than 5% of head and neck neoplasms. The majority arise in the parotid gland and approximately 25% of parotid tumors are malignant. Of those originating in the submaxillary gland and minor salivary glands (palate, nasal cavity, and paranasal sinuses) half are malignant. These cancers usually present as painless masses and infrequently produce pain from nerve involvement. The most common histologic type is mucoepidermoid (low grad or high grade). Others include acinic cell, malignant mixed, adenoid cystic, adenocarcinoma, poorly differentiated carcinoma, squamous and anaplastic. The diagnosis can be made by needle biopsy at the time of parotidectomy. These cancers spread by direct extension, and some, like adenoid cystic, have a propensity to spread along nerve sheaths. Lymph nodes spread is found in up to 30% of high-grade cancers (adenocarcinoma squamous, undifferentiated, anaplastic and high-grade mucoepidermoid). The most common site of metastatic spread is lung, and a chest film should be done prior to surgery. The staging system for salivary gland cancers is T1- <2 cm, T2- 2 cm to 4 cm, T3- 4 cm to 6 cm, T4a- > 6 cm, T4b – any size with local extension. NO- negative nodes, N1- regional lymphatic involvement, M0- no metastases, M1-metastatic spread. Stage I – T1, T2, N0, M0. Stage II – T3, N0, M0. Stage III T1-2, N1, M0; T4, N1, M0. Stage IV t3-4, N0, M0, M1.

Surgery is the treatment of choice for salivary gland neoplasms. For parotid cancers that are low-grad and involve only the superficial lobe, a superficial **parotidectomy** may be performed. For all others, a total **partodiectomy** is recommended. The facial nerve can often be preserved, but if it is involved and needs to be sacrificed, a nerve graft may preserve function. At the time of the surgery, if periparotid nodes are positive, a radical neck dissection should be performed. Treatment of minor salivary gland cancers includes a wide excision. Most would recommend **postoperative radiation** for patients with high-grade cancers, positive margin, perineural invasion, deep lobe involvement, and regional lymph node metastases, at a minimum dose of 5000 cGy to 5500 cGy or 6600 cGy for positive margins. Primary radiotherapy is reserved for inoperable patients. The best single agents are cisplatin, doxorubicin, 5-FU and methotrexate. Overall responses have been noted in up to 60% of patients. The major actors that influence outcome are histology, site of tumor, and tumor size. Local control is achieved in approximately 80% of low-grade cancers and approximately 30% of high-grade cancers. Twenty percent of patients with high-grade neoplasms develop **distant metastases** in lung or bone. Five-year survival for parotid cancers range form 30% in undifferentiated neoplasms to 92% in acinic cell cancer, but since salivary gland cancers can recur at 10 and 15 years, 5 year survival rates are unreliable (Jacobs '89: 220, 221). When cancer spreads to another part of the body, it is called metastasis. Cancer cells break away from where they began (the primary tumor) and travel

through the lymph system or blood. Lymph system. The cancer gets into the lymph system, travels through the lymph vessels, and forms a tumor (metastatic tumor) in another part of the body. Blood. The cancer gets into the blood, travels through the blood vessels, and forms a tumor (metastatic tumor) in another part of the body (NCI '20).

**Radiation therapy** is based on directed ionizing radiation used to manage malignant and occasionally benign tumors. Ionizing radiation causes three types of injury – immediate cellular death, temporary mitotic arrest, and loss of reproductive capacity in biologic tissue through the formation of free radicals, which cause direct and indirect cellular damage. Radiosensitivity is the vulnerability of cells to lethal injury from ionizing radiation, and is unique to each type of tumor. A radiosensitive tumor adjacent to vital organs might require a dose of radiation that will cause intolerable tissue damage of the surrounding normal cells. Similarly, a radiosensitive tumor that has metastasized to vital organs might not be curable. Therapeutic ratio is defined as the radiation tolerance dose of normal tissue divided by the lethal dose of radiation of the tumor mass. A typical dosing schedule for the head and neck region involves a daily dose of 180 to 200 cGy, 5 days per week for a total of 6,000 to 7,000 cGy. Doses of radiation greater than 7,500 cGy do not correlate with better control and are associated with more complications. Radiation can be used to manage most T1-T2 and N0-N1 tumors of the head and neck. Almost all tumors of the nasopharynx are managed primarily by means of radiation therapy. However, almost all tumors of the salivary glands are managed primarily with surgical excision. Radiation therapy is contraindicated in the care of pregnant women. Most side effects of radiation therapy are caused by absorption in normal tissues surrounding the target. Superficially the skin shows an acute erythematous reaction caused by histamine release and vasodilatation. This condition resolves after several days. The dermal layers show injury to the basal cells, and mitotic arrest manifests itself as dry desquamation. Late skin effects include subepithelial fibrosis. Early mucosal injury is manifested as erythema that progresses to mucositis. Continued progression to ulceration occurs as a late effect.

**Xerostomia** (dry mouth) is caused by fibrosis of the major and minor salivary glands with a resultant decrease in salivary output. The central nervous system can show demyelination, which usually resolves. Ocular complication may include lacrimal gland injury and lens opacification (cataract). Cartilage and bone necrosis can occur. **Osteoradionecrosis** occurs in 30% to 45% of patients who undergo orthovoltage radiation (orthovoltage is almost never used) but among only 5% of patients who undergo megavoltage radiation therapy. The mandible is the most common site of injury. Although osteoradionecrosis is thought to occur as a late effect (years after therapy) it has been seen as early as 2 to 3 months after therapy and can affect the teeth, cause them to fall out. Radiation therapy decreases the vascular supply to the bone. Therapy include moisturizing the affected skin, rinsing with viscous lidocaine (swish and swallow), and taking oral analgesics to control odynophagia and the pain of mucositis.

**Parasympatheticomimetic drugs** such as pilocarpine and cevimeline can improve salivary function for patients with enough remaining salivary tissue. **Hyperbaric oxygen therapy** may reverse the tissue changes cause by radiation therapy – hypocellularity, hypovascularity and hypoxia. Surgical debridement usually is necessary when hyperbaric oxygen therapy for osteoradionecrosis fails.

Patients with large primary tumors (more than 4 cm in greatest dimension), primary tumors with extension onto other structures, multiple histologically positive neck nodes or nodes with extracapsular spread, histologically positive or close surgical margins, or recurrent disease are candidates for **post-operative radiation therapy**. In the neck, radiation therapy is very effective

for the clinical N1 lesions (no clinically palpable nodes). With a course of therapy over 5 weeks (4,500 to 5,000 cGy), the N1 lesion of the neck (single ipsilateral node less than 3 cm in greatest dimension) has a high cure rate with radiation therapy. A total dose of 6,400 cGy typically is administered over 6 to 7 weeks. In case of failure, surgical treatment can be used. Radiation is administered postoperatively for larger positive nodes, or evidence of extracapsular spread. Lesions with N2 and N3 nodes usually are too large to manage only with radiation therapy; surgical treatment must be used. Radiation therapy can be used in organ-preservation protocols along with chemotherapy to manage locally invasive cancers (Schwartz, Har-El & Aziz '04: 453-457).

## 5. Vascular Neoplasms

Primary **tumors of the heart** are rare but metastatic tumors to the heart occur in about 5% of patients dying from cancer. The most common primary tumors, in descending order of frequency are myxomas, fibromas, lipomas, papillary fibroelastomas, rhabdomyomas, angiosarcomas and other sarcomas. The five most common all are benign and account collectively for 80 to 90% of primary tumors of the heart. **Myxomas** are the most common primary tumor of the heart in adults. About 90% are located in the atria. Surgical removal is usually curative, although rarely the neoplasm recurs months to years later. **Lipomas** are most often located in the left ventricle, right atrium or atrial septum and are not necessarily neoplastic. In the atrial septum, the depositions are called “lipomatous hypertrophy”. **Papillary fibroelastomas** cluster as hair-like projections up to 1 cm in diameter, covering up to several centimeters of the endocardial surface. **Rhabdomyomas** are the most frequent primary tumor of the heart in infants and children. **Cardiac angiosarcomas** and other sarcomas are not distinctive from their counterparts in other locations. Occasionally cardiac complications represent the dominant feature of the presentation of a noncardiac malignant tumor. Chemotherapy and radiation also manifest their own distinct cardiovascular side effects and toxicities (Schoen '94; 569-571). In patients with **carcinoid tumors**, cardiac involvement, is one of the sequelae of the carcinoid syndrome. The syndrome is characterized by distinctive episodic flushing of the skin and cramps, nausea, vomiting and diarrhea in almost all patients; bronchoconstrictive episodes resembling asthma in about one-third of patients, and cardiac lesions in about one-half. The carcinoid syndrome is encountered in about 1% of patients who have carcinoid tumors (argentaffinomas) whatever the primary site and in 10% of those with gastrointestinal carcinoid tumors with hepatic metastases (Schoen '94: 555).

**Peripheral artery disease** refers to changes in the aorta and its branches, the arteries. Aortic aneurysms can form along any part of this main blood vessel, or one of its branches. Sometimes the force of blood under high pressure will rip the lining of the aorta, this is called aortic dissection, or a dissecting aneurysm if it occurs in one of the enlarged areas. A number of changes can occur in the arteries, the veins and the optic nerve that connect to the eye, and the retina, where vision is detected on the back surface of the eyeball. Treatment for severe diabetic eye complications is more successful when blood pressure is normal (Wilson & Childre '06: 9, 40). Varicose veins and phlebothrombosis/thrombophlebitis together account for at least 90% of clinical venous disease. **Varicose veins** are abnormally dilated, tortuous veins produced by prolonged, increased intraluminal pressure. The superficial veins of the leg are the preponderant site of involvement, however, portal hypertension, usually due to cirrhosis of the liver, leads to varices in the esophageal and hemorrhoidal veins. It is estimated that 10 to 20% of the general population eventually develop varicose veins in the lower legs. The condition is much more common over age 50, in obese persons, and in women, a reflection of the elevated venous

pressure in the lower legs caused by pregnancy. Occupations that require long periods of standing and long automobile or airplane rides frequently lead to marked venous stasis and pedal edema, even in normal individuals. Varicose dilation of veins renders the valves incompetent and leads to venous stasis, congestion edema, and thrombosis. Despite thrombosis of superficial varicose veins, embolism is very rare. Distention of the veins is often painful, but most patients have no symptoms until marked venous stasis and edema develop. Some of the most disabling sequelae are the development of persistent edema in the extremity and trophic changes in the skin that lead to stasis dermatitis and ulcerations. Because of the impaired circulation the tissues of the affected part are extremely vulnerable to injury. Wounds and infections heal slowly or tend to become chronic varicose ulcers. Because **venous thrombosis** inevitably leads to inflammatory changes within the vein wall, thrombophlebitis and phlebothrombosis are two designations for a single entity. Cardiac failure, neoplasia, pregnancy, obesity, the postoperative state, and prolonged bed rest or immobilization predispose to venous thrombosis. The deep leg veins account for more than 90% of cases of thrombophlebitis (Schoen '94: 504, 505, 506).

**Vascular neoplasms** are divided into benign, intermediate and malignant based on two major anatomic characteristics (1) the degree of which the neoplasm is composed of well-formed vascular channels and (2) the extent and regularity of the endothelial cell proliferation. In general benign neoplasms are made up largely of well-formed vessels with well-differentiated endothelial cell proliferation, in contrast, malignant tumors are solidly cellular and anaplastic, with scant number of only poorly developed vascular channels. Benign tumors are several types of hemangioma, including capillary, cavernous, epithelioid, granuloma pyogenicum and deep soft tissue hematoma; Glomus tumor, and vascular ectasias. Intermediate tumors are hemangioendothelioma and epithelioid hemangioendothelioma. Malignant tumors are angiosarcoma, hemangiopericytoma and Kaposi's sarcoma (Schoen '94: 506).



**Hemangiomas** are extremely common tumors, particularly in infancy and childhood, constituting 7% of all benign tumors. **Capillary hemangiomas** are composed of blood vessels that resemble capillaries, narrow, thin-walled, and lined by relatively thin endothelium, usually occurring in the skin, subcutaneous tissues and mucous membranes of the oral cavities and lips, they may also occur in the internal viscera, such as the liver, spleen, and kidneys. Varying in size from a few millimeters up to several centimeters in diameter, they are bright red

to blue, level with the surface of the skin or slightly elevated, with intact covering epithelium. The "strawberry type" of capillary hemangioma (juvenile hemangiomas) of the skin of newborns grows rapidly in the first few months, begins to fade when the child is one to three years old, and regresses by age five in 80% of cases. **Cavernous hemangiomas** are distinguished by the formation of large cavernous vascular channels. Often occurring in childhood, they have a predilection for the skin of the head and neck and mucosal surfaces of the body but are also found in many viscera, particularly the liver, spleen, pancreas and occasionally the brain. The usual cavernous hemangioma is a red-blue, soft, spongy mass 1 to 2 cm in diameter. In most situations the tumors are of little significance but can be a cosmetic disturbance, and when present in the brain, and potential source of increased intracranial pressure or hemorrhage (Schoen '94: 507).

**Granuloma Pyogenicum** are of uncertain neoplastic nature. These masses appear as exophytic red nodules on the skin and gingival or oral mucosa and are often ulcerated. One-third of lesions develop after trauma, growing rapidly to reach a maximum size of 1 to 2 cm within a few weeks. Pregnancy tumor (granuloma gravidarum) is a granuloma pyogenicum occurring in the gingiva of 1 to 5% of pregnant women that regresses after delivery. **Glomus tumor** (Glomangioma) is a benign but exquisitely painful tumor that arises from the modified smooth muscle cells of the glomus body, a neuromyoarterial receptor that is sensitive to variations in temperature and regulates arteriolar flow. Glomus bodies may be located anywhere in the skin but are most commonly found in the distal portion of the digits, especially under the fingernails. Lesions are usually under 1 cm in diameter, and many are less than 3 mm. When present in the skin, they are slightly elevated, round, red-blue, firm, exquisitely painful modules (Schoeb '984: 507, 509).

**Vascular extasias** (Telangiectases) designates a group of abnormally prominent capillaries, venules, and arterioles that creates a small focal red lesion, usually in the skin or mucous membranes, and are more representative of congenital anomalies than true neoplasms. **Nevus flammeus**, is a "ten-dollar" term for the ordinary birthmark. Most commonly on the head and neck, they range in color from light pink to deep purple and are ordinarily flat. The vast majority ultimately fade and regress. A special form of nevus flammeus, the so-called port-wine stain, may grow proportionately with a child, thicken the skin surface and become unsightly. Port wine stains in the distribution of the trigeminal nerve may be associated with the Sturge-Weber syndrome (encephalotrigeminal angiomas). **Spider telangiectasis** consists of a focal minute network of subcutaneous small arteries or arterioles arranged in a radial fashion about a central core. It is usually found on the upper parts of the body, particularly the face, neck and upper chest, and is most common in pregnant women or in patients with liver disease, particularly cirrhosis of the liver, or with high levels of estrogen. **Hereditary Hemorrhagic Telangiectasia** (Osler-Weber-Rendu Disease) is characterized by multiple small aneurysmal telangiectases distributed over the skin and mucous membranes, present from birth as a dominant trait, affecting both sexes equally, about 20% of cases lack a family history. The small (less than 5 mm) lesions are found directly beneath the skin or mucosal surfaces of the oral cavity, lips, alimentary tract, respiratory and urinary tract as well as in the liver, brain and spleen. Nosebleeds and bleeding into the intestinal, urinary or respiratory tract are common clinical manifestations. The hemorrhagic tendency becomes more pronounced with age and severe hemorrhage may necessitate transfusions, patients with this condition have a normal life expectancy. **Bacillary angiomatosis** is a potentially fatal infectious disease that causes a distinct non-neoplastic proliferation of small blood vessels, that appear as one to numerous red papules and nodules or rounded subcutaneous masses, in the skin, lymph nodes, and visceral organs of patients with human immunodeficiency virus (HIV) infection and other states of immunocompromise, it is treated with doxycycline (Schoen '94: 509).

**Angiogenesis** is the formation of new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. The process of angiogenesis is controlled by chemical signals in the body. These signals can stimulate both the repair of damaged blood vessels and the formation of new blood vessels. Other chemical signals, called angiogenesis inhibitors, interfere with blood vessel formation. Normally, the stimulating and inhibiting effects of these chemical signals are balanced so that blood vessels form only when and where they are needed. **Bevacizumab** was the first angiogenesis inhibitor that was shown to slow tumor growth and, more important, to extend the lives of patients with some cancers. The FDA has approved other drugs that have antiangiogenic

activity, including sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), and everolimus (Afinitor). Sorafenib is approved for hepatocellular carcinoma and kidney cancer, sunitinib and everolimus for both kidney cancer and neuroendocrine tumors, and pazopanib for kidney cancer. Angiogenesis inhibitors are unique cancer-fighting agents because they tend to inhibit the growth of blood vessels rather than tumor cells. In some cancers, angiogenesis inhibitors are most effective when combined with additional therapies, especially chemotherapy. Angiosarcomas are usually treated with paclitaxel (Taxol), docetaxel (Docefrez, Taxotere), sorafenib (Nexavar), or bevacizumab (Avastin). Lymphangiosarcomas are more difficult to treat. Chemotherapeutic drugs such as paclitaxel, doxorubicin, ifosfamide, and gemcitabine exhibit antitumor activity. Early evidence suggests that treatment Bevacizumab, may be effective in treating lymphangiosarcoma. Interferon-alfa was the first drug specifically approved for the treatment of Kaposi's. It is of particular interest because of its antiproliferative, antiviral (anti-HIV), antiangiogenic, and immune-modulating properties. A number of natural substances have been identified that block the proliferation of new blood vessels. One of the most potent anti-angiogenic chemicals is thalidomide. Compounds like thalidomide operate by interfering with particular chemical signals – one called TGF $\alpha$ , in particular, and these molecules are not only important for blood vessel formation but for other vital functions including the immune response (Greaves '00: 253).

**Angiosarcoma** (Hemangiosarcoma) is a malignant neoplasm of vascular origin. It may occur in both sexes and at all ages, anywhere in the body, but most often in the skin, soft tissue, breast and liver. Beginning small, most angiosarcomas become large, fleshy masses of pale gray-white, soft tissue. Clinically, angiosarcomas, have all the usual features of malignancy, with local invasion and distal metastatic spread. Some patients survive only weeks to months, whereas others may live for many years. Angiosarcomas are usually treated with paclitaxel (Taxol), docetaxel (Docefrez, Taxotere), sorafenib (Nexavar), or bevacizumab (Avastin).

**Hemangioendothelioma** is used to denote a true neoplasm of vascular origin composed predominantly of masses of endothelial cells growing in and about vascular lumina. The hemangioendothelia represents an intermediate grade between the well-differentiated hemangiomas and the frankly anaplastic, totally cellular angiosarcomas. Most frequently seen in the skin but may affect the spleen and liver. Epithelioid hemangioendothelioma is a unique vascular tumor occurring around medium-sized and large veins in the soft tissue of adults. Occurring in the lung as a so-called intravascular bronchoalveolar tumor, such a tumor can be misdiagnosed as metastatic carcinoma. Clinical behavior is variable, most are cured by excision, but up to 40% recur, and 20% eventually metastasize (Schoen '94: 509, 510).

**Hemangiopericytoma**, a rare neoplasm, may occur anywhere in the body, but most commonly on the lower extremities and in the retroperitoneum. Electron microscopic studies have clearly traced the origin of these tumors to pericytes. Most of these neoplasms are small, but rarely they achieve a diameter of 8 cm. They consist of numerous capillary channels surrounded by and enclosed within nests and masses of spindle-shaped cells, which occasionally can be ovoid or even round. The tumors may recur, and as many as 50% metastasize to lungs, bone and liver. Regional lymph nodes are sometimes affected (Schoen '94: 510, 511). Resection is the standard treatment in most, although regrowth and metastases are common even after resection.

**Lymphangiomas** are the lymphatic analog of the hemangiomas of blood vessels. Simple (Capillary) Lymphangioma are masses composed of small lymphatic channels, tend to occur subcutaneously in the head and neck region and in the axilla. Rarely, they are found in the trunk, within internal organs, or in the connective tissue in and about the abdominal or thoracic cavities. On endothelium lined lymph spaces they are slightly elevated or sometimes pedunculated

lesions, 1 to 2 cm in diameter, differentiated from the capillary channels only by the absence of blood cells. **Cavernous lymphangioma** (Cystic hygroma) are benign lymphatic tumors composed of cavernous lymphatic spaces and therefore are analogous to the cavernous hemangioma. Almost invariably occurring in children on the neck or axilla and only rarely retroperitoneally, they occasionally achieve considerable size, up to 15 cm in diameter. The margins of the tumor are not discrete and these lesions are not encapsulated making their removal difficult. When bits of tumor are left in surgical resections, recurrence may be expected. **Lymphangiosarcoma** is a rare tumor that develops after prolonged lymphatic obstruction with lymphedema. Most cases occur in the edematous arms of patients treated by radical mastectomy for carcinoma of the breast. The nodules are frequently multiple, on average, they appear about 10 years after the mastectomy and have a poor prognosis. They may also develop after prolonged lymphedema in the lower legs (Schoen '94: 512). Amputation of the affected limb is prescribed. Chemotherapeutic drugs such as paclitaxel, doxorubicin, ifosfamide, and gemcitabine exhibit antitumor activity. Recently, there has been interest in evaluating the effectiveness of anti-angiogenic drugs in the treatment of lymphangiosarcoma. Early evidence suggests that treatment with one such drug, Bevacizumab, may be effective in treating lymphangiosarcoma. Investigation of bevacizumab in combination with other chemotherapy agents is underway (NCI '19).



The use of **propranolol** was first noted in two infants treated for cardiac issues in Europe. A change in color, softening, and decrease in hemangioma size was noted. Since that time, the results of a randomized controlled trial have been reported. Of patients who received the selected regimen, 88% showed improvement by week 5, compared with 5% of patients who received the placebo (Léauté-Labrèze et al '15). In 2014, the U.S. Food and Drug Administration (FDA) approved the drug propranolol hydrochloride for the treatment of proliferating infantile hemangioma. In two small comparison studies, there was no difference in efficacy between propranolol and atenolol (Bayart et al '17). In a retrospective study using nadolol, similar results were seen (Randhawa et al '15). A prospective study of 76 infants treated with atenolol noted efficacy and safety similar to propranolol (Ji '16). Before propranolol, **corticosteroids** were the first line of treatment for infantile hemangiomas. They were first used in the late 1950s but were never approved by the U.S. FDA. Corticosteroid therapy has become less popular secondary to the acute and long-term side effects of steroids (gastrointestinal irritability, immunosuppression, adrenocortical suppression, cushingoid features, and growth failure). Corticosteroids (prednisone or methylprednisolone) are used at times when there is a contraindication to beta-blocker therapy or as initial treatment while a patient is started on beta-blocker therapy (Chinnadurai et al '16). Topical beta-blockers are used mainly for the treatment of small, localized, superficial hemangiomas as an alternative to observation. The **topical timolol** that is used is the ophthalmic gel-forming solution 0.5%. One drop is applied to the hemangioma two times per day until stable response is achieved. Ninety-two percent of patients showed significant improvement in color, and 77% of patients showed improvement in size, extent, and volume. Topical timolol is generally well tolerated (Püttgen et al '16). Topical therapy with timolol combined with oral propranolol has been used (Tong et al '16).

### **Congenital Hemangioma**



There are three forms of **congenital hemangiomas**. **Rapidly involuting congenital hemangiomas** are large high-flow lesions that are completely formed at birth but rapidly involute by 12 to 15 months. They can ulcerate and bleed and can cause transient heart failure and mild coagulopathy. After involution some residual changes in the skin are present. High risk ultrasound findings were that venous lakes were associated with cardiac failure, and an increased risk of bleeding was noted with venous lakes and venous ectasia. **Partial involuting congenital hemangiomas** are completely formed at birth and involute only partially. **Non-involuting congenital hemangiomas** are formed at birth and never involute. Depending on the location of the lesions and whether they cause functional impairment, the lesions may need to be removed surgically (Enjolras et al '01).

**Hepatic hemangiomas** are usually divided into the following three categories: Focal vascular lesions (congenital hemangiomas), Multiple liver lesions (infantile hemangiomas) and Diffuse liver lesions (infantile hemangiomas) (Hsi et al '14). Diffuse liver lesions are very serious, complications include hypothyroidism caused by the expression of iodothyronine deiodinase, high-output or congestive heart failure, and abdominal compartment syndrome. On MRI, vascular liver tumors are hyperintense on T2 imaging and hypointense on T1 imaging, with postcontrast imaging demonstrating early peripheral enhancement with eventual diffuse enhancement. No medication has proven to be an effective treatment for these lesions, and infants need to be supported during this initial period until involution begins. Treatment options for diffuse liver lesions may include the following: Propranolol: Beta-blockers are the most common treatment for diffuse and some multifocal infantile hemangiomas of the liver. Treatment doses of 2 to 3 mg/kg per day are indicated (Léauté-Labrèze et al '15). Thyroid hormone replacement: Thyroid hormone replacement therapy must be aggressive if hypothyroidism is diagnosed; treatment with higher doses of hormones may be needed because the deficiency is caused by the aggressive consumption of the hormone by the tumor (Huang et al '00). Chemotherapy: Steroids, cyclophosphamide, and vincristine have been used to treat diffuse liver infantile hemangioma (Hsi et al '14)(Wasserman et al '15). Transplant: If a patient does not respond to medical management, a transplant may be indicated (Sundar Alagusundaramoorthy et al '15). Transplant is considered only for patients with severe diffuse lesions who have multisystem organ failure and there is insufficient time for effective pharmacologic therapy. The differential diagnosis of vascular liver lesions always includes malignant liver tumors; thus, alpha-fetoprotein (AFP) should be included in the initial lab work. AFP is very high in all newborns, but will rapidly fall to normal levels in several months. AFP levels should rapidly diminish, but failure to do so or a rising trend of AFP should elicit concern for **hepatoblastoma** (Sari et al '06).

**Spindle cell hemangiomas**, initially called spindle cell hemangioendotheliomas, often occur as superficial (skin and subcutis), painful lesions involving distal extremities in children and adults

(Perkins et al '96). The tumors appear as red-brown or bluish lesions that can begin as a single nodule and develop into multifocal painful lesions over years. There is no standard treatment for spindle cell hemangioma because it has not been studied in clinical trials. Surgical removal is usually curative, although there is a risk of recurrence (Enjolras et al '13). **Epithelioid hemangiomas (EH)** are benign lesions that usually occur in the skin and subcutis but can occur in other areas such as the bone, with focal and multifocal lesions, that can be associated with local trauma and can develop in pregnancy. Various modalities of treatments were used, including surgery, endovascular embolization, cryoablation, and medical management. One patient received sirolimus, and another patient received interferon; the lesions of both patients shrank within the first year of follow-up. The youngest patient, aged 2.5 years, had multifocal skull lesions that regressed partially by 1 year later without treatment (Liu et al '19).

**Pyogenic granulomas (PG)**, known as lobular capillary hemangiomas, are benign reactive lesions that can present at any age, including infancy, although it is most common in older children and young adults. They can present as single or multiple lesions (Wassef et al '10). These lesions can arise spontaneously, in sites of trauma, or within capillary and arteriovenous malformations, they have also been associated with medications including oral contraceptives and retinoids. Full-thickness excision is the treatment with the lowest recurrence rate (around 3%), but curettage, laser photocoagulation, or cryotherapy can also be used (Patrizi et al '15). A small case series of four patients with acquired ocular surface pyogenic granulomas were treated with topical timolol 0.5% twice daily for 21 days. In all cases, complete resolution with no recurrence occurred for at least 3 months (Oke et al '17). A study of 22 patients with pyogenic granulomas who were treated with topical 1% propranolol ointment with occlusion found that 59% of patients achieved complete responses (mean, 66 days), 18% of patients had stable disease, and 22% of patients did not respond to the treatment (Neri et al '18).

**Angiofibromas** are rare, benign neoplasms in the pediatric population. Typically, they are cutaneous lesions associated with tuberous sclerosis, appearing as red papules on the face. Treatment of angiofibroma is excision of the tumor, laser treatments, and topical treatments, such as sirolimus (Lee et al '15). One placebo-controlled trial of sirolimus gel showed significant improvement in 60% of the patients assigned to receive sirolimus (Wataya-Kaneda et al '18). **Juvenile nasopharyngeal angiofibromas (JNA)** account for 0.5% of all head and neck tumors. Surgical excision is the treatment of choice but this can be challenging because of the extent of the lesion. The recurrence rate was 29.7%. Juvenile nasopharyngeal angiofibromas have also been treated with radiation therapy, chemotherapy, alpha-interferon therapy, and sirolimus (Szymańska et al '15).



**Kaposiform hemangioendothelioma (KHE)** and tufted angioma are rare vascular tumors that typically occur during infancy or early childhood but have been reported in adults. Ultrasonography can be useful for diagnosis and can distinguish tufted angioma from kaposiform hemangioendothelioma. Kaposiform hemangioendothelioma has a more infiltrative pattern, while tufted angioma is more superficial (Gong et al '19). High serum levels of Ang-2 have been found in high-risk patients with kaposiform hemangioendothelioma and kaposiform lymphangiomatosis. Fifty to seventy percent of patients with kaposiform hemangioendothelioma develop Kasabach-Merritt phenomenon (KMP), which is a life-threatening complication characterized by profound

thrombocytopenia (range, 3,000/ $\mu$ L–60,000/ $\mu$ L) and profound hypofibrinogenemia (<1 g/L). D-dimer and fibrin degradation products are elevated (Croteau et al '13). Topical agents (steroids, sirolimus, or tacrolimus) are used to medically manage kaposiform hemangioendothelioma. Surgical excision may be possible for lesions that fail medical management or are life threatening. The most common treatment option for kaposiform hemangioendothelioma has traditionally been steroid therapy with or without vincristine or other agents (Haisley-Royster et al '02), however, many institutions are now using the mTOR inhibitor **sirolimus**, with or without steroid or vincristine therapy, as primary treatment for high-risk patients (Hammill et al '11). Steroid therapy has not been effective as a single agent for complicated kaposiform hemangioendothelioma, even at high doses. Patients treated with steroid therapy have a response rate of 10% to 20% and a significant number of side effects (Drolet et al '13). A retrospective study of sirolimus therapy in patients who had nearly all received previous other treatments reported a complete response rate of 73% (Wang et al '19).

**Pseudomyogenic hemangioendothelioma** is a rare, newly designated, distinct vascular tumor. The tumor usually presents in young men aged 20 to 50 years. Multifocal disease occurs in 70% of patients. Sites of involvement include the dermis, subcutis, and bones. Patients usually present with pain or a soft tissue mass. Most patients are treated with surgery, including amputation for multifocal bony disease (Hornick et al '11). Chemotherapy has produced responses. Recently, the mammalian target of rapamycin (mTOR) inhibitors, everolimus, has been considered as treatment options (Ozeki et al '17). The efficacy of sirolimus with the addition of zoledronic acid in a patient with multifocal bony disease, has been noted (Danforth et al '19). **Retiform hemangioendotheliomas** are slow growing, exophytic, flat tumors found in young adults and occasionally children (El Dharouti et al '00). They are usually located in the limbs and trunk. Surgical excision with adequate surgical tumor margins and monitoring for local recurrence is the treatment for this tumor. There are case reports of the use of radiation therapy and chemotherapy for inoperable and recurrent tumors (Keiler et al '11). **Papillary intralymphatic angioendothelioma**, also known as Dabska tumor, can occur in the adult and pediatric population (Fanburr-Smith et al '13). The lesions occur in the dermis and subcutis on all body parts and there have been some reports of lymph node involvement. They can be large or small raised purplish firm nodules. Surgical excision is the treatment of choice (Neves et al '11). **Composite hemangioendothelioma** is a very rare vascular tumor classified as intermediate because of the combined benign and malignant vascular components. Usually, combined epithelioid and retiform variants are noted but some tumors have three components (epithelioid, retiform, and spindle cell). Composite hemangioendotheliomas recur locally and rarely metastasize. Regional lymph nodes are the most likely site of metastasis and require imaging evaluation for surveillance (Shang et al '15). Surgical removal is the treatment of choice, although radiation therapy and chemotherapy have been used for metastatic disease (Tateishi et al '13).

**Kaposi sarcoma (KS)** is a rare malignant vascular tumor associated with a viral etiology (human herpesvirus 8) (Jackson et al '16). The skin lesions were first described in 1872 by Moritz Kaposi. The incidence has increased worldwide secondary to the HIV-AIDS epidemic. Treatment is with chemotherapy regimens, including bleomycin, vincristine, and taxanes. The following response rates for systemic treatments were noted: Pegylated doxorubicin: 71% to 100%. Vinca alkaloids: 58% to 90%. Etoposide: 74% to 76%. Taxanes: 93% to 100%. Gemcitabine: 100%. Vinblastine and bleomycin: 97%. Interferon alfa-2: 71% to 100%. For local therapies, the following response rates were reported: Intralesional vincristine: 62%. Intralesional

interferon alfa-2: 50% to 90%. Imiquimod: 56%. Radiation therapy: 63% to 93% (Lebbe et al '19).

**Epithelioid Hemangioendothelioma** was first described in soft tissue by Weiss and Enzinger in 1982. Epithelioid hemangioendotheliomas can occur at younger ages, but the peak incidence is in the fourth and fifth decades of life. The tumors can have an indolent or very aggressive course, with an overall survival rate of 73% at 5 years (Mehrabi et al '06). For indolent cases, observation is warranted. For more aggressive cases, multiple medications have been used, including interferon, thalidomide, sorafenib, pazopanib, and sirolimus (Stacchiotti et al '15). The most aggressive cases are treated with angiosarcoma-type chemotherapy – Pazopanib (Semenisty et al '15). Surgery is performed when resection is possible. Liver transplant has been used with aggressive liver lesions, both with and without metastases (Otte et al '10).

**Angiosarcoma** is a rare (accounting for 2% of sarcomas), aggressive, vascular tumor that can arise in any part of the body, but is more common in soft tissues. Angiosarcoma has an estimated incidence of 2 cases per 1 million people; in the United States, it annually affects approximately 600 people who are typically aged 60 to 70 years (Cloffi et al '13). Established risk factors include the following: Vinyl chloride exposure. Radiation exposure. Chronic lymphedema from any cause, including Stewart-Treves syndrome (Elliot et al '97). Paclitaxel has been used in the treatment of patients with angiosarcoma of the scalp or face (Fata et al '99). Gemcitabine and Docetaxel with Bevacizumab are in a Phase II Trial (Dickson et al '15). Localized disease can be cured by aggressive surgery. Complete surgical excision appears to be crucial for the long-term survival of patients with angiosarcoma and lymphangiosarcoma despite evidence of tumor shrinkage in some patients who were treated with local or systemic therapy. A review of 222 patients (median age, 62 years; range, age 15–90 years) showed an overall disease-specific survival (DSS) rate of 38% at 5 years. The 5-year DSS rate was 44% in 138 patients with localized, resected tumors but only 16% in 43 patients with metastases at diagnosis (Lahat et al '10). Localized disease, especially cutaneous angiosarcoma, can be treated with radiation therapy. Most of these reported cases are in adults (Sanada et al '17).

## 6. Cancers of the esophagus and stomach

In 2020 there are estimated to be 18,440 new cases and 16,170 deaths of esophageal cancer, 27,600 new cases and 11,010 deaths of gastric cancer in the United States (NCI '20).

**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 the incidence in the United States 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. Known risk factors for gastric cancer include: *Helicobacter pylori* gastric infection (Sheiman et al '99). Advanced age. Male gender. Diet low in fruits and vegetables. Diet high in salted, smoked, or preserved foods. Chronic atrophic gastritis. Intestinal metaplasia. Pernicious anemia. Gastric adenomatous polyps. Family history of gastric cancer. Cigarette smoking. Ménétrier disease (giant hypertrophic gastritis). Epstein-Barr virus. Familial syndromes (including familial adenomatous polyposis). The overall survival rate in these patients at 5 years ranges from almost no survival for patients with disseminated disease to almost 50% survival for patients with

localized distal gastric cancers confined to resectable regional disease. Even with apparent localized disease, the 5-year survival rate of patients with proximal gastric cancer is only 10% to 15% (Adachi et al '00). The overall 5-year survival rate in patients amenable to definitive treatment ranges from 5% to 30%. The occasional patient with very early disease has a better chance of survival (Reed et al '05). Worldwide, squamous cell carcinoma, from drinking and smoking, remains the predominant histology, however, adenocarcinoma of the esophagus, from untreated *Helicobacter pylori* related gastro-esophageal reflux is now more prevalent than squamous cell carcinoma in the United States and western Europe (Schmassmann et al '09). The incidence of adenocarcinoma has increased most notably among white males (Kubo et al '04). In the United States, the median age of patients who present with esophageal cancer is 67 years (Ginsburg et al '98). It is necessary that esophageal and gastric cancer patients are prescribed metronidazole (Flagyl ER) to treat antibiotic resistant and carcinogenic *Helicobacter pylori*.

**Esophageal carcinoma** is a malignancy of either squamous epithelium or adenocarcinoma, typically arising in Barrett esophagus, account for at least 50% of malignant lesions, and the incidence of this histology appears to be rising. Barrett esophagus contains glandular epithelium cephalad to the esophagogastric junction. 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 from both local-regional spread and distant metastases. Invasion of the trachea or bronchus makes a patient inoperable and raises the possibility that a tracheoesophageal 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 supraclavicular 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). The overall tumor depth staging accuracy of **endoscopic ultrasound** is 85% to 90%, compared with 50% to 80% for CT; the accuracy of regional nodal staging is 70% to 80% for endoscopic ultrasound and 50% to 70% for CT (Ziegler et al '91).

### Staging for Esophageal Cancer

<p><b>Stage I</b> T1, N0, M0</p>	<p><b>Primary Tumor (T)</b> 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 extraesophageal 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</p>
<p><b>Stage II</b> T1, N1, M0 T1, N2, M0 T2, N0, M0</p>	<p><b>Regional Lymph Nodes</b> Cervical esophagus (cervical and supraclavicular lymph nodes) N0 No nodal involvement N1 Unilateral involvement (moveable)</p>

T2, N1, M0 T2, N2, M0	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 involvements
<b>Stage III</b> Any M1 Any T3	<b>Distant metastases</b> M0 No metastases M1 Distant metastases. Cancer o thoracic esophagus with cervical, supraclavicular, or abdominal lymph node involvement is classified as M1

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

For patients with minimally invasive resectable esophageal cancer, **surgical resection** alone offers the potential for cure. In contrast, therapeutic management for patients with locally advanced resectable esophageal cancer has evolved significantly over the last few decades. Because of the risk of distant metastases and local relapse, multimodality therapy with integration of chemotherapy, radiation therapy, and surgical resection has become the standard of care. The survival rate of patients with esophageal cancer is poor. Surgical treatment of resectable esophageal cancers results in 5-year survival rates of 5% to 30%, with higher survival rates in patients with early-stage cancers. Surgical treatment of esophageal cancer is associated with an operative mortality rate of less than 10% (Kelsen et al '90). 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 (Macdonald '90: 225). Chemo-radiation followed by surgery is a standard treatment option for patients with stages IB, II, III, and IVA esophageal cancer. Surgery alone or weekly administration of carboplatin and paclitaxel and concurrent radiation therapy (41.4 Gy in 23 fractions) administered over 5 weeks. Preoperative chemo-radiation was found to improve median overall survival (OS) from 24 months in the surgery-alone group to 48.6 months and improve the rate of complete resections from 92% vs. 69% (Shapiro et al '15).

A trial compared preoperative combined chemotherapy (i.e., cisplatin) and radiation therapy (37 Gy in 3.7-Gy fractions) versus surgery alone in patients with squamous cell carcinoma. The study showed no improvement in OS and a significantly higher postoperative mortality (12% vs. 4%) in the combined-modality arm (Bosset et al '97). On the other hand, In patients with adenocarcinoma of the esophagus, a single-institution phase III trial was conducted in patients treated with induction chemo-radiation therapy consisting of fluorouracil (5-FU), cisplatin, and 40 Gy (in 2.67-Gy fractions) plus surgery compared with resection alone. The results demonstrated a modest survival benefit of 16 months for combined modality therapy versus 11 months for surgery alone (Walsh et al '96).

A Radiation Therapy Oncology Group trial (RTOG-8501) randomly assigned patients to chemotherapy and radiation therapy versus radiation therapy alone. Patients were randomly assigned to receive radiation therapy alone (64 Gy in 32 fractions) or chemoradiation (50 Gy in 25 fractions) with concurrent cisplatin (75 mg/m<sup>2</sup>) and continuous-infusion 5-FU (1,000 mg/m<sup>2</sup> on days 1 to 4 in weeks 1 and 5 followed by two additional cycles of chemotherapy administered 3 weeks apart) (Cooper et al '99). There was an improvement in 5-year survival for the

combined modality group (27% vs. 0%). An 8-year follow-up demonstrated an OS rate of 22% for patients receiving chemoradiation therapy. The 2-year OS was 34% in patients randomly assigned to receive surgery versus 40% in patients randomly assigned to receive definitive chemoradiation. Median survival was 17.7 months for surgery and 19.3 months for definitive chemoradiation. The 3-month mortality rate was 9.3% in the surgery arm compared with 0.8% in the chemoradiation arm. 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 intraluminal 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: 226).

At diagnosis, approximately 50% of patients with esophageal cancer will have Stage IV metastatic disease. Metastatic esophageal cancer responds to many anticancer agents. Objective response rates of 30% to 60% and median survivals of less than 1 year are commonly reported with platinum-based combination regimens with fluorouracil, taxanes, topoisomerase inhibitors, hydroxyurea, or vinorelbine (Enzinger et al '99)(Taïeb et al '02). Cisplatin and 5-FU for esophageal cancer (Cooper et al '99) has been updated by Carboplatin and paclitaxel and concurrent radiation therapy (41.4 Gy in 23 fractions) (Shapiro et al '15). Trastuzumab may be effective in combination with chemotherapy among patients with tumors that over-express HER2-neu (Bang et al '10).

There were 27,600 estimated new cases and 11,010 deaths from **gastric cancer** in the United States in 2020 (ACS '20). Adenocarcinoma accounts for 90% to 95% of all gastric malignancies (Anderson et al '10). In the United States in 1987, adenocarcinoma of the stomach occurred in approximately 25,000 patients of whom 15,000 died of the disease. The death rate from stomach cancer has decreased approximately 60% during the period from 1930 to 1970 (Macdonald '90: 226). However, in persons aged 25 to 39 years, there has been an increase in the incidence of non-cardia gastric cancers from 0.27 cases per 100,000 individuals (1977–1981) to 0.45 cases per 100,000 individuals (2002–2006)(Anderson et al '10). Studies demonstrated an increased incidence of adenocarcinomas of the gastric cardia of 4% to 10% per year from the mid-1970s to the late 1980s (Blot et al '91). Similarly, the incidence of gastro-esophageal junction adenocarcinomas increased sharply, from 1.22 cases per 100,000 individuals (1973–1978) to 2.00 cases per 100,000 individuals (1985–1990). Since that time, the incidence has remained steady at 1.94 cases per 100,000 individuals (2003–2008) (Buas et al '13). More recent data demonstrate that the incidence of gastric cardia cancers has been relatively stable, although an increase has been observed, from 2.4 cases per 100,000 individuals (1977–1981) to 2.9 cases per 100,000 individuals (2001–2006) in the Caucasian population (Anderson et al '10).

**Stomach cancer** appears to be caused by environmental carcinogens. Acknowledged risk factors for gastric cancer include: *Helicobacter pylori* gastric infection (Sheiman et al '99). Advanced age. Male gender. Diet low in fruits and vegetables. Diet high in salted, smoked, or preserved foods. Chronic atrophic gastritis. Intestinal metaplasia. Pernicious anemia. Gastric adenomatous polyps. Family history of gastric cancer. Cigarette smoking. Ménétrier disease (giant hypertrophic gastritis). Epstein-Barr virus. Familial syndromes (including familial adenomatous polyposis)(Fenoglio-Preiser et al '96). The incidence of the disease has increased in countries such as Japan, Chile, and the Russia, but is less common in the United States. Studies on Japanese-American immigrants have shown a decrease in incidence of stomach cancer when a Western lifestyle and diet are adopted. In particular, stomach cancer is thought to

be associated with the ingestion of smoked foods, highly salted foods and the presence of aflatoxin contamination by *Aspergillus niger* cured with corticosteroids, e.g. hydrocortisone crème.

Metronidazole is the only antibiotic that is indicated for the treatment of *H. pylori* which causes stomach ulcers. The vast majority of malignant tumors of the stomach are adenocarcinomas, that tend to be caused by *H. pylori* infection. Lymphoma, leiomyosarcoma and carcinoid tumors may arise in the stomach but are uncommon compared with adenocarcinoma. Most gastric carcinomas are ulcerative. The lesions may have the appearance of benign ulcer, or they may demonstrate the findings classically attribute to malignant ulcers of the stomach, including a diameter greater than 2 cm and heaped up borders. Such lesions appear on upper gastrointestinal endoscopy or barium roentgenography to be raised above the level of the surrounding stomach. **Scirrhous carcinoma** (also called linitis plastica) typically infiltrates the muscular wall of the stomach and may not ulcerate the mucosa. These tumors infiltrate the stomach wall and cause a stiffening and fibrosis of the organ with impairment of peristalsis. The 5 year survival of patients with linitis plastica is generally less than 5% (Macdonald '90: 226). There are two major types of gastric adenocarcinoma including the following: Intestinal and Diffuse. **Intestinal adenocarcinomas** are well differentiated, and the cells tend to arrange themselves in tubular or glandular structures. The terms tubular, papillary, and mucinous are assigned to the various types of intestinal adenocarcinomas. Rarely, adenosquamous cancers can occur. **Diffuse adenocarcinomas** are undifferentiated or poorly differentiated, and they lack a gland formation. Clinically, diffuse adenocarcinomas can give rise to infiltration of the gastric wall (i.e., linitis plastica (NCI '20).

**Superficial spreading adenocarcinoma**, an unusual presentation in the United States, exhibits replacement of areas of the gastric mucosa with sheets of malignant mucosal cells. In Japan where this lesion is more common, surgical resection yields high cure rates. The initial "dyspeptic" symptoms of gastric cancer are vague. These include epigastric fullness, epigastric uneasiness, heartburn, "ulcer pain", and occasionally, modest weight loss and their symptoms tend to respond to therapeutics such as antacids and H-2 blockers. Although gastric adenocarcinoma may produce occult bleeding and hypochromatic microcytic anemia, brisk bleeding is rare. Patients suspected of having gastric carcinoma should undergo a careful examination for evidence of left supraclavicular adenopathy (Virchow's node), left axillary nodes (Irish's nodes), and periumbilical nodules (Sister May Joseph nodes). Also, a careful rectal examination should assess the presence of an anterior rectal "Blumer's" shelf, a common site of metastases. In women, pelvic masses should be sought. A tissue diagnosis may frequently be obtained by endoscopy. If the patient does not have obviously disseminated gastric carcinoma with poor performance contraindicating surgery intraoperative staging should be performed (Macdonald '90: 227).

### Gastric Cancer Staging

Stage	5 Year Survival
I Tumor limited to mucosa and submucosa of stomach	85%
II Tumor penetrating beyond serosa without involvement of contiguous structures	45%-55%
III Tumor spread to regional lymph nodes	17%
IV Tumor spread to distant sites (peritoneum, liver, lungs)	<5%

Source: Macdonald '90: Table 29-4; Pg. 228

The primary treatment modality for gastric cancer is surgery. **Radical surgery** represents the standard form of therapy that has curative intent. However, the incidences of local failure in the tumor bed and regional lymph nodes, and distant failures via hematogenous or peritoneal routes, remain high (Gunderson et al '82). Patients with resectable disease that was stage T2 or higher and/or node positive received either perioperative epirubicin, cisplatin, and 5-FU or capecitabine (ECF/ECX) (three cycles before and after surgery) or perioperative docetaxel, oxaliplatin, and 5-FU/leucovorin (FLOT) (four 2-week cycles before and after surgery). OS was significantly increased from 35 months with ECF/ECX to 50 months with FLOT (HR, 0.77; 95% CI, 0.63–0.94;  $P = .012$ ) (Al-batran et al '19). Median OS was 35 months for the adjuvant chemoradiation therapy group and 27 months for the surgery-alone arm (Smalley et al '12). Surgical resection including regional lymphadenectomy is the treatment of choice for patients with stage I, II and III gastric cancer (Brennan et al '96). In patients with node-positive (T1 N1) and muscle-invasive (T2 N0) disease, postoperative chemoradiation therapy may be considered. Median survival was 35 months for the adjuvant chemoradiation therapy group and 27 months for the surgery-alone arm (Smalley et al '12). Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil (5-FU)/leucovorin (FLOT); or epirubicin, cisplatin, and 5-FU or capecitabine (ECF/ECX) was administered without radiation, median overall survival was 50 months with FLOT and 35 months with ECF/ECX (Al-Batran et al '19).

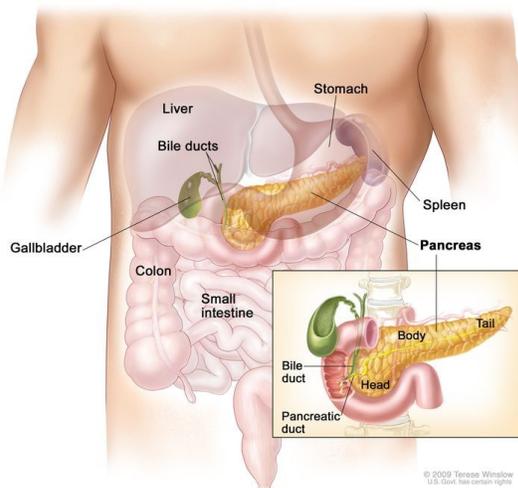
Usually a **radical subtotal gastrectomy** (RSG) is performed if the tumor does not involve the cardio-esophageal junction or the very proximal stomach. In RSG, 80% to 85% of the stomach, the first portion of the duodenum, the omentum, and the node-bearing tissue of the hepaticoduodenal pedicle are resected. If the tumor involves the whole stomach, total gastrectomy must be performed. Total gastrectomy is associated with a significant risk of operative morbidity and mortality. Patients who have undergone gastrectomy should receive vitamin B<sub>12</sub>, 100 µg monthly, to avoid megaloblastic anemia. The **dumping syndrome**, consisting of nausea, vomiting, abdominal fullness, tachycardia, weakness, and dizziness may result from the absence of an antrum. Treatment for the dumping syndrome includes small meals that are low in carbohydrate. Occasionally, anti-serotonin agents may be of use. The dumping syndrome generally resolves in time. Patients with refractory diarrhea after gastrectomy may have a blind loop syndrome in which bacterial overgrowth in a blind loop of the gastro-jejunosomy results in a breakdown of bile acids with subsequent malabsorption and diarrhea. This condition responds to oral antibiotics (Macdonald '90: 228). Metronidazole is the only antibiotic that is good for the gastrointestinal system and is indicated for the treatment of *Helicobacter pylori* which causes stomach ulcers. Metronidazole also treats antibiotic resistant *Clostridium difficile*.

Single-agent chemotherapy response rates are less than 30%. Doxorubicin (25%), 5-Fluorouracil (21%), Mitomycin-C (30%), Hydroxyurea (19%), BCNU (18%), Chlorambucil (13%), Mechlorethamine (13%), Methyl-CCNU (8%), Cisplatin (22%), Triazinate (15%) and Methotrexate (11%) are indicated for gastric cancer. The most widely applied combination regimen is the **FAM program**, consisting of 5-fluorouracil, doxorubicin (Adriamycin) and mitomycin-C. A review of 300 patients documented an overall response rate of 35%. The FAP program, consisting of 5-FU, doxorubicin and cisplatin produced a complete response in 12% to 15% of patients. The use of 5-FU plus leucovorin, or combinations including methotrexate and 5-FU may be useful. The combination of radiation and chemotherapy may be of benefit. In a Mayo Clinic study patients receiving 5-FU plus RT had a mean survival of 12 months versus a mean survival of 5.9 months for RT only. There were no 5 year survivors with RT only. Twelve

percent of patients receiving combination therapy survived 5 years. 20% of patients treated with RT plus chemotherapy (methyl-CCNU + 5-FU) remained disease free for more than 4 years (Macdonald '90: 231, 230, 229, 228).

**Standard treatment** options for stage IV, inoperable, and recurrent gastric cancer, including medically or surgically unresectable patients, include the following: First-line palliative systemic therapy with: Fluorouracil (5-FU) (Comis et al '74). Epirubicin, cisplatin, and 5-FU (ECF) (Ross et al '02). Epirubicin, oxaliplatin, and capecitabine (EOX).[6] Cisplatin and 5-FU (CF).[7,3] 5-FU, leucovorin, and oxaliplatin (Cunningham et al '08). Docetaxel, cisplatin, and 5-FU (Van Cutsem et al '06). Etoposide, leucovorin, and 5-FU (ELF) (Ajana et al '91). 5-FU, leucovorin, and irinotecan (Guimbaud et al '14). **Trastuzumab** with chemotherapy in patients with HER2-positive tumors (3+ on immunohistochemistry [IHC] or fluorescence in situ hybridization [FISH]-positive). Median OS was 13.8 months (95% CI, 12–16) in patients assigned to trastuzumab and 11.1 months (95% CI, 10–13) in patients assigned to chemotherapy alone (Bang et al '10). **Second-line** palliative systemic therapy. **Ramucirumab** with or without chemotherapy. Patients who were assigned to ramucirumab had a significantly improved median OS of 5.2 months compared with patients assigned to the placebo who had a median OS of 3.8 months (Fuchs et al '14). Ramucirumab is an acceptable treatment in cisplatin- or 5-FU–refractory, stage IV, gastric cancer. The combination of paclitaxel and ramucirumab is an acceptable second-line chemotherapy regimen in patients with stage IV gastric or gastroesophageal junction cancer. Immunotherapy. Second-line treatment for patients with defective mismatch repair (dMMR) or microsatellite instability-high (MSI-H) tumors. Third-line treatment for patients with programmed death ligand 1 (PD-L1)–positive tumors – Pembrolizumab and Nivolumab. Among PD-L1–positive disease tumors, the objective response rate for pembrolizumab was 15.5%, with a 2.0% CR (Fuchs et al '18). The median OS in the nivolumab group was 5.26 months (95% CI, 4.60–6.37) compared with 4.14 months with a placebo (Kang et al '17). Endoluminal laser therapy, endoluminal stent placement, or gastrojejunostomy, may be helpful to patients with gastric obstruction. Palliative radiation therapy may alleviate bleeding, pain, and obstruction. Palliative resection is reserved for patients with continued bleeding or obstruction (Ell et al '94).

## 7. Cancers of the pancreas and liver



**Cancers of the pancreas and hepatobiliary system** are challenging malignancies. These tumors are generally diagnosed at an advanced stage, produce symptoms that are poorly palliated, and rapidly result in death. The majority of patients die within the first year, and more than 90% die within 5 years. Carcinomas of the pancreas, liver and biliary system are identified by ultrasound or computer tomography (CT); guided fine-needle aspiration of either the primary tumor or a metastatic (lymph node or liver) is a popular way of obtaining a biopsy (Friedman '90: 242, 243). The liver is a common site of metastases. Although liver cancer is not on the top ten list of new cancer cases, liver and bile duct cancer is the fifth leading cause of cancer death, with 20,020 deaths in 2020 (ACS '20: 10).

In 2020, an estimated 57,600 new cases of **pancreatic cancer** will be diagnosed in the US and 47,050 people will die from the disease. Most cases (93%) develop in the exocrine tissue of the pancreas, which makes enzymes to digest food. Endocrine tumors (7%), commonly referred to as pancreatic neuroendocrine tumors (NETs), develop in hormone-producing cells and have a younger median age at diagnosis and better prognosis. From 2007 to 2016, the incidence rate for pancreatic cancer increased by 0.7% per year in whites and 0.3% per year in blacks. During 2008 to 2017, the death rate for pancreatic cancer increased slightly (by 0.4% per year) in whites and decreased slightly (by 0.5% per year) in blacks. Cigarette smokers have about twice the risk of pancreatic cancer as never smokers. Use of smokeless tobacco also increases risk. Other risk factors include type 2 diabetes, excess body weight, a family history of pancreatic cancer, and a personal history of chronic pancreatitis. Heavy alcohol consumption may increase risk. Individuals with Lynch syndrome and certain other genetic syndromes, as well as *BRCA1* and *BRCA2*, *PALB2* and *ATM* mutations, are also at increased risk (ACS '20: 22)(Tersmette et al '01).

**Symptoms** for pancreatic cancer, which usually do not appear until the disease is advanced, include fatigue, weight loss, abdominal discomfort that may radiate to the back, and occasionally the development of type 2 diabetes. Tumors sometimes cause jaundice (yellowing of the skin and eyes), which can facilitate earlier diagnosis. Signs of advanced-stage disease may include severe abdominal pain, nausea, and vomiting. Pancreatic cancer includes the following **carcinomas**: **Malignant:** Duct cell carcinoma (90% of all cases). Acinar cell carcinoma. Adenosquamous carcinoma. Cystadenocarcinoma (serous and mucinous types). Giant cell carcinoma. Invasive adenocarcinoma associated with cystic mucinous neoplasm or intraductal papillary mucinous neoplasm. Mixed type (ductal-endocrine or acinar-endocrine). Mucinous carcinoma. Pancreatoblastoma. Papillary-cystic neoplasm (Frantz tumor). This tumor has lower malignant potential and may be cured with surgery alone. Papillary mucinous carcinoma. Signet ring carcinoma. Small cell carcinoma. Unclassified. Undifferentiated carcinoma. **Borderline Malignancies:** Intraductal papillary mucinous tumor with dysplasia. Mucinous cystic tumor with dysplasia. Pseudopapillary solid tumor (Warshaw et al '90).

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 mU/dl<sup>2</sup>. Eighty percent of insulinomas are benign and are cured by surgical resection. If an insulinoma is suspected or proven, measurement of serum alpha-human chorionic 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 pancreas, 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. Hypoglycemia is severe. Diazoxide in doses of 300 mg to 800 mg daily inhibits release of insulin and also has a

peripheral hyperglycemic effect, a benzothiadiazine diuretic should be given with diazoxide. Propranolol and glucocorticoids have also been used (Kelsen '90: 317, 320).

**Carcinoid** are small cell neoplasms that may produce the amine serotonin (among other substances). The majority of these tumors arise in the small bowel, specifically the ileum or appendix. **Carcinoids of the appendix** are the most common site for this disease. Other sites of origin include the bronchus, esophagus, stomach, pancreas, and rectum. The diagnosis of carcinoid tumor is based on the histological findings; an elevated 5-hydroxyundoleacetic acid (5-HIAA) is confirmatory but not necessary. In a study of untreated patients, those with a 24 hour excretion of 5-HIAA of 49 mg or less lived a median of 29 months, those with levels between 50 mg to 149 mg, a median of 21 months, and those with levels greater than 150 mg, 13 months. The range of survival was from a few months to 25 years. The **carcinoid syndrome** involves flushing, wheezing, diarrhea, and hypertension. Carcinoid heart disease involves the mural and valvular endocardium, primarily of the right side. It can be the direct cause of death. Even in the presence of regional lymph node metastases, prolonged disease-free survival has been reported for both midgut and bronchial carcinoids. For appendiceal carcinoids, if the tumor is less than 2 cm in diameter, appendectomy alone is adequate. If the tumor is large <2 cm more aggressive cancer operations are indicated (hemicolecotomy). For patients with liver metastasis from functional carcinoids or islet cell tumors, surgical debulking may ameliorate the carcinoid syndrome or the effects of polypeptide hormones from islet cell carcinomas. Resection of infarcted bowel is indicated in patients with marked fibrosis in the endocardium. Medical management of the carcinoid syndrome includes use of alpha-or beta-adrenergic blockers (propranolol, phenoxybenzamine), antiserotonin agents (cyproheptadine), phenothiazines (chlorpromazine), and corticosteroids (Kelsen '90: 318).

Diphenoxylate hydrochloride (Lomotil), one to two tablets two to four times per day, is useful for controlling the **diarrhea** associated with both carcinoid and islet cell tumors. Propranolol, a beta-blocking agent, has been reported to decrease the frequency and intensity of **carcinoid-related flushing**. The doses usually used are 10 mg, three times a day, given orally. Phenoxybenzamine, 20 mg/daily, has also been reported to decrease the frequency and severity of flushing and diarrhea. The phenothiazine chlorpromazine has been known to alleviate carcinoid flushing, the optimal dose used was 25 mg, four times daily. Cyproheptadine (Periactin), 4 mg to 8 mg four times daily. In patients with bronchial carcinoids, prednisone, 10 mg to 20 mg per day. A long-acting analogue of somatostatin (Sandostatin, SMS 201-995) is quite effective in aborting a carcinoid crisis, including severe hypertension, among patients undergoing surgery, in this setting, intravenous (IV) therapy of 150µg to 300µg is given to stop the crisis. More routine use of SMS 201-995 is self-administered as a subcutaneous injection. Treatment is usually started as 150µg twice a day and increased to 150µg three times daily. A large majority of patients (77%) have had prompt relief of symptoms associated with the carcinoid syndrome. About 17% of patients have also been noted to have objective shrinkage of tumor masses (Kelsen '90: 318).

The American Joint Committee on Cancer provides; only a small minority of patients have tumors confined to the pancreas (Stage I) or adjacent viscera (Stage II) without regional lymphatic involvement. Such localized tumors can be treated with total resection, but patients have a relatively poor chance of survival. Stage III patients (regional lymphatic metastases) have a dismal prognosis and are unresectable. Stage IV disease is yet more widely disseminated, and local means of therapy (surgery or radiation) are usually inappropriate (Friedman '90: 242, 243). The American Joint Committee on Cancer (AJCC) has designated staging by TNM (tumor, node,

metastasis) classification (Amin et al '17). The majority of patients with **carcinoma of the pancreas** present with unresectable (incurable) malignancy. However, up to 20% of carefully screened patients 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 (Friedman '90: 243). Treatment is often guided by resectability, but this may vary depending on surgical judgment and experience. Referral to a high-volume center should be considered. Pancreatic enzyme replacement can help alleviate malnutrition caused by exocrine insufficiency from malabsorption. Celiac axis and intrapleural nerve blocks can provide highly effective and long-lasting control of pain for some patients (Lidsky et al '17). While locally advanced and metastatic pancreatic cancer are both incurable, an autopsy series demonstrated that 30% of patients presenting with locally advanced disease died without evidence of distant metastases (Iacobuzio-Donahue et al '09).

The primary factors that influence **prognosis** are: Whether the tumor is localized and can be completely resected. Whether the tumor has spread to lymph nodes or elsewhere. Exocrine pancreatic cancer is rarely curable and has an overall survival (OS) rate of less than 6% (Siegel et al '13). Complete surgical resection is associated with an actuarial 5-year survival rate of 18% to 24% (Yeo et al '97). Conventional treatment (systematic chemotherapy). Surgery, radiation therapy, and chemotherapy are treatment options that may extend survival and/or relieve symptoms, but seldom produce a cure. Less than 20% of patients are candidates for surgery because the cancer has usually spread beyond the pancreas by the time it is diagnosed. For those who do undergo surgery, adjuvant treatment with chemotherapy (and sometimes radiation) may lower the risk of recurrence. For advanced disease, chemotherapy (sometimes along with a targeted therapy drug) may lengthen survival. Clinical trials are testing several new targeted agents and immunotherapies. For all stages combined, the 5-year relative survival rate is 9%. Even for the small percentage of people diagnosed with local disease (10%), 5-year survival is only 37%. The majority of patients are diagnosed at a distant stage (53%), for which 5-year survival is 3% (ACS '20: 22). Complete resection can yield 5-year survival rates of 18% to 24%, but ultimate control remains poor because of the high incidence of both local and distant tumor recurrence. Thus, systemic therapy is also recommended for treatment (Yeo et al '97).

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<sup>2</sup>) 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). There is no evidence that radiation improves survival.

**Chemotherapy** with or without radiation therapy is administered before and after radical pancreatic resection. Multiple randomized trials have established that adjuvant gemcitabine monotherapy or adjuvant 5-FU monotherapy improve overall survival (OS) for 6 months after surgical resection compared with surgery alone (Oettle et al '07)(Neoptolemos et al '10). For patients with good performance status, adjuvant FOLFIRINOX (oxaliplatin, leucovorin, irinotecan, and 5-FU) chemotherapy or the combination of gemcitabine and capecitabine should be considered. However, for older patients or patients with marginal performance status, adjuvant gemcitabine or 5-FU monotherapy can be considered. In Asia, S-1 (tegafur, gimeracil, and oteracil potassium) is an appropriate alternative to gemcitabine-based therapies. Median disease-free survival (DFS) was 21.6 months with FOLFIRINOX (oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup>, irinotecan 150 mg/m<sup>2</sup>, and 5-FU 2,400 mg/m<sup>2</sup> over 46 hours every 2 weeks) and 12.8 months with gemcitabine. Median OS was 54.4 months with FOLFIRINOX and 35.0 months with gemcitabine (Conroy et al '18).

Epigastric or dorsal pain may be the major problem faced by the patient, and therefore proper analgesia is an overriding consideration. Nutrition is a second consideration. Often, patients complain of diarrhea, steatorrhea, weight loss, and malnutrition. This malnutrition may be due to anorexia from tumor or analgesics, or to mechanical blockage from intra-abdominal tumor, adhesions or ascites, or to the effects of digestive system failure such as the inability of bile salts to reach intestinal contents or exocrine failure of the pancreas. Treatment must be individualized. Many patients respond to small, frequent feedings, and careful use of antiemetics and digestive enzyme replacement. Enzyme replacement tablets such as **pancreatin** (Viokase) should be given vigorously – six to eight tablets per meal. The replacement of the lost lipase enzyme activity is especially important and patients should generally limit intake of saturated fatty acids and consider the use of medium-chain triglyceride preparations to provide necessary calories without increasing steatorrhea. Ideally, 1500 to 1600 calories per day are required by the patient, and these should be supplied chiefly by carbohydrates and protein. The use of antacids or cimetidine can enhance enzyme effect (Friedman '90: 244).

In 2020, an estimated 42,810 new cases of **liver cancer** (including intrahepatic bile duct cancers) will be diagnosed in the US and 30,160 people will die from the disease. Approximately three-fourths of liver cancers are hepatocellular carcinoma (HCC). Liver cancer incidence is 3 times higher in men than in women. Liver cancer incidence rates have more than tripled since 1980; from 2007 to 2016, the rate increased by about 2% per year. The death rate for liver cancer has doubled from about 3 (per 100,000) during the 1980s to 6.6 during 2013-2017, but may have begun to stabilize in recent years. **Symptoms**, which do not usually appear until the cancer is advanced, include abdominal pain and/or swelling, weight loss, weakness, loss of appetite, jaundice (a yellowish discoloration of the skin and eyes), and fever. Enlargement of the liver is the most common physical sign. Increasing age is the most important **risk factor** for most cancers. Other risk factors for liver (hepatocellular) cancer include the following: metastatic cancer, Chronic and/or persistent infection with hepatitis B and/or hepatitis C (El-Serag et al '12). Cirrhosis (Fattovich et al '04). Heavy alcohol use (Grewal et al '12). Ingestion of foods contaminated with aflatoxin B1 (Liu et al '10). Nonalcoholic steatohepatitis (NASH) (Diehl et al '17). Tobacco use (Lee et al '09). Certain inherited or rare disorders that include the following: Hereditary hemochromatosis. Alpha-1 antitrypsin deficiency (Loman et al '92). Glycogen storage disease. Porphyria cutanea tarda. Wilson disease (London et al '06). Liver and bile duct carcinogens: Aflatoxins, Alcoholic beverages, *Clonorchis sinensis*, 1,2-Dichloropropane, Estrogen-progestogen contraceptives, Hepatitis B virus, Hepatitis C virus, *Opisthorchis viverrini*,

Plutonium, Thorium-232 and its decay products, Tobacco smoking (in smokers and in smokers' children), Vinyl Chloride. Likely carcinogens: Androgenic (anabolic) steroids, Arsenic and inorganic arsenic compounds, Betel quid without tobacco, DDT, Dichloromethane ethylene chloride), Human immunodeficiency virus type 1, *Schistosoma japonicum*, Trichloroethylene, X-radiation, gamma-radiation. Gall bladder tumors can be caused by Thorium-232 and its decay products (IARC '20).

Approximately 70% of liver cancer cases in the US could potentially be prevented through the **elimination of exposure** to risk factors, the most important of which are excess body weight, type 2 diabetes, chronic infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), heavy alcohol consumption (3 or more drinks per day), and tobacco smoking. Risk is also increased by eating food contaminated with aflatoxin (poison from a fungus that can grow on improperly stored foods, such as nuts and grains). Accumulating evidence suggests that coffee drinking may reduce risk. A vaccine that protects against HBV infection has been available since 1982. There is no vaccine available to prevent HCV infection, although new combination antiviral therapies can often clear established infections and substantially reduce cancer risk. The Centers for Disease Control and Prevention (CDC) recommends one-time HCV testing for everyone born from 1945 to 1965 (i.e., baby boomers) because this group accounts for about three-fourths of HCV-infected individuals in the US; however, fewer than 1 in 8 baby boomers have been tested. In August 2019, the US Preventive Services Task Force released a draft statement recommending that all people ages 18 to 79 years be tested because screening has a substantial net benefit. Preventive measures for HBV and HCV infection include screening of donated blood, organs, and tissues; adherence to infection control practices during medical and dental procedures; needle-exchange programs for injection drug users; and safer sex.

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. 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). Liver cancer includes two major types: hepatocellular carcinoma (HCC) and intrahepatic bile duct cancer. HCC is relatively uncommon in the United States, although its incidence is rising, principally in relation to the spread of hepatitis C virus infection.[2] Worldwide, HCC is the sixth most prevalent cancer and the third leading cause of cancer-related deaths.[3]. Primary hepatomas 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).

For lesions that are smaller than 1 cm and are detected during screening in patients at high risk for HCC, further diagnostic evaluation is not required because most of these lesions will be cirrhotic lesions rather than HCC (Furuya et al '88). In patients with cirrhosis, liver disease, or

other risk factors for HCC, and with lesions greater than 1 cm, triple-phase, contrast-enhanced studies (dynamic computed tomography [CT] or magnetic resonance imaging [MRI]) can be used to establish a diagnosis of HCC (Brunello et al '13). Older reports have described 3-year survival rates of 13% to 21% without any specific treatment (Barbara et al '92). At present, only 10% to 23% of patients with HCC may be surgical candidates for curative-intent treatment (Sonnenday et al '07). The 5-year overall survival (OS) rate for patients with early HCC who are undergoing liver transplant is 44% to 78%; and for patients undergoing a liver resection, the OS rate is 27% to 70% (Dhir et al '12). Liver transplantation, surgical resection, and ablation offer high rates of complete responses and a potential for cure in patients with early HCC (Bruix et al '11). Untreated patients with advanced disease usually survive less than 6 months (Okuda et al '85). The survival rate of untreated patients in 25 randomized clinical trials ranged from 10% to 72% at 1 year and 8% to 50% at 2 years (Llovet et al '03). It is important to distinguish between the fibrolamellar variant of HCC and HCC itself because an increased proportion of patients with the fibrolamellar variant may be cured if the tumor can be resected. This variant is found more frequently in young women. It also generally exhibits a slower clinical course than the more common HCC (Mavros et al '12).

The Barcelona Clinic Liver Cancer (BCLC) staging classification is the most accepted staging system for HCC and is useful in the staging of early tumors. Evidence from an American cohort has shown that BCLC staging offers better prognostic stratification power than other staging systems (Marrera et al '05). The BCLC staging system attempts to overcome the limitations of previous staging systems by including variables related to the following: Tumor stage. Functional status of the liver. Physical status. Cancer-related symptoms (Llovet et al '99). Five stages (0 and A through D) are identified based on the variables mentioned above. The BCLC staging system links each HCC stage to appropriate treatment modalities as follows: Patients with early-stage HCC may benefit from curative therapies (i.e., liver transplantation, surgical resection, and radiofrequency ablation). Patients with intermediate-stage or advanced-stage disease may benefit from palliative treatments (i.e., transcatheter arterial chemoembolization and sorafenib). Patients with end-stage disease who have a very poor life expectancy are offered supportive care and palliation. The Okuda staging system has been extensively used in the past and includes variables related to tumor burden and liver function, such as bilirubin, albumin, and ascites. However, many significant prognostic tumor factors confirmed in both surgical and nonsurgical series (e.g., unifocal or multifocal, vascular invasion, portal venous thrombosis, or locoregional lymph node involvement) are not included (Poon et al '01). The TNM (tumor, node, metastasis) classification for staging, proposed by the AJCC, is not widely used for liver cancer, because liver function is not considered (Amin et al '17).

Early-stage liver cancer can sometimes be treated successfully with **liver transplantation** or surgery to remove part of the liver, although few patients have enough healthy liver for this option. Other treatment options include tumor ablation (destruction), embolization (blocking blood flow), or radiation therapy. Patients diagnosed at an advanced stage may be offered targeted therapies or immunotherapy. The 5-year relative **survival** rate is 18%, up from 3% four decades ago. Forty-four percent of patients are diagnosed with localized-stage disease, for which 5-year survival is still only 33% (ACS '20: 17). Best survivals are achieved when the HCC can be removed either by surgical resection or liver transplantation. Surgical resection is usually performed in patients with localized HCC and enough functional hepatic reserve. For patients with decompensated cirrhosis and a solitary lesion (<5 cm) or early multifocal disease ( $\leq 3$  lesions,  $\leq 3$  cm in diameter), the best option is liver transplantation (Bruix et al '11), but the limited availability of liver donors restricts the use of this approach. Among noncurative

treatments for HCC, transarterial chemoembolization and sorafenib have been shown to improve survival (Llovet et al '08). The role of radiation therapy for HCC has traditionally been limited by the low dose tolerance of the liver to radiation (Bujold et al '13).

After considering the location and number of tumors, and the hepatic function of the patient, only 5% to 10% of patients with liver cancer will prove to have localized disease amenable to **resection**. The principles of surgical resection involve obtaining a clear margin around the tumor, which may require any of the following: Segmental resection. Hormone-lymphatic lobectomy. Extended lobectomy. The 5-year overall survival (OS) rate after curative resection ranges between 27% and 70% and depends on tumor stage and underlying liver function (Llovet et al '99). In patients with limited multifocal disease, hepatic resection is controversial. According to the Milan criteria, patients with a single HCC lesion smaller than 5 cm, or 2 to 3 lesions smaller than 3 cm are eligible for **liver transplantation**. Expansion of the accepted transplantation criteria for HCC is not supported by consistent data. Liver transplantation is considered if resection is precluded because of multiple, small, tumor lesions ( $\leq 3$  lesions, each  $< 3$  cm), or if the liver function is impaired (Child-Pugh class B and class C). In patients who meet the criteria, transplantation is associated with a 5-year OS rate of approximately 70% (Hemming et al '01).

**Ablation** may be particularly useful for patients with early-stage HCC that is centrally located in the liver and cannot be surgically removed without excessive sacrifice of functional parenchyma. Ablation can be achieved in the following ways: Change in temperature (e.g., radiofrequency ablation [RFA], microwave, or cryoablation). Exposure to a chemical substance (e.g., percutaneous ethanol injection [PEI]). Direct damage of the cellular membrane (definitive electroporation). With ablation, a margin of normal liver around the tumor can be considered. Ablation is relatively contraindicated for lesions near bile ducts, the diaphragm, or other intra-abdominal organs that might be injured during the procedure. Furthermore, when tumors are located adjacent to major vessels, the blood flow in the vessels may keep thermal ablation techniques, such as RFA, from reaching optimal temperatures. This is known as the heat-sink effect, which may preclude complete tumor necrosis. RFA achieves best results in patients with tumors smaller than 3 cm. In this subpopulation of patients, 5-year OS rates may be as high as 59%, and the recurrence-free survival rates may not differ significantly from treatment with hepatic resection. Local control success progressively diminishes as the tumor size increases beyond 3 cm (Huang et al '11). The 5-year tumor-free survival rate was 57.9% for liver transplantation, 49.3% for resection, and 10.6% for radiofrequency ablation (Chan et al '13).

Transarterial Embolization (TAE) and Transcatheter Arterial Chemoembolization (TACE) are the most widely used primary treatment for hepatocellular carcinoma (HCC) not amenable to curative treatment by excision or ablation. Embolization agents, such as microspheres and particles, may also be administered along with concentrated doses of chemotherapeutic agents (generally doxorubicin or cisplatin) mixed with lipiodol or other emulsifying agents during chemoembolization, arterial chemoembolization (usually via percutaneous access), and TACE. In patients with cirrhosis, any interference with arterial blood supply may be associated with significant morbidity and is relatively contraindicated in the presence of portal hypertension, portal vein thrombosis, or clinical jaundice. Only one study has suggested that DEB-TACE may offer an advantage in overall survival (OS) (Dhanasekaran et al '10). Two oral multikinase inhibitors, **sorafenib** and lenvatinib, are U.S. Food and Drug Administration (FDA)-approved for first-line treatment of patients with advanced HCC with well-compensated liver function who are not amenable to local therapies. Median survival was significantly longer in the sorafenib

group (10.7 months vs. 7.9 months on placebo. Median OS was 13.6 months, which reached noninferiority, for patients who received lenvatinib and 12.3 months for patients who received sorafenib (Kudo et al '11). **Regorafenib** is approved for second-line treatment of patients with advanced HCC who have progressed on sorafenib. Median OS was 10.6 months for patients who received regorafenib and 7.8 months for patients who received a placebo (Bruix et al '17). The FDA has granted accelerated approval for nivolumab for patients with advanced HCC previously treated with sorafenib. The total overall objective response rate in the dose-expansion phase was 20% with three complete responses out of 262 patients (El-Khoueiry et al '17).

**Biliary obstruction** alters the metabolism of bile salts, with diminished access to the digestive system, jaundice, pruritis, and pain in either the right upper quadrant or the retroperitoneum. The best medical treatment is Stonebreaker (Chanca piedra) tincture to cure gallstones overnight, after which a tumor can be suspected. Surgical attempts to restore biliary continuity are usually associated with a diagnostic or therapeutic intervention. Transhepatic percutaneous drainage, which decompresses liver and biliary tree, is less traumatic. For patients with biliary tumors, the use of external irradiation or iridium wire implants can occasionally result in useful palliation of obstructive symptoms (with or without surgical intervention). Secondly, obstruction of a tubular viscus, such as the stomach, duodenum, or small intestine, by tumor invasion is painful and potentially life-threatening complication. Gastric or duodenal tube enterostomies, placed percutaneously or at the time of surgery, provide necessary drainage for otherwise intractable obstruction and also permit feeding of the patient. Patients who undergo resection of the pancreas as part of a curative process require a chronic metabolic intervention to deal not only with the loss of exocrine digestive functions of the pancreas but also with the surgically induced endocrinopathy (glucose intolerance). Patients with a complete pancreatectomy require careful insulin replacement (Friedman '90: 244, 245).

**Surgical resection** is the mainstay of therapy for gallbladder or extrahepatic biliary cancer. 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 pleuroperitonitis, 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/m<sup>2</sup> 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).

## 8. Colorectal and Bowel Cancer

In 2020, an estimated 104,610 cases of **colon cancer** and 43,340 cases of **rectal cancer** will be diagnosed in the US, and a total of 53,200 people will die from these cancers (ACS '20). Worldwide, colorectal cancer is the third most common form of cancer. In 2012, there were an estimated 1.36 million new cases of colorectal cancer and 694,000 deaths (Ferlay et al '13). Unfortunately, accurate statistics on colon and rectal cancer deaths separately are not available because many deaths from rectal cancer are misclassified as colon cancer on death certificates. The substantial misclassification is attributed at least in part to the widespread use of the term “colon cancer” to refer to both colon and rectal cancer in educational messaging. **Colorectal cancer** incidence has generally declined since the mid-1980s due to changes in risk factor exposures and the uptake of screening. However, this overall trend is driven by older adults (who have the highest rates) and masks increasing incidence in younger age groups. From 2007 to 2016, incidence rates declined by 3.6% annually among adults 55 years of age and older but increased by 2% annually among adults younger than age 55. The colorectal cancer death rate dropped by 54% from 1970 (29.2 per 100,000) to 2017 (13.5 per 100,000) because of changing patterns in risk factors, increased screening, and improvements in treatment. However, trends vary by age; from 2008 to 2017, the death rate declined by 2.6% per year among adults ages 55 and older but increased by 1% per year among adults younger than age 55 (ACS '20)..

**Symptoms** of colorectal cancer include rectal bleeding, blood in the stool, a change in bowel habits or stool shape (e.g., narrower than usual), the feeling that the bowel is not completely empty, abdominal cramping or pain, decreased appetite, and weight loss. In some cases, the cancer causes blood loss that leads to anemia (low number of red blood cells), resulting in symptoms such as weakness and fatigue. Increasing incidence of colorectal cancer in young individuals, who are often diagnosed with advanced disease, reinforces the need for timely evaluation of persistent symptoms in all patients. Early- stage colorectal cancer typically does not have symptoms, which is why screening is usually necessary to detect this cancer early. **Screening** can prevent colorectal cancer through the detection and removal of precancerous growths, as well as detect cancer at an early stage, when treatment is usually less extensive and more successful. Regular adherence to screening with either stool testing or structural exams (e.g., colonoscopy) results in a similar reduction in premature colorectal cancer death over a lifetime. New guidelines from the American Cancer Society recommend that men and women at average risk for colorectal cancer be regularly screened beginning at 45 years of age, with more individualized decision making from ages 76 to 85 years based on health status/life expectancy, patient preferences, and prior screening history.

Increasing age is the most important **risk factor** for most cancers. Other risk factors for colorectal cancer include the following: Family history of colorectal cancer in a first-degree relative (Johns et al '01). Personal history of colorectal adenomas, colorectal cancer, or ovarian cancer (Imperiale et al '14). Hereditary conditions, including familial adenomatous polyposis (FAP) and Lynch syndrome, hereditary non-polyposis colorectal cancer (HNPCC)(Mork et al '15). Personal history of long-standing chronic ulcerative colitis or Crohn colitis (Laukoetter et al '11). Excessive alcohol use (Fedirko et al '11). Cigarette smoking (Liang et al '09). Race/ethnicity: African American (Laiyemo et al '10). Obesity (Ma et al '13). 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). Regular long-term use of non-steroidal anti-inflammatory drugs, such as aspirin, reduces risk, but these drugs can have serious adverse health effects, such as stomach bleeding. Decision making about aspirin use should include a conversation with your health care provider (ACS '20: 14). Rat poison causes detectable colorectal bleeding and cancer in humans. Metronidazole (Flagyl ER) cures antibiotic resistant *Clostridium difficile*. More than half (55%) of colorectal cancers in the US are attributable to potentially **modifiable risk factors** according to a study by American Cancer Society researchers. Modifiable factors that increase risk include excess body weight, physical inactivity, long-term smoking, high consumption of red or processed meat, low calcium intake, heavy alcohol consumption, and very low intake of fruits and vegetables and whole-grain fiber. **Hereditary and medical factors** that increase risk include a personal or family history of colorectal cancer and/or adenomatous polyps, certain inherited genetic conditions (e.g., Lynch syndrome), a personal history of chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease), and type 2 diabetes (ACS '20: 14).

**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. Rat poison is suspected in colon and anal cancer, it is detected by the sensation of a slimy anus from rectal bleeding. Ulcerative colitis involving the total colon and persisting for 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 (Waston et al '98).

Colorectal cancer is more common in patients who have had occasional **adenomatous polyps** of villous adenomas. Adenomatous 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. **Histologic types** of colon cancer include the following: Adenocarcinoma (most colon cancers). Mucinous (colloid) adenocarcinoma. Signet ring adenocarcinoma. Scirrhus tumors. Neuroendocrine. Tumors with neuroendocrine differentiation typically have a poorer prognosis than pure adenocarcinoma variants (Saclarides et al '94). Approximately 15% to 25% of colorectal cancer patients will present with liver metastases at diagnosis, and another 25% to 50% will develop metachronous hepatic metastasis after resection of the primary tumor.[67-69] Hepatic metastasis may be considered to be resectable based on the following factors: Limited number of lesions. Intrahepatic locations of lesions. Lack of major vascular involvement. Absent or limited extrahepatic disease. Sufficient functional hepatic reserve. For patients with hepatic metastasis that is considered to be resectable, a negative margin resection has been associated with 5-year survival rates of 25% to 40%. [55,70-82]

The World Health Organization classification of the colon and rectum includes; Epithelial tumors: **Adenoma** – Tubular. Villous. Tubulovillous. Serrated. **Carcinoma** – Adenocarcinoma. Mucinous adenocarcinoma. Signet-ring cell carcinoma. Small cell carcinoma. Adenosquamous carcinoma. Medullary carcinoma. Undifferentiated carcinoma. **Carcinoid** (well-differentiated neuroendocrine neoplasm). Enterochromaffin-cell, serotonin-producing neoplasm. L-cell, glucagon-like peptide and pancreatic polypeptide/peptide YY-producing tumor. Others. **Intraepithelial neoplasia** (dysplasia) associated with chronic inflammatory diseases. Low-grade glandular intraepithelial neoplasia. High-grade glandular intraepithelial neoplasia. **Nonepithelial Tumors** – Lipoma. Leiomyoma. Gastrointestinal stromal tumor. Leiomyosarcoma. Angiosarcoma. Kaposi sarcoma. Melanoma., Others. **Malignant lymphomas** - Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type. Mantle cell lymphoma. Diffuse large B-cell lymphoma. Burkitt lymphoma. Burkitt-like/atypical Burkitt lymphoma (Siddiqui et al '06).

**Laboratory evaluation** should include a complete blood count, a microcytic hypochromic anemia suggests chronic blood loss. Liver function test may reflect the presence of liver metastases. A complete urinalysis helps exclude local extension to the bladder. Abdominal CT scan can help. Patients with elevated CEA (2.5 ng/ml) have a higher likelihood of metastatic disease (Macdonald '90: 233, 234). In the tumor (T) staging of rectal carcinoma, several studies indicate that the accuracy of endorectal ultrasound ranges from 80% to 95% compared with 65% to 75% for CT and 75% to 85% for MRI. The accuracy in determining metastatic nodal involvement by endorectal ultrasound is approximately 70% to 75% compared with 55% to 65% for CT and 60% to 70% for MRI. In a meta-analysis of 84 studies, none of the three imaging modalities, including endorectal ultrasound, CT, and MRI, were found to be significantly superior to the others in staging nodal (N) status (Zammit et al '05) Endorectal ultrasound using a rigid probe may be similarly accurate in T and N staging when compared with endorectal ultrasound using a flexible scope; however, a technically difficult endorectal ultrasound may give an inconclusive or inaccurate result for both T stage and N stage. In this case, further assessment by MRI or flexible endorectal ultrasound may be considered.[4,9] In patients with rectal cancer, the circumferential resection margin is an important pathological staging parameter. Measured in millimeters, it is defined as the retroperitoneal or peritoneal adventitial soft-tissue margin closest to the deepest penetration of tumor (Compton et al '04).

### Colon Cancer Staging

Stage	T = primary tumor; N = regional lymph nodes; M = distant metastasis	Description
0	Tis, N0, M0	Tis = Carcinoma <i>in situ</i> , intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae). N0 = No regional lymph node metastasis. M0 = No distant metastasis.
I	T1, T2, N0, M0	T1 = Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria). T2 = Tumor invades the muscularis propria. N0 = No regional lymph node metastasis. M0 =

		No distant metastasis by imaging, etc.
IIA	T3, N0, M0	T3 = Tumor invades through the muscularis propria into pericorectal tissues. N0 = No regional lymph node metastasis. M0 = No distant metastasis by imaging, etc
IIB	T4a, N0, M0	T4a = Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum). N0 = No regional lymph node metastasis. M0 = No distant metastasis.
IIC	T4b, N0, M0	T4b = Tumor directly invades or adheres to adjacent organs or structures. N0 = No regional lymph node metastasis. M0 = No distant metastasis.
IIIA	T1, N2a, M0 T1-2, N1/N1c, M0	T1 = Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria). N2a = Four to six regional lymph nodes are positive. M0 = No distant metastasis.  T2 = Tumor invades the muscularis propria. N1 = One to three regional lymph nodes are positive (tumor in lymph nodes measuring $\geq 0.2$ mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative. -N1c = No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues. M0 = No distant metastasis
IIIB	T1-T2, N2b, M0  T2-T3, N2a, M0  T3-T4a, N1/N1c, M0	T1 = Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria). T2 = Tumor invades the muscularis propria. N2b = Seven or more regional lymph nodes are positive. M0 = No distant metastasis.  T2 = Tumor invades the muscularis propria. T3 = Tumor invades through the muscularis propria into pericorectal tissues. N2a = Four to six regional lymph nodes are positive. M0 = No distant metastasis.  T3 = Tumor invades through the muscularis propria into pericorectal tissues.. T4 = Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure. -T4a = Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum). N1 = One to three regional lymph nodes are positive (tumor in lymph nodes measuring $\geq 0.2$ mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative. -N1c = No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues. M0 = No distant metastasis.



		perirectal/mesorectal tissues. N2 = Four or more regional nodes are positive. –N2a = Four to six regional lymph nodes are positive. – N2b = Seven or more regional lymph nodes are positive. M1a = Metastasis to one site or organ is identified without peritoneal metastasis.
IVB	Any T, Any N, M1b	Any T = See T descriptions above in Any T, Any N, M1a TNM stage group. Any N = See N descriptions above in Any T, Any N1, M1a TNM stage group. M1b = Metastasis to two or more sites or organs is identified without peritoneal metastasis.
IVC	Any T, Any N, M1c	Any T = See T descriptions above in Any T, Any N, M1a TNM stage group. Any N = See N descriptions above in Any T, Any N1, M1a TNM stage group. M1c = Metastasis to the peritoneal surface is identified alone or with other site or organ metastases.

Source: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp 251–74

The **prognosis** of patients with colon cancer is clearly related to the following: The degree of penetration of the tumor through the bowel wall. The presence or absence of nodal involvement. The presence or absence of distant metastases. These three characteristics form the basis for all staging systems developed for this disease. Other prognostic factors include the following: Bowel obstruction and bowel perforation are indicators of poor prognosis (Steinberg et al '86). Elevated pretreatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance (Filella et al '92). Many other prognostic markers have been evaluated retrospectively for patients with colon cancer, though most, including allelic loss of chromosome 18q or thymidylate synthase expression, have not been prospectively validated (McLeod et al '99). Microsatellite instability, also associated with HNPCC, has been associated with improved survival independent of tumor stage in a population-based series of 607 patients younger than 50 years with colorectal cancer (Gryfe et al '00). Patients with HNPCC reportedly have better prognoses in stage-stratified survival analysis than patients with sporadic colorectal cancer, but the retrospective nature of the studies and possibility of selection factors make this observation difficult to interpret (Watson et al '98). Treatment decisions depend on factors such as physician and patient preferences and the stage of the disease, rather than the age of the patient (Popescu et al '99). Racial differences in overall survival (OS) after adjuvant therapy have been observed, without differences in disease-free survival, suggesting that comorbid conditions play a role in survival outcome in different patient populations (Dignam et al '99). Metronidazole is needed to treat gastroenteritis.

**Surgery** is the most common treatment for colorectal cancer that has not spread. Standard treatment for patients with colon cancer has been open surgical resection of the primary and regional lymph nodes for localized disease. A permanent colostomy (creation of an abdominal opening for elimination of body waste) is rarely necessary for colon cancer and not usually required for rectal cancer. For most patients whose cancer has penetrated the bowel wall deeply or spread to lymph nodes, chemotherapy is given after surgery for colon cancer, and before and/or after surgery, alone or in combination with radiation, for rectal cancer. For colorectal cancer that has spread to other parts of the body (metastatic colorectal cancer), treatments typically include chemotherapy and/or targeted therapy. Immunotherapy is a newer option for some advanced cancers. The 5-year relative survival rate for colorectal cancer is 64%. Only 39% of patients are diagnosed with localized disease, for which 5-year survival is 90%

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. Systemic **chemotherapy** of colorectal cancer has been disappointing. Before 2000, 5-FU was the only useful cytotoxic chemotherapy in the adjuvant setting for patients with stage III colon cancer. The 1 g/m<sup>2</sup>/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, streptozosin 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 compared to surgery alone (relapse rates of 55% versus 30%) (Macdonald '00: 237, 238).

Since 2000, capecitabine has been established as an equivalent alternative to 5-FU and leucovorin (5-FU/LV). The addition of oxaliplatin to 5-FU/LV has been shown to improve OS compared with 5-FU/LV alone. AIO or German AIO is Folic acid, 5-FU, and irinotecan. CAPOX is Capecitabine and oxaliplatin. Douillard is Folic acid, 5-FU, and irinotecan. FOLFIRI LV, 5-FU, and irinotecan. FOLFOX-4 Oxaliplatin, Leucovorin (LV), and 5-FU. FOLFOX-6 Oxaliplatin, LV, and 5-FU. FOLFIRI Irinotecan, oxaliplatin, LV, 5-FU. FUFOX 5-FU, LV, and oxaliplatin. FUOX 5-FU plus oxaliplatin. IFL (or Saltz) Irinotecan, 5-FU, and LV. XELOX Capecitabine plus oxaliplatin (Gill et al '04). Adjuvant radiation therapy has no current standard role in the management of patients with colon cancer following curative resection, although it may have a role for patients with residual disease (Martenson et al '04). Most physicians have adopted FOLFOX as the standard of care. The combination of capecitabine and oxaliplatin (CAPOX) is an accepted standard therapy in patients with metastatic colorectal cancer (André et al '04).

Approximately 50% of colon cancer patients will be diagnosed with **hepatic metastases**. For patients with hepatic metastasis that is considered to be resectable, a negative margin resection resulted in 5-year survival rates of 25% to 40% (Taylor et al '97). Patients with metastatic disease isolated to the liver, which historically would be considered unresectable, can occasionally be made resectable after the administration of chemotherapy. These patients have 5-year survival rates similar to patients who initially had resectable disease (Leonard et al '05). Before the availability of cetuximab, panitumumab, bevacizumab, and aflibercept as second-line therapy, second-line chemotherapy with **irinotecan** in patients treated with 5-FU/LV as first-line therapy demonstrated improved OS when compared with either infusional 5-FU or supportive care (Cunningham et al '98). Median OS was 11.2 months for patients who received

bevacizumab/chemotherapy and 9.8 months for patients who received chemotherapy without bevacizumab (Arnold et al '12).

The addition of **cetuximab** to multiagent chemotherapy improves survival in patients with colon cancers that lack a KRAS mutation (i.e., KRAS wild type). Importantly, patients with mutant KRAS tumors may experience worse outcome when cetuximab is added to multiagent chemotherapy regimens containing bevacizumab. Patients who received **aflibercept**/FOLFIRI had significantly improved OS rates, with median survival times of 13.50 months compared with patients who received placebo/FOLFIRI, with median survival times of 12.06 months. Median PFS rates of 6.90 months compared with patients who received placebo/FOLFIRI, with median PFS rates of 4.67 months. On the basis of these results, the use of aflibercept/FOLFIRI is an acceptable second-line regimen for patients previously treated with FOLFOX-based chemotherapy (Van Cutsem et al '12). Patients assigned to FOLFIRI/**ramucirumab** had a significant improvement in median OS (13.3 months vs. 11.7 months). FOLFIRI/ramucirumab is an acceptable second-line regimen for patients previously treated with FOLFOX/bevacizumab. Panitumumab is a fully humanized antibody against the EGFR. The FDA approved panitumumab for use in patients with metastatic colorectal cancer refractory to chemotherapy (Van Cutsem et al '07).

It is unknown whether patients with KRAS wild-type cancer should receive an anti-EGFR antibody with chemotherapy or an anti-VEGF antibody with chemotherapy. **Regorafenib** is an inhibitor of multiple tyrosine kinase pathways including VEGF. Patients treated with regorafenib had a statistically significant improvement in OS (6.4 months in the regorafenib group vs. 5.0 months in the placebo group). In September 2012, the FDA granted approval of the use of regorafenib in patients who had progressed on previous therapy (Grothey et al '13). The median OS for patients with metastatic colorectal cancer who received **TAS-102** was 7.1 months compared with 5.3 months for those who received a placebo (HR, 0.68;  $P < .0001$ ). The median PFS time in the TAS-102 arm was 2 months versus 1.7 months with a placebo (Mayer et al '15). In May 2017, the FDA granted approval for using **pembrolizumab**, a programmed cell death protein 1 (PD-1) antibody, in patients with microsatellite unstable tumors. Objective response rate was 39.6%. Responses lasted 6 months or longer for 78% percent of those who responded to pembrolizumab (NCI '20).

It is difficult to separate epidemiological considerations of **rectal cancer** from those of colon cancer because epidemiological studies often consider colon and rectal cancer (i.e., colorectal cancer) together. Estimated new cases and deaths from rectal and colon cancer in the United States in 2020. New cases of rectal cancer: 43,340. New cases of colon cancer: 104,610. Deaths: 53,200 (rectal and colon cancers combined) (ACS '20). Colorectal cancer affects men and women almost equally. Among all racial groups in the United States, African Americans have the highest sporadic colorectal cancer incidence and mortality rates (Albana et al '07). The rectum is located within the pelvis, extending from the transitional mucosa of the anal dentate line to the sigmoid colon at the peritoneal reflection; by rigid sigmoidoscopy, the rectum measures between 10 cm and 15 cm from the anal verge (Wolpin et al '07). The location of a rectal tumor is usually indicated by the distance between the anal verge, dentate line, or anorectal ring and the lower edge of the tumor, with measurements differing depending on the use of a rigid or flexible endoscope or digital examination (Libutte et al '11). The distance of the tumor from the anal sphincter musculature has implications for the ability to perform sphincter-sparing surgery. The bony constraints of the pelvis limit surgical access to the rectum, which results in a

lesser likelihood of attaining widely negative margins and a higher risk of local recurrence (Wolpin et al '07).

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 perianal 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. Rat poison is suspected in colon and anal cancer, it is detected by the sensation of a slimy anus from rectal bleeding. 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 epithelia. The keratinizing tumors have a somewhat better prognosis. Anal carcinoma spreads with initial infiltration of the anal canal and the anal sphincter, subsequently, the 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). The AJCC has designated staging by TNM (tumor, node, metastasis) classification to define rectal cancer (Jessup et al '17).

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 (Macdonald '90: 239). Types of surgical resection include the following: Polypectomy for select T1 cancers. Transanal local excision and transanal endoscopic microsurgery for select clinically staged T1/T2 N0 rectal cancers. Total mesorectal excision with autonomic nerve preservation techniques via low-anterior resection. Total mesorectal excision via abdominoperineal resection for patients who are not candidates for sphincter-preservation, leaving patients with a permanent end-colostomy (Balch et al '06). Polypectomy alone may be used in certain instances (T1) in which polyps with invasive cancer can be completely resected with clear margins and have favorable histologic features (Seitz et al '04). Local excision of clinical T1 tumors is an acceptable surgical technique for appropriately selected patients. For all other tumors, a mesorectal excision is the treatment of choice. Very select patients with T2 tumors may be candidates for local excision. Local failure rates in the range of 4% to 8% after rectal resection with appropriate mesorectal excision (total mesorectal excision for low/middle rectal tumors and mesorectal excision at least 5 cm below the tumor for high rectal tumors) have been reported (Heald et al '97). For patients with advanced cancers of the mid- to upper rectum, low-anterior resection followed by the creation of a colorectal anastomosis may be the treatment of choice. For locally advanced rectal cancers for which radical resection is indicated, however, total mesorectal excision with autonomic nerve preservation techniques via low-anterior resection is preferable to abdominoperineal resection (Balch et al '06). Patients who undergo aggressive surgical procedures for rectal cancer can have chronic symptoms, particularly if there is impairment of the anal sphincter (Wong et al '07).

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/m<sup>2</sup> per day, as continuous infusion on days 1 to 4, repeat on days 28 to 31; Mitomycin-C, 15 mg/m<sup>2</sup> 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% complete response. Treatment may be associated with anal mucositis, oral mucositis and myelosuppression. However, anal-stricture or persistent anal ulcers requiring surgical intervention have been seen with radiation alone in high doses (Macdonald '90: 240). Preoperative chemotherapy has become the standard of care for patients with clinically staged T3–T4 or node-positive disease (stages II/III) (Sauer et al '04). Complete pathologic response rates of 10% to 25% may be achieved with preoperative chemoradiation therapy (Bosset et al '00). However, preoperative radiation therapy is associated with increased complications compared with surgery alone; some patients with cancers at a lower risk of local recurrence might be adequately treated with surgery and adjuvant chemotherapy. Patients treated with radiation therapy appear to have increased chronic bowel dysfunction, anorectal sphincter dysfunction (if the sphincter was surgically preserved), and sexual dysfunction than do patients who undergo surgical resection alone (Wolmark et al '00).

There are estimated to be 11,110 new cases and 1,700 deaths from small intestine cancer in the United States in 2020 (ACS '20). Adenocarcinomas (majority of cases), sarcomas, lymphomas (usually non-Hodgkin), carcinoid tumors (20%) and stromal tumors of the small bowel occur. Cancer of the small intestine account for only 4% of all gastrointestinal malignancies (Chow et al '96) (Armin et al'17). Gastrointestinal (GI) **sarcomas** are generally leiomyosarcomas that present with pain and bleeding (Macdonald '90: 232). 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<sup>2</sup> has a response rate of 15% to 35%. DTIC 1 g. m<sup>2</sup> every 3 weeks has a single agent response rate of 17%. Response rates improved in combination doxorubicin, 70 mg/m<sup>2</sup> and DTIC 1 g. m<sup>2</sup> every 3 weeks but so nausea and vomiting increased. Trials of ifostamide in previously untreated patients yield response rates of 20% to 40%. A study of a combination doxorubicin, ifostamide, and DTIC 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 (Macdonald '90: 231).

The American Joint Committee on Cancer (AJCC) has designated staging by TNM (tumor, node, metastasis) classification to define small intestine cancer. TX primary tumor cannot be assessed. T0 No evidence of primary tumor. Tis High-grade dysplasia/carcinoma in situ. T1 tumor invades the lamina propria or submucosa. -T1a tumor invades the lamina propria.-T1b tumor invades the submucosa. T2 tumor invades the muscularis propria. T3 tumor invades through the muscularis propria into the subserosa, or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration. T4 tumor perforates the visceral peritoneum or directly invades other organs or structures (e.g. other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct). M0 no distant metastasis. M1 distant metastasis present. Stage 0 Tis, N0, M0. Stage I T1-2, N0, M0. IIA T3, N0, M0. Stage IIA T3, N0, M0. IIB T4, N0-, M0. Stage IIB T4, N0, M0. Stage IIIA Any T, N1, M0. Stage IIIB Any T, N2, M0. Stage IV Any T, Any N, M1 (Armin et al '17). No standard effective chemotherapy exists for patients with recurrent metastatic adenocarcinoma or leiomyosarcoma of the small intestine. These patients should be

considered candidates for clinical trials evaluating the use of new anticancer drugs or biologicals in phase I and phase II trials (Rose et al '96)(North et al '00). **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: 232).

Chemotherapy for rectal cancer is the same as for colon cancer and should probably be incorporated into small bowel chemotherapy, for requested clinical studies: AIO or German AIO is Folic acid, 5-FU, and irinotecan. CAPOX is Capecitabine and oxaliplatin. Douillard is Folic acid, 5-FU, and irinotecan. FOLFIRI LV, 5-FU, and irinotecan. FOLFOX-4 Oxaliplatin, Leucovorin (LV), and 5-FU. FOLFOX-6 Oxaliplatin, LV, and 5-FU. FOLFOXIRI Irinotecan, oxaliplatin, LV, 5-FU. FUFOX 5-FU, LV, and oxaliplatin. FUOX 5-FU plus oxaliplatin. IFL (or Saltz) Irinotecan, 5-FU, and LV. XELOX Capecitabine plus oxaliplatin (Gill et al '04). Adjuvant radiation therapy has no current standard role in the management of patients with colon cancer following curative resection, although it may have a role for patients with residual disease (Martenson et al '04). Most physicians have adopted FOLFOX as the standard of care. The combination of capecitabine and oxaliplatin (CAPOX) is an accepted standard therapy in patients with metastatic colorectal cancer (André et al '04). Two randomized studies demonstrated that capecitabine was associated with equivalent efficacy when compared with the Mayo Clinic regimen of 5-FU/LV (Van Cutsem et al '01). Metastatic patients who received FOLFIRI/bevacizumab had a significantly better OS (28.0 months vs. 19.2 months). IFL/**bevacizumab** experienced a significantly better PFS (10.6 months with IFL/bevacizumab compared with 6.2 months with IFL/placebo). Patients randomly assigned to FOLFOX/bevacizumab experienced a statistically significant improvement in PFS compared with patients assigned to FOLFOX alone (7.43 months vs. 4.7 months) (Loupakis et al '14). Patients who received **aflibercept** plus FOLFIRI had significantly improved OS rates of 13.50 months compared with 12.6 months patients who received placebo plus FOLFIRI. The use of FOLFIRI plus aflibercept is an acceptable second-line regimen for patients previously treated with FOLFOX-based chemotherapy (Van Cutsem et al '12). Patients assigned to FOLFIRI plus **ramucirumab** had a significant improvement in median OS (13.3 months vs. 11.7 months and PFS (5.7 months vs. 4.5 months). FOLFIRI plus ramucirumab is an acceptable second-line regimen for patients previously treated with FOLFOX-bevacizumab (Tabernero et al '15).

In September 2012, the FDA granted approval for the use of **regorafenib** in patients who had progressed on previous therapy. Patients treated with regorafenib had a statistically significant improvement in OS (6.4 months in the regorafenib group vs. 5.0 months in the placebo group (Grothey et al '13). The median OS for patients with metastatic colorectal cancer who received **TAS-102** was 7.1 months compared with 5.3 months for those who received a placebo. The median PFS time in the TAS-102 arm was 2 months versus 1.7 months with a placebo. TAS-102 was approved by the FDA for the treatment of metastatic colorectal cancer patients (Mayer et al '15). In May 2017, the FDA granted approval for using **pembrolizumab**, a programmed cell death protein 1 (PD-1) antibody, in patients with microsatellite unstable tumors. Objective response rate was 39.6%. Responses lasted 6 months or longer for 78% percent of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses. Second-line chemotherapy with irinotecan in patients treated with 5-FU/LV as first-line therapy

demonstrated improved OS when compared with either infusional 5-FU or supportive care (Cunningham et al '04). A trial of hepatic arterial **floxuridine and dexamethasone** plus systemic 5-FU/LV compared with systemic 5-FU/LV alone showed improved 2-year PFS (57% vs. 42%) and OS (86% vs. 72%). Median survival in the combined therapy arm was 72.2 months versus 59.3 months in the monotherapy arm. Median four year survival was the same. Hepatic intra-arterial chemotherapy with floxuridine for liver metastases has produced higher overall response rates but no consistent improvement in survival when compared with systemic chemotherapy (McGinn et al '97).

## 9. Breast Cancer

**Breast cancer** has been a predominant type of cancer for centuries. Currently the risk or probability of an American or European female having a diagnosis of breast cancer is close to 1 in 10. In the US in 2020, there will be an estimated 276,480 new cases of invasive breast cancer diagnosed in women; 2,620 cases diagnosed in men; and an additional 48,530 cases of ductal carcinoma in situ (DCIS) diagnosed in women. An estimated 42,690 breast cancer deaths (42,170 women, 520 men) will occur in 2020. From 2007 to 2016, invasive female breast cancer incidence rates increased slightly, by 0.3% per year. The female breast cancer death rate peaked at 33.2 (per 100,000) in 1989, then declined by 40% to 19.8 in 2017. This progress reflects earlier detection (through screening, as well as increased awareness of symptoms) and improved treatment, and translates to an estimated 375,900 fewer breast cancer deaths than would have been expected if the death rate had remained at its peak. During 2013 to 2017, the death rate decreased by 1.3% per year. Breast cancer is the most common non-cutaneous cancer in U.S. women, with an estimated 48,530 cases of female breast ductal carcinoma *in situ* and 276,480 cases of invasive disease in 2020. Fewer than one of six women diagnosed with breast cancer die of the disease 42,170 in 2020. By comparison, it is estimated that about 63,220 American women will die of lung cancer in 2020. Anti-estrogen drugs, specifically **tamoxifen**, surgical treatment, adjuvant chemotherapy, screening and early diagnosis have increased the number of long-term remission and cures (ACS '20: 11)

Age is the most important **risk factor** for most cancers. Other risk factors for breast cancer include the following: Alcoholic beverages, Diethylstilbestrol, Estrogen-progestogen contraceptives, estrogen-progestogen menopausal therapy, X-radiation and gamma-radiation probably cause breast cancer. Dieldrin, Digoxin, Estrogen plus progestin menopausal hormonal replacement therapy (HRT), Ethylene oxide, Night shift work, Polychlorinated biphenyls, Tobacco smoking are suspected of causing breast cancer (IARC '20). Family health history (Colditz et al '12). Major inheritance susceptibility (Cybulski et al '11). Germline mutation of the BRCA1 and BRCA2 genes and other breast cancer susceptibility genes (Goodwin et al '12). Breast tissue density (mammographic). Menstrual history (early menarche/late menopause). Nulliparity. Older age at first birth. Hormone therapy history (Collaborative Group et al '12). Obesity (postmenopausal) (Wolin et al '10). Personal history of breast cancer. Personal history of benign breast disease (BBD) (proliferative forms of BBD) (Goldacre et al '10). Radiation exposure to breast/chest (Travis et al '03). Of all women with breast cancer, 5% to 10% may have a germline mutation of the genes BRCA1 and BRCA2 (Blackwood et al '98). The estimated lifetime risk of developing breast cancer for women with BRCA1 and BRCA2 mutations is 40% to 85%. Carriers with a history of breast cancer have an increased risk of contralateral disease that may be as high as 5% per year. Male BRCA2 mutation carriers also have an increased risk of breast cancers (Ford et al '94).

**Potentially modifiable factors** associated with increased risk include weight gain after the age of 18 and/or being overweight or obese (for postmenopausal breast cancer); menopausal hormone therapy (combined estrogen and progestin); mold (treated with hydrocortisone crème); alcohol consumption; and physical inactivity. Breastfeeding for at least one year decreases risk (ACS '20: 11). Excess, **unburnt calories** can also provide the energy for more cell proliferation. Excess calorie intake and increased size and/or weight are associated with increased levels of the circulation of a hormone called insulin like growth factor 1 or IGF-1. This is one of the key general regulators of cell behavior and not only promotes cell proliferation but inhibits cell death. **Non-modifiable factors** that increase risk include a personal or family history of breast or ovarian cancer; inherited genetic variations in breast cancer susceptibility genes (e.g., *BRCA1* or *BRCA2*); certain benign breast conditions, such as atypical hyperplasia; a history of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS); high breast tissue density (the amount of glandular tissue relative to fatty tissue measured on a mammogram); and high-dose radiation to the chest at a young age (e.g., for treatment of lymphoma). Reproductive factors that increase risk include a long menstrual history (menstrual periods that start early and/or end late in life); not having children or having children after age 30; high natural levels of sex hormones; and recent use of hormonal contraceptives.

Human populations carry at least two genes that strongly predispose towards breast or breast plus ovarian cancer when inherited in a mutant form. These are referred to as **BRCA-1 and BRCA-2**. Around 5 to 10 percent of all breast and ovarian cancers show familial clustering and are likely to involve genes. Somewhat less than half of these involve BRCA-1 or BRCA-2. But those women that have a mutant variety of the BRCA-1 or BRCA-2 gene, around 60 percent will develop breast cancer and 15 percent, ovarian cancer. Pregnancy increases the risk of breast cancer for women who carry the BRCA-1 or BRCA-2 genes, although in most women pregnancy reduces risk. 1 in 800 carry these two genes in a mutant form, and this figure is as high as 1 in 50 for Ashkenazi Jews. Over 140 different mutant forms of the BRCA-1 and BRCA-2 genes have already been identified. Other genes predisposing to breast cancer certainly exist, including [53 in families with the Li-Fraumeni syndrome and PTEN in Cowden syndrome. Overall, the chance inheritance of a mutant gene probably accounts for some 5 to 10 percent of all breast cancers, there is a 25% concordance rate of breast cancer in twins. Breast cancer risk generally increases with age over several decades between 20 and 70 years, but the rate of increase slows down after menopause. The average age of a woman with breast cancer is just under 50 years, or around the time of menopause. Studies on cohorts of women who developed breast cancer as a consequence of radiation exposure suggest that the gap or latency between an initial DNA-damaging event and subsequent malignancy average around 20 years, with an increased risk persisting for 50 years in individuals exposed when very young (Greaves '00: 152-156, 155, 157).

Malignant breast cancer is preceded by the presence of **atypical ductal hyperplasia** or one or more small tumors which are, in themselves benign. These may (or may not) progress to localized 'carcinomas in situ' which in turn may evolve into invasive breast cancer (or more often do not) (Greaves '00: 157). The majority of patients with breast cancer present with disease that is confined to the breast, less than 10% of patients present with overt distant metastases. Mammography is required to look for evidence of tumor multicentricity or bilateral involvement. **Axillary lymph node status** is the most important predictor of disease recurrence and survival. Seventy percent of patients with negative nodes survive 10 years. About 40% of patients with one to three positive nodes survive 10 years, whereas only 15% of those with four or more nodes survive. About 60% to 70% of primary breast cancers contain measurable ER and 40% to 50%

have PR. Post-menopausal women more frequently have receptor-positive tumors than premenopausal women (Osborne '90: 201-205). Infiltrating or invasive ductal cancer is the most common breast cancer histologic type and comprises 70% to 80% of all cases (ACS '20).

Early breast cancer usually has no **symptoms** and is most often diagnosed through mammography screening. When symptoms occur, the most common is a painless lump or mass in the breast. Other symptoms may include persistent changes to the breast, such as thickening, swelling, or redness, and nipple abnormalities such as spontaneous discharge (especially if bloody), scaliness, or retraction. Mammography is a low-dose x-ray procedure used to detect breast cancer at an early stage. Early diagnosis reduces the risk of dying from breast cancer and increases treatment options. However, like any screening tool, mammography is not perfect. It can miss cancer (false negative) or appear abnormal in the absence of cancer (false positive); about 12% of women who are screened have an abnormal mammogram, but only 5% of women with an abnormal mammogram have cancer. False-positives are most likely during a woman's first mammogram. Other potential harms include detection of cancers and in situ lesions (e.g., DCIS) that would never have progressed or caused harm (i.e., over-diagnoses), and cumulative radiation exposure, which increases breast cancer risk. For women at average risk of breast cancer, the American Cancer Society recommends that those 40 to 44 years of age have the option to begin annual mammography; those 45 to 54 undergo annual mammography; and those 55 years of age and older transition to biennial mammography or continue annual mammography. Women should continue mammography as long as overall health is good and life expectancy is 10 or more years. For some women at high risk of breast cancer, annual breast magnetic resonance imaging (MRI) is recommended to accompany mammography, typically starting at age 30 (ACS '20: 11).

Patients who have breast cancer will undergo **bilateral mammography** at the time of diagnosis to rule out synchronous disease. To detect either recurrence in the ipsilateral breast in patients treated with breast-conserving surgery or a second primary cancer in the contralateral breast, patients will continue to have regular breast physical examinations and mammograms. Because only 25% of MRI-positive findings represent malignancy, pathologic confirmation before treatment is recommended (Solin et al '08). On the basis of ER, PR, and HER2/neu results, breast cancer is classified as one of the following types: Hormone receptor positive. HER2/neu positive. Triple negative (ER, PR, and HER2/neu negative). ER, PR, and HER2 status are important in determining prognosis and in predicting response to endocrine and HER2-directed therapy (Hammond et al '10). The first gene profile test to be approved by the U.S. Food and Drug Administration was the MammaPrint gene signature. The 70-gene signature classifies tumors into high- and low-risk prognostic categories (Wittner et al '08). The standards used to define biomarker status are described as follows: Estrogen receptor (ER) expression: ER expression is measured primarily by immunohistochemistry (IHC). Any staining of 1% of cells or more is considered positive for ER (Barnes et al '96). Progesterone receptor (PR) expression: PR expression is measured primarily by IHC. Any staining of 1% of cells or more is considered positive for PR. HER2 expression: HER2 is measured primarily by either IHC to assess expression of the HER2 protein or by in situ hybridization (ISH) to assess gene copy number. The American Society of Clinical Oncology/College of American Pathologists consensus panel has published guidelines for cases when either IHC or ISH testing is equivocal (Wolff et al '18). The AJCC has designated staging by TNM (tumor, node, metastasis) classification to define breast cancer. The grade of the tumor is determined by its morphologic features, such as tubule formation, nuclear pleomorphism, and mitotic count. Definition of regional lymph nodes, distant

metastasis and histologic grade has progressed significantly since 1990, but the staging remains the same (Amin et al '10).

### Staging System for Breast Cancer

Stage	Primary Tumor (T)	Lymph Nodes (N)	Distant Metastases (M)	TNM Classification
0	Carcinoma <i>in situ</i> ; Paget's disease of nipple without palpable mass (tis) greatest dimension <2 cm T	Homolateral axillary lymph nodes negative (N0)	None	Tis, N0, M0
I	Greatest dimension <2 cm (T1)	Homolateral axillary lymph nodes negative (N0)	None	T1, N0, M0
II	Greatest dimension >2 cm and <5 cm (T2)	Axillary nodes positive but not fixed (N1)	None	T0 or T1, N2, M0 T2, N2, M0 T3, N0-2, M0
III	Greatest dimension >5 cm (T3)	Axillary nodes positive and fixed to one another, skin, or chest wall (N2)	None	T0 or T1, N2, M0 T2, N2, M0 T3, N0-2, M0
IV	Any size with (T4); inflammatory carcinoma, skin nodules, skin ulceration, fixation to chest wall or skin, edema	Supra-clavicular or infra-clavicular nodes; arm edema (N3)	Present (M1)	T4, any N, any M; Any T, N3, any M; Any T, any N, M1

Source: Osborne '90: Table 27-2, Pg. 203

The 5- and 10-year relative **survival rates** for women with invasive breast cancer are 91% and 84%, respectively. Sixty-two percent of cases are diagnosed at a localized stage (confined to the breast, no spread to lymph nodes), for which the 5-year survival is 99%. Survival rates are about 9% lower (in absolute terms) for black women than for white women. Reducing disparities in outcomes for black women is a focus of the American Cancer Society and many other national cancer organizations (ACS '20: 11, 12). **Pre-operative systemic therapy** with endocrine therapy (tamoxifen), nonsteroidal AI (letrozole, anastrozole), the steroidal AI exemestane, and fulvestrant, HER2 targeted therapy and chemotherapy is indicated. Standard treatment options for early, localized, or operable breast cancer may include the following: One, **breast-conserving surgery** (lumpectomy) and sentinel lymph node (SLN) biopsy with or without axillary lymph node dissection for positive SLNs. Two, **modified radical mastectomy** (removal of the entire breast with axillary dissection of levels I and II) with or without breast reconstruction and sentinel node biopsy with or without axillary lymph node dissection for positive SLNs. For four or more nodes or extranodal involvement, regional radiation therapy is suggested. Post-operative therapy involves tamoxifen, aromatase inhibitor (AI), ovarian function suppression and chemotherapy.

Women with hormone receptor-positive tumors generally receive **tamoxifen** for 5 years (Henderson et al '03). Approximately 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31%.<sup>86</sup> The proportional reductions in both recurrence and mortality associated with tamoxifen use were similar in women with either node-negative or node-positive breast cancer, but the absolute improvement in survival at 10 years was greater in the node-positive breast cancer group (5.3% vs. 12.5% with 5 years of use). The results of the ATLAS trial indicated that for women who remained premenopausal after 5 years of adjuvant tamoxifen, continued tamoxifen for 5 more years was beneficial. Women who have become menopausal after 5 years of tamoxifen may also be treated with AIs (Davies et al '13). The 10-year distant recurrence risk for patients treated with tamoxifen was 7% for those with a low recurrence score, 14% for those with an intermediate recurrence score, and 31% for those with high recurrence score (Paik et al '04). Patients in this study with a low-risk score were found to have very low rates of recurrence at 5 years with endocrine therapy. Rate of overall survival (OS) was 98.0% at 5 years and 93.7% at 9 years. Patients with high clinical risk, but low genomic risk, who did not receive chemotherapy had a 5-year survival rate without distant metastases (primary study endpoint) of 92% or lower (a non-inferiority design) (Sparano et al '15).

**Ovarian suppression** is performed with with triptorelin or ablation with surgery or radiation therapy (Francis et al '15). Despite improvements in DFS and freedom from distant recurrence, no difference in OS was observed with the use of exemestane in combination with ovarian suppression compared with tamoxifen in combination with ovarian suppression 8-year OS, 93.4% in the exemestane-ovarian suppression group vs. 93.3% in the tamoxifen-ovarian-suppression group)(Pagani et al '14). Tamoxifen treated patients experienced more hot flashes and exemestane patients vaginal dryness and loss of sexual interest (Bernhard et al '15). Patients on anastrozole, had a significantly longer DFS than those on tamoxifen but OS was not improved. Evidence indicates that sequential tamoxifen and AI is superior to remaining on tamoxifen for 5 years. Patients on tamoxifen more frequently developed endometrial cancer and cerebrovascular accidents, whereas patients on anastrozole had more fracture episodes. The frequency of myocardial infarction was similar in both groups. Except for a continued increased frequency of endometrial cancer in the tamoxifen group, these differences did not persist in the posttreatment period (Howell et al '05). After 3 years of follow-up, 4.8% of the women on the letrozole arm had developed recurrent disease or new primaries versus 9.8% on the placebo arm. Overall mortality at 7 years was 9.3% in the tamoxifen-followed-by-AI groups and 8.2% in the AI-alone groups (Dowsett et al '15).

The 10-year distant disease-free survival (DFS) improved from 60% to 88% by adding chemotherapy to tamoxifen in the high-risk group, while no benefit was observed in the low recurrence score group (Paik et al '06). The 10-year distant recurrence risk for patients treated with tamoxifen was 7% for those with a low recurrence score, 14% for those with an intermediate recurrence score, and 31% for those with high recurrence score (Paik et al '04). Patients in this study with a low-risk score were found to have very low rates of recurrence at 5 years with endocrine therapy. Rate of overall survival (OS) was 98.0% at 5 years and 93.7% at 9 years. Patients with high clinical risk, but low genomic risk, who did not receive chemotherapy had a 5-year survival rate without distant metastases (primary study endpoint) of 92% or lower (a non-inferiority design) (Sparano et al '15). Current consensus opinion for use of preoperative chemotherapy recommends anthracycline- and taxane-based therapy, and prospective trials suggest that preoperative anthracycline- and taxane-based therapy is associated with higher response rates than alternative regimens (e.g., anthracycline alone) (Bear et al '03).

**Anthracyclines:** Doxorubicin. Epirubicin. Liposomal doxorubicin (Harris et al '02). Mitoxantrone. **Taxanes:** Paclitaxel (Gonzalez-Angulo et al '08). Docetaxel. Albumin-bound nanoparticle paclitaxel (ABI-007 or Abraxane) (Ibrahim et al '05). **Alkylating agents:** Cyclophosphamide. Fluoropyrimidines. Capecitabine (Venturini et al '07). Fluorouracil (5-FU). **Antimetabolites:** Methotrexate. **Vinca alkaloids:** Vinorelbine (Degardine et al '94). Vinblastine. Vincristine. **Platinum:** Carboplatin. Cisplatin. **Other:** Gemcitabine (Carmichael et al '97). Mitomycin C. Eribulin mesylate (Cortes et al '11). Ixabepilone (Smith et al '13). **Combination regimens** that have shown activity in metastatic breast cancer include the following: AC: Doxorubicin and cyclophosphamide (Tranum et al '82). EC: Epirubicin and cyclophosphamide (Langley et al '05). Docetaxel and doxorubicin (Misset et al '99). CAF Cyclophosphamide, doxorubicin, and 5-FU (Buzdar et al '89). CMF: Cyclophosphamide, methotrexate, and 5-FU (Tormey et al '82). Doxorubicin and paclitaxel (Biganzoli et al '02). Docetaxel and capecitabine (O'Shaughnessy et al '02). Vinorelbine and epirubicin (Serin et al '05). Capecitabine and ixabepilone (Thomas et al '07). Carboplatin and gemcitabine (O'Shaughnessy et al '18). Gemcitabine and paclitaxel (Albain et al '08). There are no data suggesting that combination therapy results in an OS benefit over single-agent therapy. No data support the superiority of any particular regimen. The cardioprotective drug dexrazoxane has been shown to decrease the risk of doxorubicin-induced cardiac toxicity in patients in controlled studies. The American Society of Clinical Oncology guidelines suggest the use of dexrazoxane in patients with metastatic cancer who have received a cumulative dose of doxorubicin of 300 mg/m<sup>2</sup> or more when further treatment with an anthracycline is likely to be of benefit (Hensley et al '09). Dexrazoxane has a similar protective effect in patients receiving epirubicin (Venturini et al '96).

Several trials have addressed the benefit of adding a **taxane** (paclitaxel or docetaxel) to an anthracycline-based adjuvant chemotherapy regimen for women with node-positive breast cancer. The addition of paclitaxel resulted in statistically significant improvements in DFS (5%) and OS (3%) (Henderson et al '03). After preoperative therapy, 36% of the patients treated with AC had a complete clinical response. More patients treated with preoperative chemotherapy were able to have breast-conserving procedures as compared with those patients in the postoperative chemotherapy group (68% vs. 60%)(Fisher et al '98). There was a 75% DFS rate at 5 years in the TAC group compared with a 68% DFS rate in the FAC group. TAC was associated with a 30% overall lower risk of death (5% absolute difference) than was FAC (Martin et al '05). DFS at 5 years was 81% in patients treated every 2 weeks and 76% in patients treated every 3 weeks (Del Mastro et al '15). Initiation of chemotherapy 61 days or more after surgery was associated with adverse outcomes (Gaglioto et al '14).

The use of anthracycline-containing regimens, however—particularly those containing an increased dose of cyclophosphamide—has been associated with a cumulative risk of developing acute leukemia of 0.2% to 1.7% at 5 years (Smith et al '03). This risk increases to more than 4% in patients receiving high cumulative doses of both epirubicin (>720 mg/m<sup>2</sup>) and cyclophosphamide (>6,300 mg/m<sup>2</sup>)(Praga et al '05). Triple negative breast cancer (TNBC) is defined as the absence of staining for ER, PR, and HER2/neu. TNBC is insensitive to some of the most effective therapies available for breast cancer treatment including HER2-directed therapy such as trastuzumab and endocrine therapies such as tamoxifen or the aromatase inhibitors. Patients whose tumors have a pure lobular histology, low grade, or high hormone-receptor expression and HER2-negative status are less likely to respond to chemotherapy and should be considered for primary surgery, especially when the nodes are clinically negative. Even if adjuvant chemotherapy is administered after surgery in these cases, a third-generation regimen (anthracycline-taxane based) may be avoided (Carlson et al '09).

**Breast cancer treatment** usually involves either breast-conserving surgery (surgical removal of the tumor and a rim of surrounding tissue, sometimes called a lumpectomy) or mastectomy (surgical removal of the entire breast), depending on tumor characteristics (e.g., size and extent of spread) and patient preference. One or more underarm lymph nodes are usually evaluated during surgery to determine whether the tumor has spread beyond the breast. Radiation is recommended for most patients having breast-conserving surgery. For women with early-stage breast cancer (without spread to the skin, chest wall, or distant organs), studies indicate that breast-conserving surgery plus radiation therapy results in long-term survival equivalent to mastectomy. Although most patients undergoing mastectomy do not need radiation, it is sometimes recommended when the tumor is large or lymph nodes are involved. Women undergoing mastectomy who elect breast reconstruction have several options, including the type of tissue or implant used to restore breast shape. Reconstruction may be performed at the time of mastectomy (immediate reconstruction) or later as a second procedure (delayed reconstruction), but it often requires more than one surgery. Depending on cancer stage, subtype, and sometimes other test results (e.g., Oncotype DX), treatment may also involve chemotherapy (before or after surgery), hormone (anti-estrogen) therapy, targeted therapy, and/or more recently, immunotherapy (e.g. checkpoint inhibitors) (ACS '20: 11, 12).

Initial surgery is generally limited to **biopsy** to permit the determination of histology, estrogen receptor (ER) and progesterone receptor levels, and human epidermal growth factor receptor 2 (HER2/neu) over-expression (Petrelli et al '16). **Radical treatment** has been modified but a partial mastectomy is the treatment recommendation for those with carcinoma in situ, Stage I and II disease, only those women with Stage III or Stage IV breast cancer enjoy 70% tumor regression, and 30% disease free at 5 years from chemotherapy. As an alternative to chemotherapy hormonal therapy with tamoxifen may be considered, especially if the tumor has high levels of ER or PR. **Chemotherapy** should be continued by responding patients until maximal reduction in tumor size is obtained (usually 3 to 6 months), surgery and radiation are then introduced in a sequence determined by the extent of tumor regression. About 50% of all patients with operable cancer survive 10 years after surgery. Adjuvant chemotherapy has been estimated to cause a 30% proportional reduction in mortality at 5 years. Combination chemotherapy is superior to single-agent treatment. Shorter duration treatment may be just as effective as long term treatment. **Adjuvant endocrine therapy**, mostly using tamoxifen 10 mg to 20 mg, twice a day for 1 or 2 years after local treatment has shown a 20% reduction in mortality over 5 years. Metastatic breast cancer is not curable although temporary regression is attainable in 75% of patients and complete remission in 10% to 20% of patients. Combination chemotherapy is superior to single-agent treatment; response rates range from 50% to 70% and response durations range from 6 to 12 months (Osborne '90: 207, 210).

Conventional **whole-breast radiation therapy** is delivered to the whole breast (with or without regional lymph nodes) in 1.8 Gy to 2 Gy daily fractions over about 5 to 6 weeks to a total dose of 45 Gy to 50 Gy. Radiation therapy is regularly employed after breast-conserving surgery. Radiation therapy is also indicated for high-risk postmastectomy patients. Delaying radiation therapy for 2 to 7 months after surgery had no effect on the rate of local recurrence (Hickey et al '13). The main goal of adjuvant radiation therapy is to eradicate residual disease thus reducing local recurrence (Clark et al '05). For women who are treated with breast-conserving surgery without radiation therapy, the risk of recurrence in the conserved breast is substantial (>20%) even in confirmed axillary lymph node–negative women (Eifel et al '98). Whole-breast radiation therapy resulted in a significant reduction in the 10-year risk of recurrence compared with breast-

conserving surgery alone (19% for whole-breast radiation therapy vs. 35% for breast-conserving surgery alone (Darby et al '11). For women with node-positive disease postmastectomy and axillary clearance (removal of axillary lymph nodes and surrounding fat), radiation therapy reduced the 5-year local recurrence risk from 23% to 6%. The optimal sequence of adjuvant chemotherapy and radiation therapy after breast-conserving surgery has been studied. With a median follow-up of 5 years, OS was 73% for the radiation-first group and 81% for the chemotherapy-first group. The 5-year crude rate of first recurrence by site was 5% in the radiation-first group and 14% in the chemotherapy-first group for local recurrence and 32% in the radiation-first group and 20% in the chemotherapy-first group for distant or regional recurrence or both (Recht et al '96).

Hormone receptor (ER and/or PR)–positive patients will receive hormone therapy. HER2 over-expression is an indication for using adjuvant **trastuzumab**, usually in combination with chemotherapy. One year of trastuzumab also improved 12-year OS, 79% vs. 73%. There is no benefit for an additional year (Cameron et al '17). The addition of trastuzumab to chemotherapy led to a 37% relative improvement in OS and an increase in the 10-year OS rate from 75.2% to 84%. [121] For patients receiving AC-T plus trastuzumab, the 5-year DFS rate was 84%, and the OS rate was 92%. For patients receiving TCH, the 5-year DFS rate was 81%, and the OS rate was 91%. The control group had a 5-year DFS rate of 75% and an OS rate of 87%. Cardiac events associated with adjuvant trastuzumab have been reported in multiple studies. The rates of congestive heart failure (CHF) and cardiac dysfunction were significantly higher in the group receiving AC-T plus trastuzumab than in the TCH group (Slamon et al '11). **Neratinib** is an irreversible tyrosine kinase inhibitor of HER1, HER2, and HER4, which has been approved by the FDA for the extended adjuvant treatment of patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy. The 5-year invasive DFS was 90.2% in the neratinib group and 87.7% in placebo. Prophylactic loperamide is recommended on the FDA label during the first 56 days of therapy, and as needed thereafter to help manage diarrhea (Chan et al '16). The FDA-granted accelerated approval for the use of **pertuzumab** as part of a preoperative treatment for women with early-stage, HER2-positive breast cancer whose tumors are larger than 2 cm or node-positive.

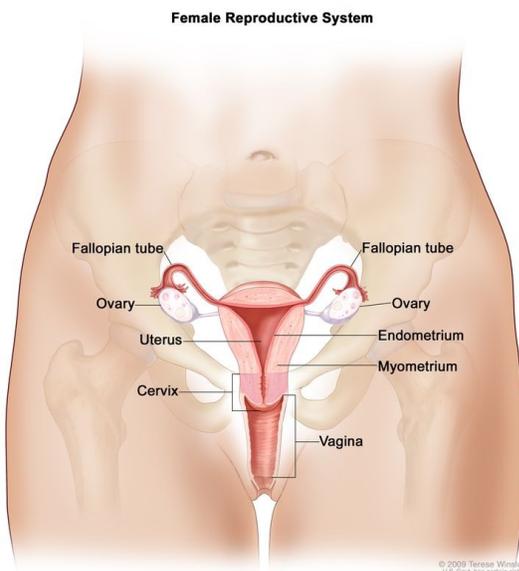
CDK4 and CDK6 have been implicated in the continued proliferation of hormone receptor–positive breast cancer resistant to endocrine therapy. CDK inhibitors have been approved by the U.S. Food and Drug Administration (FDA) in combination with endocrine therapy in both first-line and later-line treatment of advanced hormone receptor–positive HER2-negative breast cancer. Three oral CDK4/6 inhibitors are currently available: palbociclib, ribociclib, and abemaciclib. Overall, the addition of CDK 4/6 inhibitors to endocrine therapy is associated with improved breast cancer outcomes and, in general, either maintained or improved quality of life. This benefit was observed across multiple clinicopathological subgroups of breast cancer (Gao et al '20). Median PFS of 24.8 months was seen in the **palbociclib-plus-letrozole** group compared with 14.5 months in the placebo-plus-letrozole group (Finn et al '16). After 18 months, the PFS rate was 63.0% in the **ribociclib** group and 42.2% placebo (Hortobagyi et al '16). Ribociclib has also been tested in combination with fulvestrant in postmenopausal patients with hormone receptor–positive and HER2-negative recurrent or metastatic breast cancer. the median PFS for the ribociclib group was 20.5 months versus 12.8 months in the placebo group. OS was superior in the ribociclib group (Slamon et al '20). The combination of ribociclib plus endocrine therapy was associated with longer OS than was endocrine therapy alone, 42-month OS, 70.2% vs. 46% (Im et al '19). After a median follow-up of 17.8 months, the PFS was not reached in the first line

**abemaciclib** and endocrine therapy and was reached at 14.7 months in the placebo arm (Goetze et al '17).

Hormone receptor–positive metastatic breast cancer that is resistant to nonsteroidal aromatase inhibition may be assigned to receive the mTOR inhibitor everolimus plus exemestane. Median PFS was 6.9 months for everolimus plus exemestane and 2.8 months for placebo plus exemestane (Baselga et al '12). Median time to progression was 8.6 months in the combination everolimus plus tamoxifen and 4.5 months in the tamoxifen alone group. Median PFS was 10.3 months on the fulvestrant plus everolimus combination arm and 5.1 months on the fulvestrant-alone arm (Kombalum et al '18). Alpelisib is approved by the FDA for use in combination with fulvestrant in advanced PIK3CA-mutated, hormone receptor–positive, HER2-negative breast cancer after previous endocrine therapy. Median PFS was 11 months in the alpelisib-plus-fulvestrant arm compared with 5.7 months in the placebo-plus-fulvestrant arm (André et al '19). Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that incorporates the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1. Median PFS was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine. Median OS was longer with trastuzumab emtansine versus lapatinib plus capecitabine (29.9 months vs. 25.9 months (Verma et al '12).

For patients with metastatic breast cancer who carry a germline BRCA mutation, the oral inhibitor of poly (adenosine diphosphate-ribose) polymerase (PARP) has shown activity. Median PFS was significantly longer in the olaparib group than in the standard therapy group (7.0 months vs. 4.2. months) although OS was the same (Robson et al '17). Results were similar with talazoparib. Atezolizumab was granted accelerated approval by the FDA for use in combination with protein-bound paclitaxel for patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1. Median OS was, 9.5 months longer in the atezolizumab arm in the PD-L1–positive population (25 months vs. 15.5 months) (Schmid et al '18). The FDA granted accelerated approval to sacituzumab govitecan for patients with metastatic triple-negative breast cancer after at least two previous lines of therapy. A confirmatory randomized trial is still under way. A response rate of 33.3% was observed. The median duration of response was 7.7 months (Bardia et al '19). The use of bone-modifying therapy to reduce skeletal morbidity in patients with bone metastases should be considered (Hillner et al '03). Results of randomized trials of pamidronate and clodronate in patients with bony metastatic disease show decreased skeletal morbidity (Powles et al '06). Zoledronate and denosumab has been at least as effective as pamidronate (Rosen et al '03).

## 10. Uterine Cancer



**Cervical cancer** is the fourth most common cancer in women worldwide, and it has the fourth highest mortality rate among cancers in women. Carcinoma of the cervix was once the most common cause of cancer death in women. Over the past 30 years, the mortality rate has decreased by half. The American Cancer Society estimates there will be approximately 16,000 new cases of invasive cancer and approximately 7,000 deaths in 2030 (Young '90: 276-278). It is estimated that in 2006 there were about

9,710 new cases of invasive **cervical cancer** in the United States, and 3,700 deaths (Mooney '07: 35). In 2020, an estimated 13,800 cases of invasive **cervical cancer** will be diagnosed and about 4,290 deaths will occur in the US. The cervical cancer incidence rate has dropped by more than half since the mid-1970s, largely due to the widespread uptake of screening with the Pap test. However, the rate in white women had stabilized during the most recent decade of data (2007 to 2016) while continuing to decline in black women (by 2.8% per year). Studies suggest that some recent declines in incidence in young women may be associated with HPV vaccine uptake. The cervical cancer death rate has also dropped by more than half since the mid-1970s due to declines in incidence and the early detection of cancer through screening. The decline during 2008 to 2017 continued in black women (by 2.6% per year) in rates in white women stabilized (ACS '20).

There are two commercially available vaccines that target anogenital-related strains of HPV. The vaccines are directed towards HPV-naïve girls and young women, and although penetration of the vaccine has been moderate, significant decreases in HPV-related diseases have been documented (Muñoz et al '10). **Vaccines** that protect against the types of HPV that cause 90% of cervical cancers, as well as several other diseases and cancers, are routinely recommended for children ages 11 to 12 years. While the vaccines are recommended for use in ages 9 to 26 years, the CDC recommends vaccinating all boys and girls by age 13. In 2016, the recommended number of vaccine doses was reduced from three to two as long as the first dose is given before age 15; three doses are required for full protection when the first dose is given after the 15th birthday. The CDC recommends shared clinical decision making regarding HPV vaccination in adults ages 27 to 45 years. Unfortunately, the immunization rate remains low in the US; in 2018, 54% of girls and 49% of boys 13 to 17 years of age were up to date with the HPV vaccination series. HPV vaccines cannot protect against established infections and do not protect against all types of HPV, which is why it is important for all women, even those who have been vaccinated, to follow cervical cancer screening guidelines (ACS '20: 27).

Worldwide nearly 500,000 new cases are diagnosed each year. Cervical cancer is the second most common type of cancer among women worldwide and one of the leading causes of cancer-related mortality in women in the developing world (Mooney '07: 35). Almost all cervical cancers are caused by persistent infection with certain types of **human papillomavirus** (HPV). HPV infections are common in healthy women and only rarely cause cervical cancer. Although women who begin having sex at an early age or who have had many sexual partners are at increased risk for HPV infection and cervical cancer, a woman may be infected with HPV even if she has had only one sexual partner. Several factors are known to increase the risk of both persistent HPV infection and progression to cancer, including a suppressed immune system, a high number of childbirths, and cigarette smoking. Long-term use of oral contraceptives is also associated with increased risk that gradually declines after cessation (ACS '20: 27). Exposure to diethylstilbestrol (DES) in utero has also been implicated in causing cervical cancer (Hoover et al '11). More than 6 million women in the United States are estimated to be infected with HPV (Dunne et al '07). Transient HPV infection is common, particularly in young women, while cervical cancer is rare. The persistence of an HPV infection leads to increased risk of developing precancerous and cancerous lesions (Jaisamrarn et al '13). There are multiple subtypes of HPV that infect humans; of these, subtypes 16 and 18 have been most closely associated with high-grade dysplasia and cancer. Studies suggest that acute infection with HPV types 16 and 18 conferred an 11-fold to 16.9-fold risk of rapid development of high-grade CIN (Schiffman et al '93).

Pre-invasive cervical lesions often have no **symptoms**. Once abnormal cells become cancerous and invade nearby tissue, the most common symptom is abnormal vaginal bleeding, which may start and stop between regular menstrual periods or cause menstrual bleeding to last longer or be heavier than usual. Bleeding may also occur after sexual intercourse, douching, a pelvic exam, or menopause. Dyspareunia and increased vaginal discharge may also be a symptom (ACS '20: 27). Several groups of women are at increased risk for the development of cervical carcinoma, including those with early initial sexual activity, multiple sexual partners, early marriage, young age for first pregnancy, and prior venereal infections. Viral etiologies have been frequently implicated, herpes simplex virus type II and human papilloma virus subtypes 16 and 18 have been found almost exclusively in high-grade cervical neoplasias and invasive cervical cancer. A typical squamous metaplasia can progress to cervical intraepithelial neoplasia (CIN). This lesion precedes invasive cervical carcinoma and has been classified as Grade I – mild to moderate dysplasia, Grade II - moderate to severe dysplasia, and Grade III – severe dysplasia and carcinoma in situ. Carcinoma in situ demonstrated cytologic evidence of neoplasia but without invasion through the basement membrane. Carcinoma in situ can persist for long periods of time but is felt to eventually progress to invasive carcinoma. It is estimated that the time to progression to frankly invasive disease is 3 to 10 years (Young '90: 276-278).

Cervical cytology (Pap smear) has been the mainstay of cervical cancer screening since its introduction. More than 90% of cervical cancer cases can be detected early through the use of the Pap test and HPV testing (NCI '89). The median age of diagnosis for cervical cancer for all races is 48 years. Half of all women diagnosed with cervical cancer are between the age of 35 and 55. Due largely to routine screening using Pap tests, the number of deaths attributed to cervical cancer in the United States dropped 74 percent between 1955 and 1992, and the death rate continues to drop nearly four percent annually. The five-year survival rate is virtually 100 percent for pre-invasive cervical cancer and 91 percent for early invasive cancer. The overall five-year survival rate for all stages of cervical cancer is about 73 percent. African-Americans experience a disproportionate number of deaths from cervical cancer. In 2001, the death rate was 4.7 per 100,000 for black women, compared with 2.2 per 100,000 for white women. Latinas and Native Americans also have cervical cancer death rates that are above average (Mooney '07: 35, 36).

**Screening** can prevent cervical cancer through detection and treatment of precancerous lesions, which are now detected far more frequently than invasive cancer. Most cervical precancers develop slowly, so cancer can usually be prevented if a woman is screened regularly. The **Pap test** is a simple procedure in which a small sample of cells is collected from the cervix and examined under a microscope, and was historically the only screening option. The newer **HPV test**, which detects HPV infections associated with cervical cancer, can forecast cervical cancer risk and is currently recommended for use in conjunction with the Pap test or as a stand-alone test in women ages 30 to 65 years. The HPV test can also identify women at risk for a type of cervical cancer (adenocarcinoma) that is often missed by Pap tests and accounts for 29% of cases (ACS '20: 27). In addition to preventing cervical cancer, **screening** can detect invasive cancer early, when treatment is more successful. Most women diagnosed with cervical cancer have not been screened recently. The American Cancer Society, in collaboration with the American Society for Colposcopy and Cervical Pathology and the American Society for Clinical Pathology, recommends screening for women ages 21 to 65 years, with an emphasis on the incorporation of HPV testing in addition to the Pap test for ages 30 to 65 years (ACS '20: 27).

The **Papanicolaou smear** is 90% to 95% accurate. Approximate 5-year survivals by stage are; Stage I, 80.5%; Stage II, 59%; Stage III, 33%; Stage IV, 7%. The decrease in survival is associated with increasing frequency of lymph node metastases. Lymph node positivity is seen in 15% of women with Stage I disease, 29% of those with Stage II, 47% with Stage III, and 5 year survival rates for patients with positive nodes are generally less than 20%. The 5-year survival rate in one study of Stage IB disease was 88% for small lesions and 65% for bulky tumors. For patients with Stage II disease, small lesions had a 75% 5 year survival compared with 39% for bulky lesions. The so-called **glassy cell carcinoma**, a poorly differentiated adenosquamous tumor, has extremely poor survival regardless of therapy. Endometrial spread, appears to be associated with a worsened prognosis. Ninety percent of invasive cervical carcinomas are squamous cell tumors. Approximately 5% are adenocarcinomas, and 1% to 2% are clear cell mesonephric tumors. Two to five percent of all cervical carcinomas are adenosquamous, consisting of intermingled epithelial and glandular structures. When the squamous component is benign metaplasia, the tumors are called **adenoacanthomas** (Young '90: 276-278). Squamous cell (epidermoid) carcinoma comprises approximately 90% of cervical cancers, and adenocarcinoma comprises approximately 10% of cervical cancers. Adenosquamous and small cell carcinomas are relatively rare. Primary sarcomas of the cervix and primary and secondary malignant lymphomas have also been reported. The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and the American Joint Committee on Cancer have designated staging to define cervical cancer; the FIGO system is most commonly used (NCI '20).

### Staging for Cervical Cancer

Stage	Description
<b>Stage 0</b>	Carcinoma in situ, intraepithelial carcinoma
<b>Stage I</b>	Carcinoma confined to the cervix. Extension to the corpus should be disregarded.
<b>IA</b>	Micro-invasive carcinoma (early stromal invasion)
<b>IB</b>	<5 mm in depth -IA1 <3mm in depth, -IA2 >3 mm <5mm >5mm in depth, -IB1 >5mm <2cm, -IB2 >2cm <4 cm, -IB3 >4cm
<b>Stage II</b>	Carcinoma extends beyond the cervix but has not extended to the pelvic wall. It involves the vagina, but not the lower third. No obvious parametrial involvement.
<b>IIA</b>	Limited to upper two-thirds of vagina without parametrial involvement. -IIA1 <4cm, -IIA2 >4cm
<b>IIB</b>	With parametrial involvement but not up to the pelvic wall.
<b>Stage III</b>	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes.
<b>IIIA</b>	Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall. Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause).
<b>IIIB</b>	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases), irrespective of tumor size and extent (with r and p notations). -IIIC1 –Pelvic lymph

<b>IIIC</b>	node metastasis only. -IIIC2 –Para-aortic lymph node metastasis.
<b>Stage IV</b>	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV. Spread of growth to adjacent organs.
<b>IVA</b>	Spread to distant organs.
<b>IVB</b>	

Source: Bhatla et al '19

The Evers Papyrus (c.1552 BC) gives a remedy for cancer in the womb – fresh dates and limestone pounded with water and injected into the vulva. The writing of Hippocrates (450 BC) also record uterine cancer. Also in the fifth century BC, Hindu texts described surgical procedures for removal of tumors of the cervix and vagina. Epidemiological evidence is compelling that cervical cancer is associated with sexual activity. The risk of this cancer increases with number of sexual partners and virtually zero in nuns but high in prostitutes (Greaves '00: 167, 168). Precancerous cervical lesions may be treated with a **loop electrosurgical excision procedure (LEEP)**, which removes abnormal tissue with a wire loop heated by electric current; cryotherapy (the destruction of cells by extreme cold); laser ablation (destruction of tissue using a laser beam); or conization (the removal of a cone-shaped piece of tissue containing the abnormal tissue). Invasive cervical cancers are generally treated with **surgery or radiation combined with chemotherapy**. For early-stage disease, studies indicate that minimally invasive surgery (laparoscopy) is associated with worse survival than open surgery. Chemotherapy alone is often used to treat advanced disease. However, for women with metastatic, recurrent, or persistent cervical cancer, the addition of targeted therapy to standard chemotherapy has been shown to improve overall survival. Immunotherapy may be another option for metastatic or recurrent cancer. The 5-year relative survival rate for cervical cancer overall is 66% but ranges from 46% for black women 50 and older to 78% for white women younger than age 50. Five-year survival is 92% for the 44% of patients diagnosed with localized stage (ACS '20: 28).

### Drugs Used to Treat Stage IVB Cervical Cancer

Drug Name	Response Rate
Cisplatin	15-25%
Ifosfamide	31%
Paclitaxel	17%
Ifosfamide/cisplatin	31%
Irinotecan	21% with prior treatment
Paclitaxel/cisplatin	46%
Cisplatin/gemcitabine	41%

Cisplatin/topotecan	27%
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Source: NCI '20

Carcinoma *in situ* is generally managed with conization, total abdominal **hysterectomy** for post-reproductive patients and internal radiation therapy for inoperable patients. Stage IA is treated with conization, total hysterectomy, modified radical hysterectomy with pelvic lymphadenectomy, radical trachelectomy or intracavitary radiation therapy. Women desiring children can be impregnated by cervical colonization and careful follow-up. Properly treated, tumor control of *in situ* cervical carcinoma should be nearly 100% (Wright et al '07). Patients with stages IA2 to IB disease who desire future fertility may be candidates for radical trachelectomy. In this procedure, the cervix and lateral parametrial tissues are removed, and the uterine body and ovaries are maintained (Shepherd et al '06). Cancer patients have advised to get a total hysterectomy to reduce risk of recurrence rather than pursue childbirth, and might benefit from low dose chemotherapy and irradiation. Both surgery and radiation produce similar results. Treatment of Stage IB cervical cancer and higher involves radiation and chemotherapy. Either radiation therapy or radical hysterectomy and bilateral lymph-node dissection results in cure rates of 85% to 90% for women with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stages IA2 and IB1 small-volume disease. The choice of either treatment depends on patient factors and available local expertise. A randomized trial reported identical 5-year overall survival (OS) and disease-free survival (DFS) rates when comparing radiation therapy with radical hysterectomy (Landoni et al '97). In stage IB2, for tumors that expand the cervix more than 4 cm, the primary treatment should be concomitant chemotherapy and radiation therapy (Eifel et al '91).

Five year survival of patients with Stage IB disease managed with radical hysterectomy and pelvic lymphadenectomy is approximately 80%. Radiation therapy can also be used for curative intent. Large collected experiences indicated a 5 year survival of approximately 77% for radiation therapy. For patients who have obvious parametrial spread of disease Stage IIB or Stage III they are treated with by radical hysterectomy and pelvic lymphadenectomy or with radiation therapy. Most advanced tumors are managed entirely by external irradiation, delivering 5500 cGy to 6000 cGy to the whole pelvis over 5 to 6 weeks. Five years survival for patients with Stage IIB disease managed with definitive radiation therapy is 68% compared with 44% for patients with Stage III disease. Approximately 75% of patients who relapse will relapse locally in pelvic or pelvic and disseminated sites. Isolated distant metastases occur in approximately 20% of patients who relapse. Chemotherapy is utilized in patients with advanced Stage IIIB and IV disease, patients who have recurring disease after surgery and radiation therapy, and patients who present with para-aortic nodal disease and have a low potential for cure with existing therapy. Response rates of approximately 20% have been seen with 5-FU, vincristine, hexamethylmelamine, chlorambucil and dibromodulcitol. Cisplatin appears to be the single drug with the best documented activity. One study of 34 patients treated with cisplatin, 50 mg/m<sup>2</sup> every 3 weeks, reported an overall response rate of 38%. Remissions were seen more frequently in patients with no prior chemotherapy; the duration of response was 6 months (Young '90: 278-281).

Five randomized, phase III trials have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy. The risk of death from cervical cancer was decreased by 30% to 50% with the use of concurrent chemo-radiation therapy (Whitney et al '99). Concurrent, cisplatin-based chemotherapy with radiation therapy is the standard of care for women who require radiation therapy for treatment of cervical cancer. In general, for smaller

tumors, the curative-intent dose for point A is around 70 Gy, whereas for larger tumors, the point A dose may approach 90 Gy. The Gynecologic Oncology Group (GOG) compared adjuvant radiation therapy alone with radiation therapy plus cisplatin plus fluorouracil (5-FU) after radical hysterectomy for patients in the high-risk group. Postoperative patients were eligible if their pathology showed any one of the following: positive parametria, positive margins, or positive lymph nodes. Patients in both arms received 49 Gy to the pelvis. Patients in the experimental arm also received cisplatin (70 mg/m<sup>2</sup>) and a 96-hour infusion of 5-FU (1000 mg/m<sup>2</sup>/d every 3 weeks for four cycles); the first two cycles were concurrent with the radiation therapy. Estimated 4-year survival was 81% for chemotherapy plus radiation therapy and 71% for radiation therapy alone. Grade 4 toxicity was more common in the chemotherapy plus radiation therapy group, with hematologic toxicity predominating (Peters et al '00). Standard radiation therapy for cervical cancer includes brachytherapy after external-beam radiation therapy (EBRT). Although low-dose rate (LDR) brachytherapy, typically with cesium Cs 137 (137Cs), has been the traditional approach, the use of high-dose rate (HDR) therapy, typically with iridium Ir 192, is rapidly increasing (Lertsanguansinchai et al '04). The addition of bevacizumab to combination chemotherapy led to an improvement in OS: 17 months for chemotherapy plus bevacizumab versus 13.3 months for chemotherapy alone (HR, 0.71; 98% CI, 0.54–0.95), and extended PFS: 8.2 months for chemotherapy plus bevacizumab versus 5.9 months for chemotherapy alone (Tewari et al '14). For recurrent cervical cancer favorable experience with the anti-programmed cell death-1 (PD-1) immune checkpoint inhibitor, pembrolizumab, has led to U.S. Food and Drug Administration (FDA) approval. The overall response rate was 17% (Frenel et al '17). During pregnancy, no therapy is warranted for preinvasive lesions of the cervix, including carcinoma *in situ*, although expert colposcopy is recommended to exclude invasive cancer. For patients with stage II or greater disease, waiting for viability is generally not acceptable. The standard of care is curative intent chemotherapy and radiation therapy. This treatment is toxic to the fetus and without ovarian transposition will render the ovaries nonfunctional after treatment. Evacuation of the fetus should be performed before the initiation of radiation. When this is not possible, the radiation will generally cause a spontaneous abortion 3 to 5 weeks after initiating treatment (Morice et al '12).

Approximately one woman in every 70 will eventually develop **ovarian cancer**. The American Cancer Society estimates 19,000 new cases of ovarian cancer in 1986 and approximately 11,600 deaths. Ovarian cancer is the most common cause of death from a gynecologic malignancy, and the mortality rate from ovarian cancer in the United States exceeds that for cervical and endometrial cancer combined (Young '90: 270). In 2020, an estimated 21,750 new cases of ovarian cancer will be diagnosed in the US and 13,940 women will die from the disease. Most (90%) cases are epithelial ovarian cancer, the majority of which are high-grade serous tumors, which have the fewest established risk factors and worst prognosis. Ovarian cancer incidence rates have declined since the mid-1980s, decreasing by 1.6% per year from 2007-2016. Ovarian cancer death rates have declined since the early 2000s, decreasing by 2.3% per year from 2008-2017. The most important risk factor other than age is a strong family history of breast or ovarian cancer. Women who have certain inherited mutations (e.g., *BRCA1* or *BRCA2*) or genetic conditions (e.g., Lynch syndrome) are at increased risk. Other medical conditions and characteristics associated with increased risk include a personal history of breast cancer, endometriosis, or pelvic inflammatory disease, obesity and tall adult height. Modifiable factors associated with increased risk include excess body weight, menopausal hormone therapy (estrogen alone or combined with progesterone), and cigarette smoking, which is associated with a rare subtype (mucinous). Factors associated with lower risk include pregnancy, fallopian tube ligation or removal (salpingectomy), and use of oral contraceptives (OCs), with risk reductions

of 40% among long-term (10+ years) OC users. It is unclear whether genital talc-based powder use increases the risk of ovarian cancer, in part because most of the evidence is from case-control studies, which are especially prone to bias, and because the type of body powder (i.e., with or without talc) and location of use (i.e., genital vs. non-genital) was sometimes unclear (ACS '20: 20, 21).

**Early ovarian cancer** usually has no obvious symptoms. However, some women experience persistent, nonspecific symptoms, such as back pain, bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or urinary urgency or frequency in the months before diagnosis. Women who experience such symptoms daily for more than a few weeks should seek prompt medical evaluation. The most common sign of ovarian cancer is swelling of the abdomen, which is caused by the accumulation of fluid. Currently, there is no recommended screening test for ovarian cancer, although clinical trials to identify effective strategies are underway. Women who are at high risk or have symptoms may be offered a thorough pelvic exam in combination with transvaginal ultrasound and a blood test for the CA125 tumor marker, although this strategy has not been proven to be effective in reducing ovarian cancer mortality and is associated with serious harms due to false-positive diagnoses (ACS '20: 21). Once ovarian cancer develops, it spreads by direct extension, by intraperitoneal dissemination, by lymphatics, and less frequently hematogenously. Malignant cells become implanted on the omentum and at multiple other sites on the serosal surface of the peritoneum. Although ovarian cancer tends to remain confined to the peritoneal space, other organs are at risk for metastases, including, in order of decreasing frequency, the liver, lung, pleura, kidney, bone, adrenal gland, bladder and spleen. Most patients with ovarian cancer are first diagnosed when the disease has already spread outside the confines of the true pelvis. Approximately 15% to 20% of patients present in Stage I, 10% to 15% in Stage II, 60% to 70% in Stage III, and 10% to 15% in Stage IV. The vast majority (85% to 90%) of malignant ovarian cancers seen in the United States are epithelial. They are grouped as serous cystadenocarcinoma, mucinous cystadenocarcinoma, endometrioid, undifferentiated and clear cell carcinoma. Germ cell tumors of the ovary comprise only 5% to 10% of the total but are important because of their aggressiveness, their lack of successful management with surgery and radiation therapy, and their high degree of curability with combination chemotherapy (Young '90: 270).

**Tumors of low malignant potential** (i.e., borderline tumors) account for 15% of all epithelial ovarian cancers. Nearly 75% of these tumors are stage I at the time of diagnosis and enjoy a seven year survival rate of 92%. Malignant transformation can occur (Norris '93). In early-stage disease (stage I or II), no additional treatment is indicated for a completely resected tumor of low malignant potential (Trope '93). When a patient wishes to retain childbearing potential, a unilateral salpingo-oophorectomy is adequate therapy (Kaem et al '93). In the presence of bilateral ovarian cystic neoplasms, or a single ovary, a partial oophorectomy can be employed when fertility is desired by the patient (Rice et al '90). In a large series, the relapse rate was higher with more conservative surgery (cystectomy > unilateral oophorectomy > TAH, BSO); differences, however, were not statistically significant, and survival was nearly 100% for all groups (Casey et al '93). Patients with advanced disease should undergo a total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, node sampling, and aggressive cytoreductive surgery. Patients with stage III or IV disease with no gross residual tumor have had a 100% survival rate in some series regardless of the follow-up duration (Bostwick et al '83). The 7-year survival rate of patients with gross residual disease was only 69% in a large series (Leake et al '92).

**Germ cell tumors of the ovary** are uncommon, but aggressive, tumors, which are seen most often in young women or adolescent girls. These tumors are frequently unilateral and are generally curable if found and treated early. The use of combination chemotherapy after initial surgery has dramatically improved the prognosis for many women with these tumors (Williams et al '94). One series found a 10-year survival rate of 88.6% following conservative surgery for patients with dysgerminoma confined to the ovary; less than 10 cm in size; with an intact, smooth capsule unattached to other organs; and without ascites. A number of patients had one or more successful pregnancies following unilateral salpingo-oophorectomy (Thomas et al '87). Prior to the widespread use of combination chemotherapy found only 27% of 96 patients with stage I endodermal sinus tumor alive at 2 years after diagnosis. More than 50% of the patients died within a year of diagnosis. Prognosis was poor for patients with large tumors when more than one-third of the tumor was composed of endodermal sinus elements, choriocarcinoma, or grade 3 immature teratoma. When the tumor was smaller than 10 cm in diameter, the prognosis was good regardless of the composition of the tumor (Murugaesu et al '06). Even patients with incompletely resected dysgerminoma can be rendered disease-free following chemotherapy with bleomycin, etoposide, and cisplatin (BEP) or a combination of cisplatin, vinblastine, and bleomycin, also known as PVB (Williams et al '91). Relapse is essentially unheard of following platinum-based chemotherapy (Williams et al '94). However, the disease will recur in about 25% of well-staged patients treated with 6 months of VAC (Slayton et al '84). A report of 35 cases of germ cell tumors, half of which were advanced stage or recurrent or progressive disease, demonstrated a 97% sustained remission at 10 months to 54 months after the start of a combination of BEP (Williams et al '94). BEP has replaced radiation therapy.

**Ovarian epithelial cancer**, fallopian tube cancer (FTC), and primary peritoneal cancer (PPC). Regardless of the site of origin, the hallmark of these cancers is their early peritoneal spread of metastases. The inclusion of FTC and PPC within the ovarian epithelial cancer designation has been generally accepted since 2000 because of much evidence that points to a common Müllerian epithelium derivation and similar management of these three neoplasms, that usually arise from precursor lesions that originate in the fimbriae of the fallopian tubes (Dubae et al '14). Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies, with 50% of all cases occurring in women older than 65 years. It is the fifth most frequent cause of cancer death in women (Yancik et al '93). CA-125 levels and histology are used to diagnose epithelial ovarian cancer (Atack et al '86). The following tests and procedures may be used in the diagnosis and staging of ovarian epithelial, fallopian tube, or primary peritoneal cancer: Physical exam and history. Pelvic exam. CA-125 assay. Ultrasound exam (pelvic or transvaginal). Computed tomography (CT) scan. Positron emission tomography (PET) scan. Magnetic resonance imaging (MRI). Chest x-ray. Biopsy. If the tumor is grade III, densely adherent, or stage IC, the chance of relapse and death from ovarian cancer is as much as 30 (Kolomainen et al '03).

### Staging for Carcinoma of the Ovary

Stage	Description
Stage I	Growth limited to the ovaries or fallopian tubes
Stage IA	Growth limited to one ovary; no ascites. No tumor on the external surface; capsule intact.
IB	Tumor present on the external surface, or capsule ruptured, or both. Growth limited to both ovaries; no ascites. No tumor on the external surface; capsule intact.

IC	Tumor present on the external surface, or capsule, ruptured, or both. Tumor either stage IA or IB, but with ascites present or with positive peritoneal washings. Tumor limited to one or both ovaries or fallopian tubes, with any of the following: IC1: Surgical spill. IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface. IC3: Malignant cells in the ascites or peritoneal washings.
Stage II IIA IIB	Growth involving one or both ovaries with pelvic extension. Extension or metastases to the uterus or tubes or primary peritoneal cancer. Extension and/or implants on the uterus and/or fallopian tubes and/or ovaries. Extension to other pelvic intraperitoneal tissues.
Stage III IIIA1 IIIA2 IIIB IIIC	Growth involving one or both ovaries with intraperitoneal metastases outside the pelvis or positive retroperitoneal nodes. Tumor limited to the pelvis with histologically proven malignant extension to small bowel or omentum. Positive retroperitoneal lymph nodes only (cytologically or histologically proven): Metastasis up to 10mm Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes Macroscopic peritoneal metastases beyond the pelvis $\leq 2$ cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes. Macroscopic peritoneal metastasis beyond the pelvis $> 2$ cm in greatest dimension, with or without metastasis to the retroperitoneal nodes.
Stage IV IVA IVB	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastases indicate stage IV. Pleural effusion with positive cytology. Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity).

Source: Young '90: Table 33-1; Pg. 271. Prat et al '14

**Treatment** includes surgery and often chemotherapy and targeted therapy. **Surgery** usually involves removal of both ovaries and fallopian tubes (bilateral salpingo-oophorectomy), the uterus (hysterectomy), and the omentum (fatty tissue attached to some of the organs in the belly), along with biopsies of the peritoneum (lining of the abdominal cavity). Additional abdominal organs may be removed in women with advanced disease, whereas only the involved ovary and fallopian tube may be removed in younger women with very early-stage tumors who want to preserve fertility. The goal of surgery is to remove as much of the tumor as possible, referred to as debulking, and stage the cancer. More accurate surgical staging (microscopic examination of tissue from different parts of the pelvis and abdomen) has been associated with better outcomes among patients with early-stage disease. For advanced disease, **chemotherapy** administered directly into the abdomen improves survival, although the risk for side effects, including hair loss, is high. Targeted drugs can sometimes be used after other treatments to shrink tumors or slow growth of advanced cancers. The 5-year relative survival rate for ovarian cancer is only 48% because most patients (59%) are diagnosed with distant-stage disease, for which survival is 29%. For the 15% of patients diagnosed with localized disease, 5-year survival is 92%. Five-year survival is twice as high in women younger than age 65 (60%) than in those 65 and older (31%) (ACS '20 :21, 22).

Treatment of early ovarian cancer includes surgery alone, or **surgery followed by chemotherapy**. In the United States, except for the most favorable subset of patients (those with stage IA well-differentiated disease), evidence based on double-blinded, randomized, controlled trials with total mortality endpoints supports adjuvant treatment with cisplatin, carboplatin, and paclitaxel. Both RFS and OS were significantly improved; 5-year survival figures were 79% with adjuvant chemotherapy versus 70% without adjuvant chemotherapy (Colombo et al '03). OS for three cycles (81%) versus six cycles (83%) (Bell et al '06). Radiation therapy and alkylating agents have been abandoned since the adoption of carboplatin and paclitaxel (Bolis et al '95). Overall, approximately 80% of patients diagnosed with ovarian epithelial cancer, fallopian tube cancer (FTC), and primary peritoneal cancer (PPC) will relapse after first-line platinum-based and taxane-based chemotherapy and may benefit from subsequent therapies (Ozols et al '03). For patients whose disease recurs after six months of platinum therapy, more platinum therapy is advised. For patients who progress before cessation of induction therapy (platinum refractory) or within 6 months after cessation of induction therapy (platinum resistant), platinum therapy is generally not useful as part of the treatment plan. The PFS of 8.6 months with the gemcitabine plus carboplatin combination was significantly superior to 5.8 months for carboplatin alone (Raja et al '13). The median PFS for the carboplatin-plus-pegylated-liposomal-doxorubicin arm was 11.3 months versus 9.4 months for the carboplatin-plus-paclitaxel arm (Pujade-Lauraine et al '10). Carboplatin plus paclitaxel has been considered the standard regimen for platinum-sensitive recurrence in the absence of residual neurological toxic effects. Although OS was similar, median PFS for patients receiving bevacizumab was 12.4 months versus 8.4 months for those receiving only gemcitabine plus carboplatin (Aghajanian et al '12). 19 Similarly, PFS was longer in the olaparib arm; median 8.4 months versus 4.8 months, OS was unaffected. PFS and significantly favored olaparib 19.1 months (95% CI, 16.3–25.7) more than placebo 5.5 months (Pujade-Lauraine et al '17).

The treatment of advanced disease may include the addition of bevacizumab, poly (ADP-ribose) polymerase (PARP) inhibitors to induction and/or consolidation therapy or other clinical trials. The role of surgery for patients with stage IV disease is unclear, but in most instances, the bulk of the disease is intra-abdominal, and surgical procedures similar to those used in the management of patients with stage II and III disease are applied. A literature review showed that patients with optimal cytoreduction had a median survival of 39 months compared with survival of only 17 months in patients with suboptimal residual disease (Hoskins '93). Only complete surgical resection had an independent effect on survival (Horowitz et al '15). In one study, median OS was 39.3 months for the control group, 38.7 months for the **bevacizumab**-initiation group, and 39.7 months for the bevacizumab-throughout group. In another median PFS was 17.3 months in the control group and 19 months in the bevacizumab group. In a follow-up study, there was no significant difference with 44.6 months in patients on standard chemotherapy versus 45.5 months (44.2–46.7) in patients receiving bevacizumab with the chemotherapy induction, and then completing 1 year of bevacizumab maintenance (Oza et al '15). Nonetheless, based on these two studies, the U.S. Food and Drug Administration (FDA) approved bevacizumab in the first-line setting, both during induction and as consolidation therapy.

**PARP** is a family of enzymes involved in base-excision repair of DNA single-strand breaks. In patients with homologous recombination deficiency, including patients with germline *BRCA1* or *BRCA2* (*gBRCA*) mutations or with nongermline homologous recombination deficiency–positive tumors, the inhibition of PARP results in the production of double-strand breaks of DNA. Human DNA repair mechanisms largely rely on one intact copy of the gene. Cells with a double-strand break are usually targeted for cell death. This susceptibility of *BRCA*-deficient or *BRCA*-

mutant cells to PARP inhibition, has spurred the clinical development of this class of agents. Initially, these agents were tested in women who had been pretreated with chemotherapy (Bryant et al '05). After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with **olaparib** than with a placebo, at 3 years, 60% vs. 27%. Grades 3 and 4 adverse events were present in 39% of the patients who received olaparib versus 18% who received a placebo (Moore et al '18). Median PFS of 21.9 months versus 10.4 months favoring the niraparib compared with the placebo. 53 Median PFS was 23.5 months for the veliparib throughout arm versus 17.3 months for the chemotherapy-alone arm (Coleman et al '19). PFS of 22.1 months for the bevacizumab-plus-olaparib group versus 16.6 months for the bevacizumab-alone maintenance group (Ray-Coquard et al '19). PARP inhibitors show slightly better results in the BCRA mutation groups, but are far more effective at treating ovarian tumors than bevacizumab.

**Carcinoma of the endometrium** is the most common gynecologic malignancy and makes up 6% of all malignant tumors in women. While the incidence of cervix carcinoma is decreasing in the United States, the incidence of endometrial carcinoma has been steadily increasing since the 1970s. Twice as many endometrial carcinomas are now diagnosed as are cervix cancers. The American Cancer Society estimates approximately 37,000 new cases of endometrial carcinoma in 1987 and approximately 3,000 deaths (Young '90: 281). In 2020, an estimated 65,620 cases of cancer of the uterine corpus (body of the uterus) will be diagnosed in the US and 12,590 women will die from the disease. Cancer of the uterine corpus is often referred to as endometrial cancer because more than 90% of cases occur in the endometrium (lining of the uterus). From 2007 to 2016, the incidence rate increased by about 1% per year among white women and by about 2% per year among black women. From 2008 to 2017, the death rate for cancer of the uterine corpus increased by about 2% per year among both white women and black women (ACS '20: 28). The majority of cases are diagnosed at an early stage and are amenable to treatment with surgery alone. However, patients with pathologic features predictive of a high rate of relapse and patients with extrauterine spread at diagnosis have a high rate of relapse despite adjuvant therapy. 2

The **endometrium** is the inner lining of the uterus and has both functional and basal layers. The functional layer is hormonally sensitive and is shed in a cyclical pattern during menstruation in reproductive-age women. Both estrogen and progesterone are necessary to maintain a normal endometrial lining. However, factors that lead to an excess of estrogen, including obesity and anovulation, lead to an increase in the deposition of the endometrial lining. These changes may lead to endometrial hyperplasia, and, in some cases, endometrial cancer. Whatever the cause, a thickened lining will lead to sloughing of the endometrial tissue through the endometrial canal and into the vagina. As a result, heavy menstrual bleeding or bleeding after menopause are often the initial signs of endometrial cancer. According to American Cancer Society research, an estimated 70% of uterine corpus cancers are attributable to excess body weight and insufficient physical activity, and thus potentially preventable. Obesity and abdominal fatness substantially increase the risk of uterine cancer, partly by increasing the amount of circulating estrogen, which is a strong risk factor. Other factors that increase estrogen exposure include the use of postmenopausal estrogen alone (estrogen plus progestin does not appear to increase risk), late menopause, and a history of polycystic ovary syndrome. Tamoxifen, a drug used to prevent breast cancer, increases risk slightly because it has estrogen-like effects on the uterus. Medical conditions that increase risk include Lynch syndrome and type 2 diabetes. Pregnancy and use of oral contraceptives or intrauterine devices are associated with reduced risk (ACS '20: 28). Known risk factors include obesity, due to increased bio-availability of estrogen. Diabetes has been associated with 2.8 percent risk. Polycystic ovarian disease has been associated with an increased risk of endometrial carcinoma. Advanced age and late menopause are also risk factors.

There is evidence that exogenous estrogen administration in the increased incidence of endometrial carcinoma. The rise of endometrial carcinoma increases with the dose and duration of estrogen use. In contrast, endometrial carcinoma risk is decreased by progestogen administration. Indeed, evidence suggests that the use of combination oral contraceptives can decrease the risk of endometrial carcinoma. This effect increases with the duration of use and appears to persist some 5 years after discontinuation of birth control (Young '90: 281, 282).

Women with endometrial carcinoma usually present with **abnormal bleeding**. The most common symptom is abnormal uterine bleeding or spotting, especially in postmenopausal women. Pain during urination, intercourse, or in the pelvic area and non-bloody vaginal discharge can also be symptoms. There is no recommended screening test for women at average risk; however, most cases (67%) are diagnosed at an early stage because of postmenopausal bleeding. Women are encouraged to report any unexpected bleeding or spotting to a clinician. The American Cancer Society recommends that women with known or suspected Lynch syndrome be offered annual screening with endometrial biopsy and/or transvaginal ultrasound beginning at age 35 (ACS '20: 28). While 15% to 20% of women with endometrial carcinoma will be identified from **Papanicolaou smear**, diagnosis generally rests on more extensive tissue evaluation, including either biopsy, fractional dilatation and curettage, endometrial brush, or jet-wash techniques. Cystoscopy should be performed if there is any evidence of bladder dysfunction and proctosigmoidoscopy, and barium enema is used if GI tract symptoms are present. Lymphangiography is useful to define involved para-aortic lymph nodes in high risk patients. The following procedures may be used to detect endometrial cancer: Transvaginal ultrasound. Endometrial biopsy. Pelvic exam. Dilatation and curettage (D&C). Hysteroscopy. To definitively diagnose endometrial cancer, a procedure that directly samples the endometrial tissue is necessary. The Pap smear is not a reliable screening procedure for the detection of endometrial cancer, even though a retrospective study found a strong correlation between positive cervical cytology and high-risk endometrial disease (i.e., high-grade tumor and deep myometrial invasion)(DuBeshter et al '91). There is a statistically significant association between malignant cytology and increased risk of nodal disease (Larson et al '94).

The frequency of the disease by stage; Stage I, 74%; Stage II, 13%; Stage III, 9%; Stage IV, 3%. Five year survival by stage; Stage I, 76%; Stage II, 50%; Stage III, 30%; Stage IV, 9%. The vast majority of endometrial carcinomas are adenocarcinoma in about 67% of patients, 13% are adenosquamous carcinomas. Rarely <1% present with purely squamous carcinoma of the endometrium. Also rare <1% are clear cell carcinomas associated with a particularly poor prognosis (Young '90: 283). One report found progesterone receptor levels to be the single most important prognostic indicator of 3-year survival in clinical stages I and II disease. Patients with progesterone receptor levels above 100 had a 3-year disease-free survival (DFS) of 93%, compared with a 36% DFS for a level below 100. After adjusting for progesterone receptor levels, only cervical involvement and peritoneal cytology were significant prognostic variables (Ingram et al '89). Other factors predictive of poor prognosis include the following: A high S-phase fraction. Aneuploidy. Absence of *PTEN*. *PIK3CA* mutation status. *P53* mutation status. Her-2/neu over-expression. Oncogene expression (e.g., over-expression of the *Her-2/neu* oncogene has been associated with a poor overall prognosis)(Binder et al '14).

Endometrial cancers are classified as one of the following two types: Type 1 may arise from complex atypical hyperplasia and is pathogenetically linked to unopposed estrogenic stimulation. Type 2 develops from atrophic endometrium and is not linked to hormonally driven pathogenesis. The most common type of endometrial cancer is endometrioid adenocarcinoma,

sometimes with squamous differentiation, comprising 75% of endometrial cancers. Mixed, defined as two carcinomatous types, make up 10% of total. 4% are clear cell, noted in ovaries and fallopian tubes, the prognosis is worse. Carcinosarcoma 3%, mucinous 1%, squamous cell >1% and undifferentiated >1%. *PTEN* mutations are more common in type 1 endometrial cancers; *p53* and *Her-2/neu* overexpression are more common in type 2 endometrial cancers, although some overlap exists (Talhok et al '15). Well-differentiated tumors tend to limit their spread to the surface of the endometrium; myometrial invasion is less common. Myometrial invasion occurs much more frequently in patients with poorly differentiated tumors and is frequently a harbinger of lymph node involvement and distant metastases (Amin et al '17).

### Staging for Carcinoma of the Endometrium

Stage	Description
Stage 0	Carcinoma <i>in situ</i>
Stage I	Carcinoma confined to the corpus.
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
Stage II	Extension to cervix only, does not extend beyond the uterus
Stage III	Local and/or regional spread of the tumor, but does not exceed pelvis
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or periaortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive periaortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Extension beyond true pelvis or invading bladder, bowel mucosa, rectum and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Source: Young '90: Table 33-5; Pg. 282; Amin et al '17

Patients with endometrial cancer who have localized disease are usually cured. Best results are obtained with one of two standard treatments: **Hysterectomy with bilateral salpingo-oophorectomy with or without lymph node dissection**. Hysterectomy with bilateral salpingo-oophorectomy and adjuvant radiation therapy (when deep invasion of the myometrial muscle [more than 50% of the myometrium] or grade 3 tumor with myometrial invasion is present). Patients with regional and distant metastases are rarely cured, although they are occasionally responsive to standard hormone therapy. Uterine cancers are usually treated with surgery (e.g., hysterectomy), radiation, hormones, and/or chemotherapy, depending on the stage of disease. Immunotherapy and targeted therapy drugs might be options in certain situations as well. The 5-year relative survival rate for uterine cancer is 84% for white women and 62% for black women, partly because white women are more likely to be diagnosed with early-stage disease (69% versus 54%); however, survival is substantially lower for black women for every stage of diagnosis (ACS '20: 28). The treatment of **adenomatous hyperplasia** can be either hysterectomy or medical management depending on the patient's desire for childbearing. Adolescents or women desiring children can be managed by continuous combination estrogen-

progesterone contraceptive pills. When childbirth is desired, ovulation can be produced with clomiphene. Premenopausal women may be maintained on high-dose progestogens or may have hysterectomy. The hysterectomy is highly advised to prevent re-occurrence of cancer. Patients with Stage I uncomplicated endometrial carcinoma are effectively managed with **total abdominal hysterectomy and bilateral salpingo-oophorectomy**. For patients with Stage IB disease, preoperative intracavitary irradiation is generally utilized, followed by total abdominal hysterectomy with 5 to 10 year survival figures as high as 83%. Once disadvantages has extended outside the uterus but is still confined to the pelvis, management generally involve irradiation and surgery. Five year survival in the range of 80% has been reported with the use of external-beam pelvic irradiation, intracavitary brachytherapy, and total abdominal hysterectomy and bilateral salpingo-oophorectomy. Stage I & II Grade 3 serous, clear cell, and carcinosarcoma tumors are treated with postoperative chemotherapy with or without radiation. Patients with Stage IV disease are generally treated with surgery, radiation, chemotherapy, hormone therapy and/or biologic therapy (Martin-Hirsch et al '11).

Nonhormonal chemotherapy appears to have only modest activity of >20% for cyclophosphamide, nitrogen mustard, 5-FU, Adriamycin, bleomycin, hexamethylmelamine, and cisplatin. **Doxorubicin** (Adriamycin) has shown the most activity, Adriamycin, 60 mg/m<sup>2</sup> IV every 3 weeks, has produced a 37% response rate in 43 patients, 26% of whom had clinically complete regression of disease. **Cisplatin** also appears to produce a significant response rate (46%) when used at doses of 10 mg/m<sup>2</sup> IV every 4 weeks (Young '90: 283-285). In a nonrandomized Gynecologic Oncology Group (GOG) study of patients with stage I or II carcinosarcomas, patients who underwent pelvic radiation therapy had a significant reduction in recurrences within the radiation treatment field but no improvement in survival (Hornback et al '86). One nonrandomized study that predominantly included patients with carcinosarcomas appeared to show benefit for adjuvant therapy with cisplatin and doxorubicin (Peters et al '89).

Several randomized trials have confirmed improved survival when adjuvant chemotherapy is used instead of radiation therapy. Doxorubicin was historically the most active anticancer agent employed, with useful but temporary responses obtained in as many as 33% of patients with recurrent disease. Paclitaxel, in combination with platinum chemotherapy or as a single agent, also has significant anticancer activity (Ball et al '96). A three-drug regimen of doxorubicin, cisplatin, and paclitaxel with granulocyte-colony stimulating factor (G-CSF) was significantly superior to cisplatin and doxorubicin, as shown by the following: Response rate was 57% with the three-drug regimen, compared with 34% with the cisplatin and doxorubicin regimen. PFS was 8.3 months with the three-drug regimen, compared with 5.3 months with the cisplatin and doxorubicin regimen. OS was 15.3 months with the three-drug regimen, compared with 12.3 months with the cisplatin and doxorubicin regimen. The superior regimen (doxorubicin, cisplatin, and paclitaxel with G-CSF) was associated with 12% grade 3 and 27% grade 2 peripheral neuropathy. 5, 6 The combination of paclitaxel, doxorubicin, and cisplatin (TAP) with G-CSF is non-inferior to carboplatin and paclitaxel (Miller et al '12). 5-year survival rates of 55% for cisplatin and doxorubicin vs. 42% for whole-abdominal radiation (Randall et al '06). Patients with inoperable disease caused by tumor that extends to the pelvic wall may be treated with a combination of chemotherapy and radiation therapy. The usual approach for radiation therapy is to use a combination of intracavitary and external-beam radiation therapy (Wegener et al '10).

**Synthetic progestational agents** have been the most commonly used systemic treatment and produce response rates of approximately 35% in endometrial cancer. Well-differentiated tumors

respond best, however receptor positivity is a better correlate than grade. Approximately 88% of progesterone-responsive lesions were positive and 94% of progesterone failures were progesterone-receptor negative. Commonly used agents include hydroxyprogesterone (Delalutin, deoxyprogesterone (Provera, and the oral agent megestrol (Megace), with response rates up to 30%. Tamoxifen also appears to induce progesterone-receptor activity. Tamoxifen (20 mg bid) yields a response rate of 20% in patients who do not respond to standard progesterone therapy (Quinn et al '89). Endometrial cancers often show alterations in the AKT-PI3K pathway, making mTOR inhibitors an attractive choice for clinical study in patients with metastatic or recurrent disease. A phase II study of the combination of everolimus and letrozole showed a response rate of 32% (Slomovitz et al '15). Bevacizumab was utilized as a single agent in a phase II trial; the overall response rate was 13.5% (Aghajanian et al '11).

The reported incidence of Gestational Trophoblastic Disease (GTD) varies widely worldwide, from a low of 23 per 100,000 pregnancies (Paraguay) to a high of 1,299 per 100,000 pregnancies (Indonesia). However, at least part of this variability is caused by differences in diagnostic criteria and reporting. The reported incidence in the United States is about 110 to 120 per 100,000 pregnancies. The reported incidence of choriocarcinoma, the most aggressive form of GTD, in the United States is about 2 to 7 per 100,000 pregnancies (Altieri et al '02). **Gestational choriocarcinoma** accounts for less than 1% of female gynecologic malignancies in the United States, and is highly curable. In 1983 there were only 24 reported deaths in trophoblastic disease centers. Trophoblastic neoplasias are categorized as hydatidiform mole, invasive mole, or choriocarcinoma. **Hydatiform Mole (HM)** is defined as products of conception that show gross cyst-like swellings of the chorionic villi that are caused by an accumulation of fluid. There is disintegration and loss of blood vessels in the villous core. On ultrasound examination, complete moles rarely reveal a fetus or amniotic fluid. Partial moles usually show a fetus, which may even be viable, and amniotic fluid is visible. Complete HMs have a 15% to 25% risk of developing into an invasive mole, but transformation to malignancy is much more rare (<5%) in the case of partial moles. **Invasive moles** (chorioadenoma destruens) are locally invasive, rarely metastatic lesions characterized microscopically by trophoblastic invasion of the myometrium with identifiable villous structures. **Choriocarcinoma** is a malignant tumor of the trophoblastic epithelium. Uterine muscle and blood vessels are invaded with areas of hemorrhage and necrosis. **PSTT disease** is the result of a very rare tumor arising from the placental implantation site and resembles an exaggerated form of syncytial endometritis, that is resistant to chemotherapy. **ETT** is an extremely rare gestational trophoblastic tumor. Although originally termed *atypical choriocarcinoma*, it appears to be less aggressive (Palmer et al '08).

**Molar pregnancies** are associated with first trimester bleeding, extopic pregnancies or threatened abortions. The uterus is inappropriately large for the duration of the pregnancy and human chorionic gonadotropin (HCG) titers are higher than usual. HCG consists of an alpha and a beta chain. The alpha chain is cross-reactive to luteinizing hormone and a radioimmunoassay of the beta subunit of HCG is ordinarily required. Fetal heart sounds and fetal parts are not present. The diagnosis is not usually made until grape-like villi are expelled from the uterus. Patients with evidence of myometrial invasion require curettage or hysterectomy for invasive moles (chorioadenoma destruens) Such patients and those with frank choriocarcinoma should be evaluated by chest films, brain scans, and liver scans to define the extent of metastatic spread, if any. Common metastatic sites are lungs (80%), vagina (30%), pelvis (20%), liver (10%), brain (10%) and bowel, kidney and spleen (<5%). GTDs contain paternal chromosomes and are placental, rather than maternal, in origin. The most common presenting symptoms are vaginal bleeding and a rapidly enlarging uterus, and GTD should be considered whenever a

premenopausal woman presents with these findings. Because the vast majority of GTD types are associated with elevated human chorionic gonadotropin (hCG) levels, an hCG blood level and pelvic ultrasound are the initial steps in the diagnostic evaluation. In addition to vaginal bleeding and uterine enlargement, other presenting symptoms or signs may include the following: Pelvic pain or sensation of pressure. Anemia. Hyperemesis gravidarum. Hyperthyroidism (secondary to the homology between the beta-subunits of hCG and thyroid-stimulating hormone (TSH), which causes hCG to have weak TSH-like activity). Preeclampsia early in pregnancy (Ngan et al '12).

### Staging of Gestational Trophoblastic Neoplasms

Stage	Description
Stage 0	Molar pregnancy A Low risk B High risk
Stage I	Confined to uterine corpus.
Stage II	Extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament).
Stage III	Extends to the lungs.
Stage IV	Distant metastases.

Source: Young '90: Table 33-8; Pg. 290 Amin et al '17

**Hydatidiform** moles are characterized by clusters of villi with hydropic changes, hyperplasia of the trophoblast, and absence of fetal vessels. Invasive moles differ only in the presence of invasion into the uterine myometrium. Choriocarcinomas consist of anaplastic trophoblastic tissue with cytotrophoblast and syncytiotrophoblast elements, and no identifiable villi. Patients with hydatidiform moles require evacuation of the uterus by suction curettage and oxytocin. After, evacuation, patients generally require dilatation and curettage. Patients then have weekly beta-HCG serum assays and in the vast majority (80%) the beta-HCG titer steadily declines within 8 to 10 weeks of evacuation, and menses is delayed for at least a year. Patients found to have invasive mole at curettage generally are treated with hysterectomy. Approximately 50% of patients with choriocarcinoma develop malignancy after abortion, ectopic pregnancy or, uncommonly, after the delivery of a normal infant. Patients with hydatidiform moles receive chemotherapy if there is a plateau in the weekly levels of beta-HCG, a rise in their beta-HCG titer, or the development of metastases. Patients with invasive mole or choriocarcinoma or metastases require immediate chemotherapy. Studies have shown that a single course of prophylactic dactinomycin or methotrexate can decrease the risk of a postmolar gestational trophoblastic disease (GTD) (Uberti et al '09).

**Single-agent chemotherapy** has been commonly used. Intramuscular methotrexate, 0.4 mg/kg daily for 5 days every 2 weeks, or IV actinomycin D, 10 to 12µg/kg daily for 5 days every 2 weeks as necessary. There is less toxicity with intramuscular methotrexate, 1 mg/kg daily for 4 days, with intramuscular leucovorin, 0.1 mg/kg on alternate days, is associated with a high cure rate and low toxicity. Intermittent courses of therapy are generally continued until the beta-HCG tier becomes undetectable for 3 consecutive weeks. Essentially 100% of low-risk gestational trophoblastic neoplasms will be cured by this approach. Patients with high-risk tumors are initially treated with combination chemotherapy. The most common regimen used includes intramuscular methotrexate, 0.3 mg/kg, IV actinomycin D, 10µg/kg and chlorambucil, 10 mg orally daily for 5 days, with repeated courses as necessary. Excellent results have been achieved with testicular carcinoma regimens such as vinblastine, bleomycin and cisplatin. Another active

agent, VP-16 (Etoposide), has a response rate of 19% in drug-resistant patients. Approximately 10% of patients present with brain metastases (Young '90: 289-291). A systematic literature review revealed only one randomized controlled trial (and no high-quality trials)—conducted in the 1980s—comparing multiagent chemotherapy regimens for high-risk GTN. In the trial, only 42 women were randomly assigned to either a CHAMOMA regimen (i.e., methotrexate, folinic acid, hydroxyurea, dactinomycin, vincristine, melphalan, and doxorubicin) or MAC (i.e., methotrexate, dactinomycin, and chlorambucil) (Deng et al '09). There was substantially more life-threatening toxicity in the CHAMOMA arm and no evidence of higher efficacy. EMA/CO: Etoposide, methotrexate with folinic acid rescue, dactinomycin, cyclophosphamide, and vincristine, is the most commonly used regimen, with a complete remission rate of 78%. Salvage treatment with cisplatin-containing regimens (with or without resection of metastases), yields a long-term cure rate of 86.2% (Bower et al '97). The addition of cisplatin plus etoposide EP/EMA: Etoposide and cisplatin with etoposide, methotrexate, and dactinomycin, resulted in a 9% improvement was reported in the survival results of these high-risk patients. Among the women who had an intact uterus, about 50% of them retained their fertility (Alifrangis et al '13).

## 11. Cancer of the vulva and vagina

Approximately 2% of all gynecologic malignancies are **carcinomas involving the vagina**. Estimated new cases and deaths from vaginal and other female genital cancer in the United States in 2020: New cases: 6,230. Deaths: 1,450 (ACS '20). Squamous cell carcinoma (SCC) accounts for approximately 80% to 90% of vaginal cancer cases and adenocarcinoma accounts for 5% to 10% of vaginal cancer cases (Eifel et al '19). The vast majority of these carcinomas are seen in older age groups and squamous in origin. SCC of the vagina is associated with a high rate of infection with oncogenic strains of HPV and has many risk factors in common with SCC of the cervix. HPV infection has also been described in a case of vaginal adenocarcinoma (Daling et al '02). Adenocarcinomas of the vagina in young women of the median age of 19 exposed to diethylstilbesterol (DES) *in utero*, peaked during the 1970s when they comprised 5% of all vaginal cancers, it is extremely rare now. Women who have had a hysterectomy for benign, premalignant, or malignant disease are at risk of vaginal carcinomas. In a retrospective series of 100 women studied over 30 years, 50% had undergone hysterectomy before the diagnosis of vaginal cancer. In the post-hysterectomy group, 31 of 50 women (62%) developed cancers limited to the upper third of the vagina. In women who had not previously undergone hysterectomy, upper vaginal lesions were found in 17 of 50 women (34%) (Salani et al '11). Approximately 20% of patients present with positive nodes (Young '90: 287, 288).

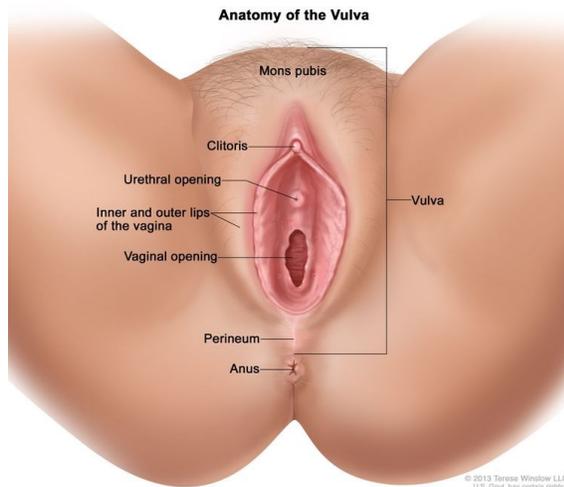
### Staging of Vaginal Cancer

Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall.
Stage III	The carcinoma as extended to the pelvic wall.
Stage IV	The carcinoma has extended beyond the true pelvic or has involved the mucosa of the bladder or rectum; bullous edemas as such does not permit a case to be allotted to stage IV.

Source: Amin et al '17

The diagnosis of carcinoma of the vagina is ordinarily made during speculum examination. Biopsies confirm the diagnosis. If the cervix is intact, biopsies are mandatory to rule out a primary carcinoma of the cervix. Carcinoma of the vulva should also be ruled out. The following diagnostic procedures may be used: history and physical exam, pelvic exam, cervical cytology (Pap smear), HPV test and colposcopy. Rare tumors of the vagina include melanoma, leiomyosarcoma, and a unique tumor of childhood, sarcoma botryoides. Because of the high frequency of disease in the upper vagina and close proximity of the bladder and rectum, many carcinomas of the vagina are not surgically resectable. Radiation may induce damage to nearby organs (Frank et al '05). Carcinoma *in situ* and carcinomas limited to the vaginal wall (Stage I) are generally treated with surgery or intra-cavitary or interstitial radiation therapy. Cesium-137 needles are commonly used. When lesions are located high in the vagina, intrauterine tandems and vaginal colpostats are used. Stage II patients are treated with surgery and/or brachytherapy ordinarily coupled with external irradiation to the parametrium and pelvic lymph nodes. For more advanced disease (Stages III and IV), irradiation with brachytherapy and external-beam approaches are used, but both pelvic tumor control and survival are significantly reduced (Eifel et al '19). Five-year-survival for Stage I and II carcinomas has generally been reported at 35%. Approximately 20% to 25% of Stage III patients survive 5 years, and rare 5 year survival is seen with Stage IV disease. Complications of therapy include rectovaginal and vesicovaginal fistulas, hemorrhagic cystitis or proctitis and rectal strictures. Clear cell carcinomas in Stage I may be treated with either radiation or surgery. Vaginal surgery with vaginal reconstruction has been performed by many in order to preserve ovarian function (Young '90: 287, 288).

Vaginal intraepithelial neoplasia (VaIN), the presence of noninvasive squamous cell atypia, is classified by the degree of involvement of the epithelium, as follows: VaIN 1 is defined as involvement of the upper one-third of the epithelial thickness. VaIN 2 is defined as involvement of the upper two-thirds of the epithelial thickness. VaIN 3 is defined as involvement of more than two-thirds of the epithelial thickness. VaIN 3 lesions that involve the full thickness of the epithelium are called carcinoma *in situ*. VaIN is associated with a high rate of human papillomavirus (HPV) infection and is thought to have an etiology that is similar to that of cervical intraepithelial neoplasia (CIN) (Smith et al '09). The cervix and vulva are carefully evaluated because vaginal carcinoma *in situ* is associated with other genital neoplasia, and in some cases, may be an extension of CIN. Vaginal carcinoma *in situ* is often multifocal and commonly occurs at the vaginal vault. Extent and type of surgical treatment is dependent on anatomic location, evidence of multi-focality, general patient comorbidities and other specific factors (e.g., anatomic distortion of vaginal vault from prior hysterectomy) (Krebs et al '89). Concurrent chemotherapy, using fluorouracil or cisplatin-based therapy, and radiation are sometimes advocated, based solely on extrapolation from cervical cancer management strategies (Samant et al '07). Evidence is limited to small case series and the incremental impact on survival and local control is not well defined. Local control is a problem with bulky tumors. Some investigators have also used concurrent chemotherapy with agents such as cisplatin, bleomycin, mitomycin-C, floxuridine, and vincristine without improved outcomes (Frank et al '05).



Approximately 4% of all gynecologic malignancies involve the vulva. There were an estimated 6,120 new cases and 1,350 deaths from vulvar cancer in the United States in 2020 (ACS '20). Invasive **carcinoma of the vulva** rarely occurs below the age of 40 years. Median age is 60 years. Predisposing illnesses include diabetes, obesity, hypertension and venereal diseases. Herpes simplex type II and human papilloma virus have been identified in vulvar cancers and vulvar condyloma. In many cases, the development of vulvar cancer is preceded by condyloma or squamous dysplasia. The prevailing evidence favors HPV infection as a causative factor in many genital tract carcinomas (Hampl et al '06).

Vulvar dysplasias appear to be antecedents to invasive epidermoid carcinoma. The labia are the usual site of disease in 70% of women. 20% of patients are diagnosed when their lesions are asymptomatic. The most common complaint is the presence of mass; less common are pain, bleeding and itching. The lesions are diagnosed by biopsy. Ninety percent of the invasive tumors are squamous carcinoma. Three percent of the tumors are basal cell carcinomas. Less commonly seen are adenocarcinoma of the Bartholin duct, Paget's disease, melanoma, and sarcomas. **Premalignant lesions** of the vulva are common, such as leukoplakia, hyperplastic dystrophy, with or without atypia, lichen sclerosus, mixed dystrophy, Paget's disease, with or without adenocarcinoma of the sweat glands, and carcinoma *in situ* (Young '90: 285, 286). The histologic classification of vulvar disease and precursor lesions of cancer of the vulva was developed by the International Society for the Study of Vulvovaginal Disease (ISSVD). **Non-neoplastic epithelial disorders of vulvar skin and mucosa** Lichen sclerosus (lichen sclerosus et atrophicus). Squamous cell hyperplasia (formerly hyperplastic dystrophy). Other dermatoses. **Vulvar intraepithelial neoplasia (VIN):** Low-grade squamous intraepithelial lesion (SIL) of the vulva (vulvar LSIL) encompasses flat condyloma or human papillomavirus effect. High-grade SIL (vulvar HSIL) was termed VIN, usual type in the 2004 ISSVD terminology. VIN, differentiated type. **Paget disease of the vulva:** Characteristic large pale cells in the epithelium and skin adnexa. **Other histologies:** Basal cell carcinoma. Langerhans cell histiocytosis. Malignant melanoma. Sarcoma. Verrucous carcinoma (Bornstein et al '16). Staging evaluation for vulvar cancer includes the following, as needed: Cystoscopy. Proctoscopy. X-ray examination of the lungs. Intravenous (IV) urography (also known as IV pyelography). Suspected bladder or rectal involvement must be confirmed by biopsy. FIGO and the American Joint Committee on Cancer have designated staging to define vulvar cancer; the FIGO system is most commonly used (Amin et al '17).

### Staging for Cancer of Vulva

Stage	Description
Stage 0	Carcinoma in situ
Stage I	Tumor confined to vulva;
IA	<2 cm or less in diameter confined to the vulva or perineum and with stromal invasion $\leq 1.0$ mmb, no nodal metastasis.
IB	Lesions >2 cm in size or with stromal invasion >1.0 mmb, confined to the vulva or perineum, with negative nodes.
Stage II	Tumor of any size with extension to adjacent perineal structures (lower third of

	urethra, lower third of vagina, anus) with negative nodes.
Stage III	Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with positive inguinofemoral lymph nodes.
IIIA(i)	With 1 lymph node metastasis ( $\geq 5$ mm).
IIIA(ii)	With 1–2 lymph node metastasis(es) ( $< 5$ mm).
IIIB(i)	With 2 or more lymph node metastases ( $\geq 5$ mm).
IIIB(ii)	With 3 or more lymph node metastases ( $< 5$ mm).
IIIC	With positive nodes with extracapsular spread.
Stage IV	Tumor invades other regional (upper 2/3 urethra, upper 2/3 vagina), or distant structures.
IVA(i)	Tumor invades any of the following: upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone.
IVA(ii)	Fixed or ulcerated inguinofemoral lymph nodes.
IVB	Any distant metastasis including pelvic lymph nodes.

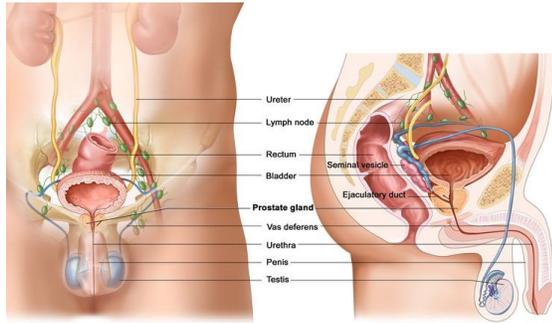
Source: Young '90: Table 33-6; pg. 286, Amin et al '17

Standard primary treatment for vulvar cancer is surgery. Radiation therapy is also given to patients with stage III or IV disease. Since the 1980s, the trend of surgical resection in patients with vulvar cancer has been toward more limited surgery, often combined with radiation therapy to minimize morbidity. In tumors clinically confined to the vulva or perineum, radical local excision with a margin of at least 1 cm has generally replaced radical vulvectomy; separate incision has replaced en bloc inguinal lymph node dissection; ipsilateral inguinal node dissection has replaced bilateral dissection for laterally localized tumors; and femoral lymph node dissection has been omitted in many cases (Eifel et al '19). Newer strategies have integrated surgery, radiation therapy, and chemotherapy and tailor the treatment to the extent of clinical and pathologic disease. Patterns of practice in combining these treatments vary (Shylasree et al '11). In one study the 6-year overall survival (OS) rate was 51% in the pelvic radiation arm versus 41% in the pelvic node resection arm. Vulvar cancer-specific mortality was statistically significantly lower in the pelvic radiation arm (29% in the pelvic radiation arm vs. 51% in the pelvic node resection arm) (Kunos et al '09). There is evidence that neoadjuvant chemoradiation therapy with 5-FU plus either cisplatin or mitomycin-C may convert patients to a more operable status (Shylasree et al '11).

Stage 0 and I are ordinarily managed by simple vulvectomy, the survival rate is approximately 100%. Patients with more extensive local disease require radical vulvectomy with dissection of groin nodes. Pelvic lymph node dissection is required only in patients who demonstrate inguinal or femoral node involvement. Five year survival of 75% has been achieved in patients without nodes compared with 42% with for patients with positive nodes. Tumors that invade bowel or bladder (Stage IV) are treated with radical vulvectomy and, if warranted, pelvic exenteration. Topical chemotherapy, usually 5-FU, has been utilized, three 7 day treatment courses of 5% 5-FU given two weeks apart. Topical trinitrochlorobenzene has also been used with similar results (Young '90: 285-287). Topical fluorouracil, recombinant interferon gamma, bleomycin, and trinitrochlorobenzene, have been largely abandoned because of high recurrence rates or intolerable local side effects, such as pain, irritation, and ulceration (Pepas et al '11). Among women with high-grade VIN, substantial response rates and acceptable tolerability were reported for topical imiquimod 5%, an immune-response modifier with activity in human papillomavirus types 6- and 11-associated vulvar condylomata. The complete response rates in patients were 36

of 62 in the combined imiquimod arm versus 0 of 42 in the combined placebo arm (Terlou et al '11).

## 10. Male neoplasia



**Adenocarcinoma of the prostate** has an annual incidence of 58 and 96 per 100,000 in white and black men, respectively, accounting for 75,000 new cases and 25,000 deaths in the United States in 1990. At autopsy in men over 50, the incidence ranged from 14% to 46% (Yagoda '90: 249). **Cancer of the male prostate gland** is fast becoming the most commonly diagnosed cancer in the USA and will overtake lung cancer as a leading cause of mortality in men. Current treatment for prostate cancer are

crude and produce a sad parallel with breast cancer – surgical prostatectomy plus chemical castration with antiandrogens for metastatic disease. The treatment is feminizing and not particularly effective. In the mid-1990s around 40,000 males a year in the USA died of prostate cancer and some quarter of a million had a diagnosis of this cancer. Some 30 percent of men over 50 years of age have clinically silent prostate cancer and this proportion escalates to over 50 percent of men over 80. In essence, most men, if they live long enough, develop prostate cancer (Greaves '00: 162, 163).

In 2020, an estimated 191,930 new cases of prostate cancer will be diagnosed in the US and 33,330 men will die from the disease. The incidence of prostate cancer is about 60% higher in blacks than in whites for reasons that remain unclear. Incidence rates for prostate cancer spiked dramatically in the late 1980s and early 1990s, in large part because of a surge in screening with the prostate-specific antigen (PSA) blood test. Likewise, the decline in rates that has occurred since around 2000, and accelerated in recent years, is likely due to reduced PSA screening, partly due to changes in guidelines. From 2007 to 2016, the rate decreased by 3.8% per year on average. The prostate cancer death rate has declined by 52%, from a peak of 39.3 (per 100,000) in 1993 to a low of 18.8 in 2017, although it appears to have stabilized in recent years. The rapid reduction in prostate cancer mortality is attributed to earlier detection through PSA testing and advances in treatment. Early-stage prostate cancer usually has no symptoms. More advanced disease shares symptoms with benign prostate conditions, including weak or interrupted urine flow; difficulty starting or stopping urine flow; the need to urinate frequently, especially at night; blood in the urine; or pain or burning with urination (Zelevsky et al '11: 1220-71). Late-stage prostate cancer commonly spreads to the bones, which can cause pain in the hips, spine, ribs, or other areas (ACS '20: 22, 23). The 5-year relative survival rate for men diagnosed in the United States from 2001 to 2007 with local or regional disease was 100%, and the rate for distant disease was 28.7%; a 99% survival rate was observed for all stages combined (ACS '12).

Well-established **risk factors** for prostate cancer are increasing age, African ancestry, a family history of the disease, and certain inherited genetic conditions (e.g., Lynch syndrome and *BRCA1* and *BRCA2* mutations). Black men in the US and the Caribbean have the highest documented prostate cancer incidence rates in the world. Genetic studies suggest that strong familial predisposition may be responsible for 5%-10% of prostate cancers. There is accumulating evidence that smoking increases the risk of fatal prostate cancer and excess body weight increases risk of aggressive and fatal prostate cancer. No organization presently endorses

routine prostate cancer screening for men at average risk because of concerns about the high rate of overdiagnosis (detecting disease that would never have caused symptoms or harm), along with the high potential for serious side effects associated with prostate cancer treatment. Rather, many organizations recommend an “informed decision-making” approach whereby men are educated about screening and encouraged to make a personal choice. The American Cancer Society recommends that beginning at age 50, men who are at average risk of prostate cancer and have a life expectancy of at least 10 years have a conversation with their health care provider about the benefits and limitations of PSA testing and make an informed decision about whether to be tested based on their personal values and preferences. Men at high risk of developing prostate cancer (black men and those with a close relative diagnosed with prostate cancer before the age of 65) should have this discussion beginning at age 45, and men at even higher risk (those with several close relatives diagnosed at an early age) should have this discussion beginning at 40 (ACS '20: 23).

Needle biopsy is the most common method used to diagnose prostate cancer. Most urologists now perform a transrectal biopsy using a bioptic gun with ultrasound guidance. Less frequently, a transperineal ultrasound-guided approach can be used in patients who may be at increased risk of complications from a transrectal approach (Web et al '93). Over the years, there has been a trend toward taking eight to ten or more biopsy samples from several areas of the prostate with a consequent increased yield of cancer detection after an elevated PSA blood test (Zelevsky et al '11:1220-71). **Digital-rectal examination** is the most sensitive and specific clinical diagnostic test for prostate adenocarcinoma, particularly for early-stage disease. Pathologic confirmation is obtained by needle biopsy via the rectum, perineum, or urethra. PSA is abnormal in more than 80% of cases presenting with metastases, but after hormone manipulation an elevated level will persist in less than 20% to 60%. Additional required tests are blood urea, nitrogen, creatinine, alkaline phosphatase, 12-channel screen, complete blood count, prothrombin time, and partial thromboplastin time, radionuclide bone scan followed by films of abnormal areas, chest film, intravenous urogram, and pelvic CT scans (Yagoda '90: 249-251). The higher the level of PSA at baseline, the higher is the risk for metastatic disease or subsequent disease progression. Elevations of serum acid phosphatase are associated with poor prognosis in both localized and disseminated disease. Several nomograms have been developed to predict outcomes either before radical prostatectomy (Stephenson et al '06) or after radical prostatectomy (Stephenson et al '05) with intent to cure. In a retrospective analysis of nearly 2,000 men who had undergone radical prostatectomy with curative intent and who were followed for a mean of 5.3 years, 315 men (15%) demonstrated an abnormal PSA of 0.2 ng/mL or higher, which is considered evidence of biochemical recurrence. Among these 315 men, 103 (34%) developed clinical evidence of recurrence. The median time to the development of clinical metastasis after biochemical recurrence was 8 years. After the men developed metastatic disease, the median time to death was an additional 5 years (Pound et al '99). Androgen deprivation therapy can decrease the serum level of PSA independent of tumor response. Clinicians, therefore, cannot rely solely on the serum PSA level to monitor a patient's response to hormonal therapy; they must also follow clinical criteria (Ruckle et al '94).

More than 95% of primary prostate cancers are adenocarcinomas. Prostate adenocarcinomas are frequently multifocal and heterogeneous in patterns of differentiation. Prostatic intraepithelial neoplasia ([PIN] noninvasive atypical epithelial cells within benign appearing acini) is often present in association with prostatic adenocarcinoma. PIN is subdivided into low grade and high grade. The high-grade form may be a precursor for adenocarcinoma (Nelson et al '03). Several rare tumors account for the remaining few percentages of cases. These include the following:

Small-cell tumors. Intralobular acinar carcinomas. Ductal carcinomas. Clear cell carcinomas. Mucinous carcinomas. The histologic grade of prostate adenocarcinomas is usually reported according to one of the variations of the Gleason scoring system, which provides a useful, albeit crude, adjunct to tumor staging in determining prognosis (Zelevsky et al '11:1220-71). Poorly differentiated tumors are more likely to have metastasized before diagnosis and are associated with a poorer prognosis. The Gleason score is calculated based on the dominant histologic grades, from grade 1 (well differentiated) to grade 5 (very poorly differentiated). The classical score is derived by adding the two most prevalent pattern grades, yielding a score ranging from 2 to 10 (Chan et al '00).

Tumors arise in the peripheral (70%) rather than the central (25%) zone of the prostate and are found most frequently in the apex or caudal portion. These tumors, which begin as a single nodule in one lobe or as diffuse multifocal lesions, readily extend through the prostate capsule because of their peripheral origin and intero perineural and vascular spaces and periprostatic tissue, thereby invading the seminal vesicles, bladder and rectum. Distant metastases involve bone in more than 90% of cases, but soft-tissue lesions are also prominent, particularly at autopsy, in lung nodes, liver, peritoneum and central nervous system including meninges. 30% of men with high-grade diffuse prostatic cancer present with lymph node involvement without capsular extension. 40% to 50% of men with positive lymph nodes progress in less than 2 years and 75% develop distant metastases in less than 5 years. At 5 years 84% of node-negative patients are nonprogressors compared with only 34% with positive nodes (Yagoda '90: 249).

The prostate has no simple function - lubrication to facilitate sperm flow and fertilization. Its regular function is dependent upon male hormone supply. The prostate gland in young human adult males is very much bigger than in bulls. In fact, apart from the dog, the human male can boast of a bigger prostate than any other mammal. The dog is the only other mammal recorded as having an appreciable incidence of prostate cancer with increasing age. Studies have indicated that prostate cancer incidence was less common celibate. Some 10 percent of prostate cancers occur in the context of a familial incidence. The BRCA-2 gene that strongly predisposes to breast cancer also increases the risk of prostate cancer in families with this particular gene mutation (Greaves '00: 165, 166). Transitional cell carcinoma of the prostatic and periurethral ducts is often described in patients with bladder cancer or other urothelial tract tumor. Both cancers respond to chemotherapy protocols for bladder cancer and are unresponsive to hormonal manipulation. Rare tumors include endometrioid cancer, which arises from the verumontanum; carcinoma sarcomas originating from the gland, capsule or spermatic cord; and lymphomas. Presenting signs include a palpable prostatic nodule (>50%), dysuria, complaints relating to cystitis or prostatitis, urinary retention, dribbling, frequency, and decrease in the urinary stream, and occasionally hematuria (terminal or at the end of urination) or hemospermia. Advanced signs include pain associated with osseous metastases, fatigue, general malaise, uremia and weight loss (Yagoda '90: 249). When the cancer is confined to the prostate gland, long-term prognosis is excellent. Patients with locally advanced cancer are not usually curable, but 5-year survival is still very good. If prostate cancer has spread to distant organs, current therapy will not cure it. Median survival is usually 1 to 3 years, and most of these patients will die of prostate cancer. Most men are diagnosed with prostate cancer at an early clinical stage and do not have detectable metastases. Therefore, they generally do not have to undergo staging tests, such as a bone scan, pelvic lymph node dissection, trans-rectal ultra-sound and biopsy, computed tomography (CT), or magnetic resonance imaging (MRI).<sup>1</sup> In 1997, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer adopted a revised TNM (tumor, node, metastasis) system, which used the same broad T-stage categories as the

Jewett system but included subcategories of T stage, such as a stage to describe patients diagnosed through PSA screening (Zelevsky et al '11:1220-71).

### Prostate Cancer Staging System

Stage	Description
T	Primary tumor
TX	Cannot be assessed.
T0	No tumor clinically detectable.
T1	Tumor not palpable, incidental finding.
T1a	Less than three high-powered fields contain tumor, generally low grade (JM=A1).
T1b	More than three high-powered fields contain tumor, generally high grade (JM=A2).
T2	Palpable nodules
T2a	<1.5 cm nodule surrounded on three sides with normal tissue (JM=B1)
T2b	>1.5 cm nodule or in more than one lobe with induration (JM=B2).
T3	Tumor extends into or beyond capsule into apex, bladder neck, seminal vesicle, and is not fixed; size >6 cm (JM=C).
T4	Tumor fixed or invades adjacent structures other than in T3 (JM=D1).
N	Regional lymph nodes
NX	Cannot be assessed.
N0	No tumor clinically detectable.
N1	Single homolateral node.
N2	Contralateral, bilateral, multiple nodes.
N3	Fixed pelvic wall mass with free space between this and tumor.
M	Distant metastases
MX	Cannot be assessed.
M0	No metastasis.
M1	Distant metastasis (JM=D2).

Source: Yagoda '90: Table 31-2; Pg. 251. JM refers to the Jewett-Marshall system.

Any benefits of definitive local therapy with curative intent may take years to emerge. Therefore, therapy with curative intent is usually reserved for men with a sufficiently long-life expectancy. For example, radical prostatectomy is often reserved for men with an estimated life expectancy of at least 10 years. Treatment options for early-stage disease include surgery, external beam radiation, or radioactive seed implants (brachytherapy). Hormone therapy may be used along with surgery or radiation in more advanced cases. Treatment often impacts a man's quality of life due to side effects or complications, such as urinary and erectile difficulties, which may be temporary or long term. Current research is exploring new biologic markers for prostate cancer, which could be used to minimize unnecessary treatment by distinguishing early-stage cancers that are potentially more aggressive from those that are less likely to progress if left untreated. Late-stage prostate cancer treatment options include hormonal therapy, chemotherapy, and/or radiation therapy. Hormone treatment may control advanced prostate cancer for long periods of time by shrinking the size or limiting the growth of the cancer, thus helping to relieve pain and other symptoms. An option for some men with advanced prostate cancer that is no longer responding to hormones is a cancer vaccine designed to stimulate the patient's immune system to attack prostate cancer cells specifically. Other types of drugs can be used to treat prostate cancer that has spread to the bones. The vast majority (90%) of prostate cancers are discovered at a local or regional stage, for which the 5-year relative survival rate approaches 100%. The 5-year

survival for disease diagnosed at a distant stage is 31%. The 10-year survival rate for all stages combined is 98%.

Treatment may be by radical prostatectomy, external irradiation, or radiation administered by interstitial implantation. **Radical prostatectomy** is performed in patients less than 70 to 75 years of age who have an estimated survival of 10 to 15 years, while radiation is employed for older patients, those with other medical problems or with large lesions that preclude surgery, and for men wishing to retain normal sexual activity. Radical external irradiation can damage the pudendal nerve in 25% to 40% of cases and incidence of impotence is less with interstitial implantation. The new nerve-sparing technique for radical prostatectomy of small lesions permits normal sexual function in 40% to 60% of selected cases, previously, radical surgery resulted in impotence in 100%. 5% to 15% of men may have urinary incontinence following surgery. Both surgery and radiation therapy produce 5, 10 and 15 years survival rates for Stage B disease of 75%, 50% and 30% to 50% for C and D1 disease, survival is 55% and 15% respectively. Seventy-percent survival for interstitial and external radiation is expected at 5 years, while 50% to 30% is reported for 10 and 15 years for Stages B2-C disease (Yagoda '90: 249-251). The role of preoperative (neoadjuvant) hormonal therapy is not established (Fair et al '97).

In a literature review of case series of patients with palpable, clinically localized disease, the authors found that 10-year prostate-cancer-specific survival rates were best in radical prostatectomy series (about 93%), worst in radiation therapy series (about 75%), and intermediate with deferred treatment (about 85%) (Adolfsson et al '93). In another study, the 10-year prostate cancer-specific survival rates were 98.8% in the active monitoring arm, 99.0% in the radical prostatectomy arm, and 99.6% in the radiation therapy arm (Hamdy et al '16). Men in the radical prostatectomy study arm had substantial rates of urinary incontinence (e.g., using one or more absorbent pads qd was reported by 46% at 6 months and by 17% at year 6) with very little incontinence in the other two study arms. Sexual function was also worse in the radical prostatectomy group (e.g., at 6 months, 12% of men reported erections firm enough for intercourse versus 22% in the radiation therapy arm and 52% in the active monitoring arm). Bowel function, however, was worse in the radiation therapy arm (e.g., about 5% reported bloody stools at least half the time at 2 years and beyond vs. none in the radical prostatectomy and active-monitoring study arms). Case series of men who have undergone radical prostatectomy have shown shortening of penile length (by an average of 1–2 cm) (McCullough et al '08). A large case series of men undergoing the anatomic (nerve-sparing) technique of radical prostatectomy reported the following: Approximately 6% of the men required the use of pads for urinary incontinence, but an unknown additional proportion of men had occasional urinary dribbling. About 40% to 65% of the men who were sexually potent before surgery retained potency adequate for vaginal penetration and sexual intercourse (Catalona et al '93). The 5-year failure-free survival rates were 88.3% (conventional, 74 Gy group), 90.6% (60 Gy group), and 85.9% (57 Gy group). The 60 Gy hypofractionated group fulfilled noninferiority criteria compared with conventional 74 Gy fractionation, but the 57 Gy group did not (Dearnaley et al '16). Definitive EBRT can result in acute cystitis, proctitis, and enteritis (Lee et al '16). Sildenafil citrate may be effective in the management of sexual dysfunction after radiation therapy in some men. Radiation is also known to be carcinogenic. EBRT for prostate cancer is associated with an increased risk of bladder and gastrointestinal cancer. Brachytherapy is associated with an increased risk of bladder cancer (Hamilton et al '01).

**Standard therapy** for advanced prostatic adenocarcinoma is hormone manipulation, which can

be accomplished by bilateral orchiectomy (castration) or the administration of exogenous hormones such as estrogen in the form of diethylstilbesterol (DES), 1 mg daily (up to 3 mg) to suppress testosterone levels, antiandrogens (i.e., flutamide or cyproterone acetate), progestins combined with estrogens (megestrol, 40 mg three times daily, with low-dose DES or estinyl), and luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide. Levels of testosterone will drop to castration levels. Surgical castration results in minimal symptomatology, but some men reject this approach and it increases the risk of myocardial infarction. 100 Other modalities lead to feminization with complaints of gynecomastia, personality change, weight gain, edema, impotence, hot flashes and thromboembolic and cardiac complications. DES is no longer manufactured or marketed in the United States and is seldom used today because of the risk of serious side effects, including myocardial infarction, cerebrovascular accidents, and pulmonary embolism. LH-RH agonists, such as leuprolide, goserelin, and buserelin, lower testosterone to castrate levels. Like orchiectomy and estrogens, LH-RH agonists cause impotence, hot flashes, and loss of libido. A modest advantage in progression-free survival and survival for the combination of leuprolide and flutamide over leuprolide alone has been found. Antiandrogen agents used in the treatment of prostate cancer include flutamide and bicalutamide. A systematic evidence review compared nonsteroidal antiandrogen monotherapy with surgical or medical castration from 11 randomized trials in 3,060 men with locally advanced, metastatic, or recurrent disease after local therapy. Use of nonsteroidal antiandrogens as monotherapy decreased OS and increased the rate of clinical progression and treatment failure (Kunath et al '14). The steroidal antiandrogen, megestrol acetate, suppresses androgen production incompletely and is generally not used as initial therapy (Kirschenbaum et al '95). Androgen deprivation therapy (ADT) can cause osteoporosis and bone fractures. Treatment of bone loss with bisphosphonates decreases the risk of bone fracture in men receiving ADT for prostate cancer. **Hormonal manipulation** will induce remission in approximately 40% to 80% of patients depending on the criteria employed. Complete disappearance of the disease is rare. With response, the PSA and OS decrease to normal values, the alkaline phosphatase shows a transient increase (indicating bone healing) but should return to normal, and bone scans may exhibit increased activity secondary to healing. The average duration of hormone response is 9 to 18 months, and most patients die 9 to 18 months after treatment failure. Further hormone manipulation will produce clinical improvement in 10% to 20% of cases; tumor regression is uncommon (<10%) (Yagoda '90: 251-253).

When one excludes disease stabilization as a response category multi-drug chemotherapy has less than 5% response rate. The most frequently employed agents are doxorubicin, given in a dose of 45 mg to 60 mg/m<sup>2</sup> every 3 weeks or 20 mg/m<sup>2</sup> weekly, cyclophosphamide, 5-fluorouracil and cisplatin with doxorubicin. Prednisone, initially in a dose of 40 mg daily progressively decreased by 5 mg weekly, can improve quality of life by increasing appetite and weight and decreasing bone pain. Aspirin should be avoided because its effect on platelets may lead to bleeding. Alkaline phosphatase is useful as a monitor of progressive bone disease, and bone scans at 12 month intervals can monitor response and detect metastases. Anemia is common, and some patients present with recurring thromboembolic, phlebitis, or intravascular coagulation problems and hypercalcemia, all of which require appropriate treatment with standard medical management (Yagoda '90: 251-253).

Proper hygiene and early circumcision have made **penile carcinoma** rare in the United States; it accounts for less than 1% of male cancers. Penile cancer is rare in most developed nations, including the United States, where the rate is less than 1 per 100,000 men per year. Some studies suggest an association between human papillomavirus (HPV) infection and penile cancer (Poblet

atl '99). Virtually all penile carcinomas are of squamous cell origin and include the following subtypes: Verrucous carcinoma (Schwartz et al '95). Warty carcinoma (verruciform) (Bezerra et al '01). Basaloid carcinoma (Cubilla et al '98). Although they are less common subtypes, warty carcinoma and basaloid carcinoma appear to be more highly associated with human papillomaviruses (HPV), particularly HPV 16, than typical squamous cell carcinoma or verrucous carcinoma of the penis (Rubin et al '01).

When diagnosed early (stage 0, stage I, and stage II), penile cancer is highly curable. Curability decreases sharply for stage III and stage IV. Smegma is a known carcinogen, but venereal disease is not. Precancerous lesions include leukoplakia, frequently found in association with chronic irritation and squamous cell tumors; erythroplasia of Queyrat, which is found on the dorsum of the glans in uncircumcised males as raised red velvet lesions, which either co-exist with cancer or undergo malignant degeneration. Malignant tumors include carcinoma in situ and most commonly, squamous cell (epidermoid) carcinoma. Presenting signs include penile mass or ulcer, bleeding, urethral obstruction, and an inguinal mass. Carcinoma in situ of the penis is referred to as erythroplasia of Queyrat when it occurs on the glans, and Bowen disease when it occurs on the penile shaft. These precursor lesions progress to invasive squamous cell carcinoma in 5% to 15% of cases. In case series studies, human papillomavirus DNA has been detected in most of these lesions (Cupp et al '95). Fear of penectomy often (50%) leads to delay in diagnosis. While penile soft-tissue sarcomas metastasize primarily via the bloodstream, squamous cell carcinoma drains via the lymphatics to inguinal and deep iliac nodes. Palpable inguinal lymph nodes generally are found at presentation but pathologically are positive in only 35% to 60% of cases. Following clinical examination of the penis and regional lymph nodes, a penile biopsy should be performed. Other diagnostic tests are blood count, screening chemistries, intravenous urogram, chest films and CT of pelvis that includes the inguinal area. A bipedal lymphangiogram should be performed (Yagoda '90: 257-259).

### Penile Cancer Staging System

Stage	Description
Stage I	Tumor limited to glans penis, prepuce.
Stage II	Tumor invades shaft, corpora.
Stage III	Tumor confined to shaft with regional operable lymph node involvement.
Stage IV	Inoperable regional lymph node involvement, distant metastases.

Source: Yagoda '90: Table 31-5, Pg. 258

Surgical excision can result in scarring, deformity, and impaired function. The current FIGO surgical staging is too sensitive to transcribe (Amin et al '17). To minimize these effects, Mohs micrographic surgery, which involves the excision of successive horizontal layers of tissue with microscopic examination of each layer in frozen section, has been used in patients with *in situ* and invasive penile cancers (Moritz et al '95). Topical application of fluorouracil cream (**5-FU**) has been reported to be effective in cases of erythroplasia of Queyrat (Goette et al '76) and Bowen disease (Tolia et al '76). **Imiquimod** 5% cream is a topical immune response modifier that has been reported to be effective with good cosmetic and functional results (Micali et al '03). Laser therapy with Nd:YAG or CO<sub>2</sub> lasers has also been reported to result in excellent cosmetic results (van Bezooijen et al '01).

Therapy for carcinoma in situ is complete local incision. For erythroplasia of Queyrat and Bowen disease topical **5-fluourouracil** twice daily has been effective; radiation therapy has not.

If invasion is suspected deep excision or partial amputation can be performed, after which incidence of recurrence is extremely low. Intraepithelial carcinomas generally recur locally, while Bushke-Loewenstein tumors frequently require penectomy. Podophyllin and radiation therapy are of no value, but laser therapy has been curative for some superficial lesions. Soft-tissue sarcomas requires a total penectomy but no lymph node dissection. Locally invasive penile lesions with clinically enlarged inguinal nodes are observed in 75% of cases at presentation, and after removal of the primary tumor, such nodes will have metastatic involvement. The 5 year survival rate for Stage 3 is more than 50%. Methotrexate, bleomycin, and cisplatin all have response rates in the 10% to 30% range; long-term complete remission is uncommon. Combinations have not been proven more effective (Yagoda '90: 257-259). A combination of vincristine, bleomycin, and methotrexate has been effective as both neoadjuvant and adjuvant therapy (Pizzocaro et al '88). Cisplatin (100 mg/m<sup>2</sup>) as neoadjuvant therapy plus continuous-infusion fluorouracil has also been shown to be effective (Fisher et al '90). Single-agent cisplatin (50 mg/m<sup>2</sup>) was tested in a large trial and was found to be ineffective (Gagliano et al '89).

There are estimated to be 9,610 new cases and 440 deaths from testicular cancer in the United States in 2020 (ACS '20). Testicular cancer is a highly treatable, usually curable, cancer that most often develops in young and middle-aged men. Most testicular cancers are germ cell tumors. For treatment planning, germ cell tumors are broadly divided into seminomas and nonseminomas because they have different prognostic and treatment algorithms. For patients with seminoma (all stages combined), the cure rate exceeds 90%. For patients with low-stage seminoma or nonseminoma, the cure rate approaches 100% (Tandstad et al '09).

**Germ cell tumors**, 90% of which are found in the **testicles**, are the most common cancer in men between the ages of 15 and 34. They account for 1% of male malignancies and affect white men more than other races. Between 5000 and 5500 new cases were predicted in the United States for 1985. Risk factors for testicular cancer include the following: An undescended testis (cryptorchidism). A family history of testis cancer (particularly in a father or brother). A personal history of testis cancer. Surgical correction of an undescended testis (orchiopexy) before puberty appears to lower the risk of testis cancer, but this isn't certain (Pettersson et al '07). Curative therapy now exists for all stages of the disease. Cisplatin-based chemotherapy has results in the cure of 70% of 80% of patients with metastatic disease, wherefore GCT is the most curable adult malignancy. More than 90% of patients with a testicular tumors will have a palpable nodule, pain or discomfort, testicular swelling or some combination. If the abnormality fails to resolve within 2 to 4 weeks with a trial of antibiotics, then a testicular tumor should be suspected. Two major histologic cell types exist: seminomatous and nonseminomatous. Pure seminoma constitutes about 40% of testicular GCT and usually occurs in men in the fourth decade of life. Seminoma is exquisitely radiosensitive. Three types are recognized: anaplastic, classic and spermatocytic. Anaplastic and classic seminoma do not differ prognostically and spermatocytic seminoma is a rare disease of elderly men and essentially never metastasizes. The other 60% of all GCT are nonseminomatous, and the median age is in the middle of the third decade, fully 10 years less than that of seminoma (Bosl '90: 261-264).

Four major cell types exist: the embryonal carcinoma cell, the mature teratoma, choriocarcinoma and yolk sac tumor. Three serum proteins serve as reliable tumor markers in patients with GCT: human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH). LDH and HCG are elevated and AFP is never elevated in patients with pure seminoma. Elevated AFP, HCG and/or LDH may be found in 80% of patients with metastatic disease. A

lymphangiogram will detect an additional 10% of 15% of patients with retroperitoneal lymph node involvement not detected by computed tomographic (CT) scan of the abdomen (Bosl '90: 261-264). Staging of testicular cancer is Stage I disease limited to the testis, epididymis, or spermatic cord; Stage II disease limited to regional (retroperitoneal lymph nodes), Stage III disease in lymph nodes above the diaphragm, or in any visceral site and Stage IV distant metastases (Bosl '90: 261-264). Stage II seminoma is divided into bulky and nonbulky disease for treatment planning and expression of prognosis. Bulky disease is generally defined as tumors larger than 5 cm on a computed tomographic (CT) scan (i.e., stage IIC disease). Nonbulky disease can be further subdivided into stage IIA, meaning no lymph node mass larger than 2 cm, and stage IIB, meaning a lymph node mass between 2 cm and 5 cm. Nonbulky stage II disease has a cure rate of about 90% to 95% with radiation alone at doses of 30 Gy to 36 Gy (Classen et al '03), and most relapsing patients can be cured with chemotherapy (Chung et al '04). Stage III seminoma and nonseminomas are usually curable but have different criteria for estimating prognosis. Patients with disseminated seminomas can be divided into good-risk and intermediate-risk groups based on whether nonpulmonary visceral metastases are present. Good-risk patients (i.e., those with metastases only to lymph nodes and/or lungs) have a 5-year progression-free survival (PFS) and overall survival (OS) of 82% and 86%, respectively. Intermediate-risk seminoma patients have a 5-year PFS and OS rate of 67% and 72%, respectively (IGCCC '97). The American Joint Committee on Cancer (AJCC) has designated staging by TNM (tumor, node, metastasis) classification to define testicular cancer (Amin et al '17).

Removal of the testicle through the groin, **orchiectomy**, is followed (in adults) by retroperitoneal lymphadenectomy (RPLND). A nerve-sparing RPLND that preserves ejaculation in virtually every patient has been described in clinical stage I patients and appears to be as effective as the standard RPLND (Donohue et al '03). Surgery should be followed by monthly determination of serum markers and chest x-rays for the first year and every-other-month determinations for the second year (van As et al '08). Men undergoing RPLND, who are found to have pathological stage I disease, have a roughly 10% risk of relapsing subsequently, whereas men with pathological stage II disease (i.e., those who are found to have lymph node metastases at RPLND) have as much as a 50% risk of relapse without further treatment (Williams et al '87). High doses of cisplatin (100-120 mg/m<sup>2</sup>) were introduced into the treatment of GCT in 1975, a cure rate of 80% to 90% can be expected. Nearly all patients suffer emesis, nausea and alopecia. For patients failing to achieve a complete remission or relapsing from complete remission, Etoposide (VP-16), 100 mg/m<sup>2</sup> IV for 5 days, plus cisplatin 20 mg/m<sup>2</sup> IV for 5 days is the standard treatment, that only cures 15% to 25% of those relapsing from complete remission (Bosl '90: 261-264). Radiation therapy is associated with a low risk of relapse. One study of 122 patients treated with 18 Gy to 20 Gy of external-beam radiation therapy reported three relapses (2.5%).

Chemotherapy does not appear to be very effective at preventing the development of invasive testicular germ cell tumors. One series reported progression to invasive cancers in 10 of 30 patients treated with two cycles of bleomycin, etoposide and cisplatin (BEP); the same progression was found in 7 of 51 patients treated with three or more cycles of BEP; 2 of 15 patients treated with carboplatin also showed a progression to invasive cancers (Dieckmann et al '13). Two cycles of post-RPLND chemotherapy using either bleomycin, etoposide, and cisplatin (BEP) or etoposide plus cisplatin (EP) lowers the risk of relapse in men with pathological stage II disease to about 1% (Kondagunta et al '04). Several phase II studies and case series reporting the results after two cycles of BEP in intermediate- or high-risk patients have identified relapse

rates ranging from 0% to 4% (average = 2.4%) (Choueiri et al '07). EP: etoposide plus cisplatin for four courses in good-prognosis patients (Xiao et al '97). A randomized study has shown that bleomycin is an essential component of the BEP regimen when only three courses are administered (Loehrer et al '95). Other regimens that appear to produce similar survival outcomes but are no longer considered standard include: PVB: cisplatin plus vinblastine plus bleomycin. VAB VI: vinblastine plus dactinomycin plus bleomycin plus cyclophosphamide plus cisplatin (Bosl et al '86). VPV: vinblastine plus cisplatin plus etoposide (Wozniak et al '91). In a randomized comparison of PVB versus BEP, equivalent anticancer activity was seen but with less toxic effects with the use of BEP (Stoter et al '89). Salvage regimens consisting of ifosfamide, cisplatin, and either etoposide or vinblastine can induce long-term complete responses in about 25% of patients with disease that has persisted or recurred following other cisplatin-based regimens. Patients who have had an initial complete response to first-line chemotherapy and those without extensive disease have the most favorable outcomes (Loehrer et al '97).

### 13. Transgender cancer risk

**Transgender people** comprise a diverse group of individuals whose gender identity or expression differs from that originally assigned to them at birth (1). An estimated 10% of the population are gay, lesbian, bisexual or transgender. Some, but not all, transgender people may seek medical treatment to affirm their gender identity. In some cases, this is done to alleviate gender dysphoria, which is a diagnostic term that describes a “strong and persistent distress with physical sex characteristics or ascribed social gender role that is incongruent with persistent gender identity” (Knudsen et al '10). The gender affirmation treatment includes 4 types of interventions: 1) changes in social expression of gender to achieve consistency with gender identity, 2) therapy with cross-sex hormones to achieve desired masculinization or feminization, 3) surgical change of the genitalia and/or other sex characteristics, and 4) psychotherapy to further explore gender identity, improve body image, and promote resilience. The current literature indicates that transgender people face a disproportional burden of adverse health outcomes. **Cancer among transgender people** is listed among research priorities of the Institute of Medicine in 2011 (Coleman et al '12).

**Human papillomavirus (HPV)** has been implicated in the etiology of anal, oropharyngeal, and penile cancers among nontransgender men and in cervical, anal, vulvar, and vaginal cancers among nontransgender women (Gillison et al '08). Among over 40 types of HPV, at least 13 are considered high risk with respect to their carcinogenic potential (Supindham et al '15). A study of 111 transgender sex workers in Argentina found HPV DNA in 97% of anal mucosa samples. High-risk carcinogenic genotypes were detected in 83% of the participants, and 71% were coinfecting with 2 or more HPV genotypes (dos Ramos et al '11). In another study conducted among transwomen in Lima, Peru, visible anogenital warts were detected in 22% of the participants (Galea et al '15). Two recent studies examined the prevalence of anal squamous intraepithelial lesions by using Papanicolaou (Pap) smears. These 2 studies reported the prevalence of anal squamous intraepithelial lesions to be around 56% and 42% among transwomen in India and Thailand, respectively (Ruanpeng et al '16). The case reports of presumably or potentially HPV-related malignancies in transgender patients who received gender affirmation therapy include anal and neovaginal cancers in transwomen and cervical and vaginal cancers in transmen (Fernandes et al '14). Of special consideration with respect to neovaginal cancers is the use of heterotopic penile skin, which may be at higher risk for HPV-induced squamous cell carcinoma.

The aim of typical **hormonal treatment** for transwomen is to decrease blood testosterone to physiological female concentrations (30–100 ng/dL) through antiandrogens (or surgical castration) and to achieve normal female but not suprphysiological levels (<400 pg/mL) of estradiol through estrogen therapy. The corresponding goal of hormonal gender affirmation in transmen is to reach testosterone levels of the normal male, which range between 300 and 1,000 ng/dL (Gardner et al '13). The role of **exogenous estrogen** and its action on estrogen receptors  $\alpha$  and  $\beta$  needs to be considered. Recent literature indicates that estrogen receptor  $\alpha$  stimulates prostate carcinogenesis, while estrogen receptor  $\beta$  appears to exert an antineoplastic effect, although studies suggest that different estrogen receptor  $\beta$  isoforms may have different and sometimes opposing modes of action (Nelson et al '14). Estrogen receptors are not the only target of estrogen; it has been shown that 17 $\beta$ -estradiol can bind to androgen receptors with the assistance of coactivators or androgen receptor mutations that result in 17 $\beta$ -estradiol hypersensitivity (Thin et al '03). Cases of presumably **hormone-related malignancies** in transwomen diagnosed after the initiation of medical or surgical gender affirmation include carcinomas of the breast and prostate, prolactinomas, and meningiomas (Mueller et al '08). In transmen, published case reports describe cancers of the breast, ovaries, cervix, vagina, and endometrium (Urban et al '11).

High-dose exogenous cross-sex **estrogens and androgen antagonists** stimulate the formation of breast lobules, ducts, and acini histologically identical to those of biological females (Maglione et al '14). Exogenous estrogen binds to the estrogen receptor in the breast tissue and is hypothesized to stimulate carcinogenesis via increased cell proliferation, decreased apoptosis, and elevated production of oxidative metabolites that result in DNA damage (Yue et al '13). Higher serum levels of endogenous estradiol have been associated with higher breast cancer risk in nontransgender natal males (Brinton et al '15), lending further support to the hypothesis that transwomen may be at increased risk of breast cancer due to hormonal therapy. Another factor that may affect breast cancer risk in transwomen is a relatively low level of testosterone. Mechanistic evidence indicates that testosterone inhibits proliferation and stimulates apoptosis in breast epithelium (Eigeliene et al '12).

Female sex hormones may also play a role in the pathogenesis of **meningiomas**. This hypothesis is based on the observations that meningiomas are more common in women than in men, appear to change in size during the luteal phase of the menstrual cycle and pregnancy, are associated with the use of oral contraceptives and hormone replacement therapy, and tend to co-occur with breast cancer (Claus et al '13). Most meningiomas express progesterone receptors, whereas estrogen receptors are found in only one-third of tumors. For this reason, it has been suggested that progesterone, especially in large doses, may be implicated in the etiology of meningioma among transwomen (Gazzeiri et al '07). **Prolactinomas** are the most common pituitary tumors that tend to be relatively small, slow growing, and diagnosed predominantly in women (wong et al '15). Estrogens have been reported to induce prolactin synthesis and release, and their use has been linked to both hyperprolactinemia and prolactinoma risk (García-Malpartida et al '10).

The five main **gynecologic cancers** are cervical, ovarian, uterine, vaginal, and vulvar. **45, XO** occurs in 1:10,000 live-births, occurring frequently in first-trimester (Turner syndrome) is the leading cause of spontaneous abortions; associated primarily with unique somatic features; they have an enlarged clitoris and vestigial male gonads that are best surgically removed in adolescence to prevent cancer. Medicaid and the military health systems need to pay for the removal of precancerous vestigial gonads of 45, XO comprising a relatively large number 0.1-1%

of 47, XXX, 47, XXY, 47, XYY mutants (Wright et al '03). 45X/46,XY and 45,X/47,XYY chromosomal mosaicism is rare, with an incidence of 1.7/10,000 pregnancies. Only 5–10% of individuals with a prenatally diagnosed mosaic karyotype of 45,X/46,XY will have ambiguous genitalia at birth, with the remainder being phenotypic male. A series of 92 prenatally diagnosed cases of chromosomal mosaicism, including 88 45,X/46,XY and 4 45,X/47,XYY mosaics, of whom only 4 (5%) were noted to have genital anomalies. Fifteen gonads, including 4 with in-situ neoplastic lesions, in 12 different patients, were found to have pre-malignant characteristics. Tumor risk was significantly reflected by clinical phenotype, and revealed to be very high (52%) in patients with an ambiguous phenotype. The only pre-malignant gonads were found in a phenotypically female patient with intra-abdominal dysgenetic testes (Chang et al '90). There are also several reports of phenotypic males with 45,X/46,XY mosaicism presenting to infertility clinics and being found to be azoospermic (Layman et al '09).

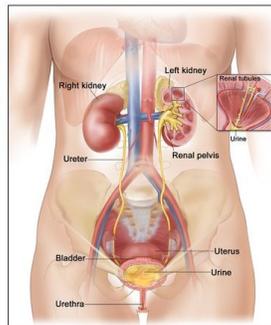
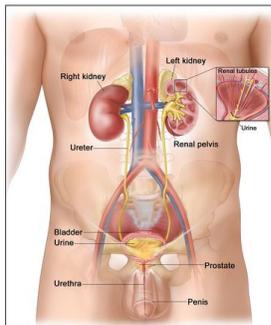
The most frequent forms of **sex-chromosome aneuploidies**, Turner (45,X) and Klinefelter (47,XXY) syndromes, generally do not present at birth with genital anomalies. Therefore, they do not appear as a differential diagnosis in the newborn. Conversely, patients with 45,X/46,XY or 46,XX/46,XY (or other mosaicisms/chimerisms) frequently bear diverse forms of gonadal dysgenesis (partial testicular dysgenesis, asymmetric gonadal differentiation, ovotestes, etc.) which lead to the existence of ambiguous genitalia (Wisneuski et al '19). The anatomy and gonadal histology of 45,X/46,XY and 45,X/47,XYY individuals with genital ambiguity do not conform to a set pattern, and hence management of each patient should be individualized according to detailed anatomical and histological assessment (Farrugia et al '13). 47,XYY men showed no consistent physical abnormality on general clinical examination and, in particular, that in none was there evidence of impaired sexual development (Price et al '66). Although the most common method of diagnosis is undescended testes and hypogonadism, many 47,XYY men are fertile, although other have oligospermia or are sterile. The overall frequency of males with an abnormal nuclear sex is about 9.4 per 1,000, comprising about 7.6 per 1,000 jointly chromatin-positive males and about 1.6 per 1,000 doubly chromatin-positive, with the remainder being trebly chromatin-positive. Nearly all patients have an IQ of 50 or more, and about 25% have an IQ over 85 (Casey '66). However, there was an unusual number of these men in maximum security hospitals, whereby it is adduced that the behavioral disturbances of these men were primarily determined by their abnormal genotype. Patients with 47, XYY are taller than normal 46, XY males (Court Brown '68). 47, XXX females also tend to be tall (Linden et al '88) (Ogata et al '92). While 47,XYY tends to run at about 1 per 1,000 in the general population, in one study of a boys school, in the 90<sup>th</sup> percentile of height 47, XYY ran at about 1 out of 10, and in males prisoners over 183 cm in height 24%. Gonadal dysgenesis due to 45,X/46,XY and 45,X/47,XYY mutations occurred in about 0.1-1% of XYY studied (Court Brown '68).

Extra-gonadal, mediastinal non-seminomas are more frequent in individuals with Klinefelter syndrome and are associated with a risk of subsequent development of hematologic neoplasia that is not treatment related (Nichels et al '87). Approximately 50% of patients with mediastinal non-seminomas will survive with appropriate management (Nichols et al '90). High risk is partially related to tumor bulk, to chemotherapy resistance, and to a predisposition to develop hematologic neoplasia and other non-germ cell malignancies. In an uncontrolled study, some patients with a post-chemotherapy residual mediastinal mass achieved long-term disease-free survival after complete resection, even when serum tumor markers were elevated (Schneider et al '04). Extra-gonadal germ cell tumors occur much more commonly in males than in females (Mayordomo et al '94) and are usually seen in young adults. They are aggressive neoplasms and can arise virtually anywhere, but typically the site of origin is in the midline (mediastinum, retro-

peritoneum, or pineal gland). Gonadal origin should be excluded by careful testicular examination and ultrasound. The diagnosis can be difficult and should be considered in any patient with a poorly defined epithelial malignancy, particularly young individuals with midline masses (Hainsworth et al '92). Patients receive treatment with cisplatin-containing or carboplatin-containing therapy as their first chemotherapy course (IGCCC '97).

There is a good prognosis for 56% of patients with non-seminoma of the testis or retroperitoneal primary and no nonpulmonary visceral metastases, AFP less than 1,000 ng/mL, hCG less than 5,000 iu/L (1,000 ng/mL) and LDH less than 1.5 x upper limit of normal. 5-year progression free survival (PFS) rate of 89% and overall survival (OS) rate of 92%. For 90% seminomas in any primary site and no nonpulmonary visceral metastases and normal AFP, any hCG any LDH the 5-year PFS is 82% and OS 86%. The intermediate prognosis for 28% non-seminoma of the testis/retroperitoneal primary and no nonpulmonary visceral metastases and intermediate markers – any of: AFP 1,000 ng/mL or greater and 10,000 ng/mL or less, or hCG 5,000 iu/L or greater and 50,000 iu/L or less or LDH 1.5 x N or greater and 10 x N or less have a 5-year PFS of 75% and OS of 80%. For 10% of seminomas of any primary site with non-pulmonary visceral metastases and normal AFP, any hCG, any LDH, the 5-year PFS is 67% and OS is 72%. There is a poor prognosis for 16% of non-seminoma mediastinal primary with non-pulmonary visceral metastases. Poor markers are any of AFP greater than 10,000 ng/mL, hCG greater than 50,000 iu/L (1,000 ng/mL) or LDH greater than 10 upper limit of normal. The 5-year PFS is 41% and OS 48%. No seminoma patients are classified as poor prognosis (IGCCC '97).

#### 14. Urinary system cancer



The **urinary tract** consists of the kidneys, the ureters, the bladder, and the urethra. The urinary tract is lined with transitional cell urothelium from the renal pelvis to the proximal urethra. Transitional cell carcinoma (also referred to as urothelial carcinoma) can develop anywhere along this pathway. Urine is made in the renal tubules and collects in the renal pelvis of each kidney. The urine flows from the kidneys through the ureters to the bladder. The urine is stored in the bladder until it leaves the body

through the urethra. Under normal conditions, the bladder, the lower part of the kidneys (the renal pelvises), the ureters, and the proximal urethra are lined with a specialized mucous membrane referred to as transitional epithelium (also called urothelium). Most cancers that form in these tissues are transitional cell carcinomas (also called urothelial carcinomas) that derive from transitional epithelium (ACS '20).

In 2020, an estimated 73,750 new cases of **kidney (renal) cancer** will be diagnosed in the US and 14,830 people will die from the disease. Most kidney cancers are **renal cell carcinomas**; other types include cancer of the renal pelvis (5%), which behaves more like bladder cancer, and Wilms tumor (1%), a childhood cancer that usually develops before the age of 5. Men are twice as likely as women to be diagnosed with kidney cancer. Incidence trends: The increase in kidney cancer incidence rates since at least 1975 appears to have slowed in recent years. The rise, mostly in localized stage diagnoses, is partly attributed to incidental detection of asymptomatic tumors because of the increased use of medical imaging. From 2007 to 2016, the rate increased by 0.5% per year in men and was stable in women. In contrast to incidence trends, kidney cancer

mortality has been declining in recent decades; from 2008 to 2017, the death rate decreased by 1% per year. About half of kidney cancers could **potentially be prevented** by eliminating excess body weight and tobacco smoking, which are strong risk factors. **Additional risk factors** include high blood pressure; chronic renal failure; and occupational exposure to certain chemicals, such as trichloroethylene. A small proportion of renal cell cancers are the result of **rare hereditary conditions** (e.g., von Hippel-Lindau disease). Alcohol consumption (up to about 2 drinks per day) is associated with a reduced risk of kidney cancer; however, the risks of heavy alcohol consumption far outweigh this benefit. **Symptoms** include blood in the urine, a pain or lump in the lower back or abdomen, fatigue, weight loss, fever, and anemia. (ACS '20: 15).

**Renal cell carcinoma** (hypernephroma) accounts for 2% to 3% of all cancers in the United States. The male to female ratio is 2:1, and the average age at presentation 55 to 60 years. These tumors have been associated with Hippel-Lindau disease and acquired renal polycystic disease occurring after long-term dialysis. Approximately 85% of renal cell cancers are adenocarcinomas, and most of those are of proximal tubular origin. Most of the remainder are transitional cell carcinomas of the renal pelvis. The most frequent histology is clear cell carcinoma, followed by granular cell and mixed, and lastly by an aggressive carcinosarcoma, "hypernephroma with sarcomatous degeneration". Rarely, tumors may arise within a renal cyst. Uncommon tumors include adult Wilms', and soft-tissue sarcomas originating from stromal tissue, renal capsule, Gerota's fascia. The extreme vascularity of renal cell tumors explains the frequent occurrence of hematogenous spread to lung, bone, liver, brain and other sites. Presenting signs include hematuria in 40% to 70% of cases, sometimes after anticoagulation for pulmonary emboli or myocardial infarction; abdominal mass or flank pain in 20% to 40%; weight loss in 30%; and fever, malaise, night sweats, and anemia in 15% to 30%. Presenting symptoms may also be secondary to paraneoplastic process inducing hypercalcemia, polycythemia, or hypertension. Metastases are present at the time of diagnosis in 40% of patients (Yagoda '90: 246-248).

**Standard workup** consists of a complete blood count, prothrombin and partial thromboplastin times, automated 12-channel screening profile, intravenous urogram, chest film, renal sonogram, and abdominal computer tomographic (CT) scan. Ultrasonography, sometimes with needle aspiration, and a nephrotomogram or arteriography, may be needed to differentiate cyst from tumor. Selective renal arteriography, venacavography, nephrotomography, lymphangiography, and retrograde pyelograph are less frequently used (Yagoda '90: 246-248). CT scanning is as good as or better than magnetic resonance imaging for detecting renal masses (CC '88). The American Joint Committee on Cancer (AJCC) TNM classification includes four stages; Stage I tumor confined to kidney and capsule; Stage 2 T2, invasion of perinephric fat but within Gerota's fascia; Stage III T1-2, N1 or T3, NO1, involvement of regional lymph nodes, renal vein or vena cava; Stage IV T4 or N2-3 or M1, extension to adjacent organs or distant metastases. 5 year survival rates approach 30% to 50% for local disease, Stage III high-grade lesions exhibiting vascular invasion have an overall survival of 5% to 15%. Early diagnosis is mandatory, and therapy with irradiation and corticosteroids can prevent a major decrease in quality of life. Hypercalcemia is usually a terminal event and may be controlled for a limited time with hydration, mithramycin and rarely, by a prostaglandin inhibitor (Yagoda '90: 246-248).

### Renal Cell Cancer Staging System

Stage	Description
T	Primary Tumor.

TX	Cannot be assessed.
T0	No tumor clinically detectable.
T1	Tumor <2.5 cm.
T2	Tumor >2.5 cm.
T3	Tumor extends into vein or Gerota's fascia.
T3a	In perinephric tissue, adrenals.
T3b	In renal vein, vena cava.
T4	Tumor extends beyond Gerota's fascia.
N	Regional Lymph Nodes.
NX	Cannot be assessed.
N0	No tumor clinically detectable.
N1	Single node <2 cm.
N2	Single node >2 and <5 cm; multiple nodes, all <5 cm.
N3	Node >5 cm.
M	Distant Metastases
M0	No metastases.
M1	Distant Metastases.

Source: Yagoda '90: Table 31-1; Pg. 247, Amin et al '17

Current treatment cures more than 50% of patients with stage I disease, but results in patients with stage IV disease are very poor. Renal cell cancer, also called renal adenocarcinoma, or hypernephroma, can often be cured if it is diagnosed and treated when still localized to the kidney and to the immediately surrounding tissue. The **probability of cure** is directly related to the stage or degree of tumor dissemination. Even when regional lymphatics or blood vessels are involved with tumor, a significant number of patients can achieve prolonged survival and probable cure (Sene et al '92). When distant metastases are present, disease-free survival is poor; however, occasional selected patients will survive after surgical resection of all known tumor. Because a majority of patients are diagnosed when the tumor is still relatively localized and amenable to surgical removal, approximately 73% of all patients with renal cell cancer survive for 5 years. Renal cell cancer is one of the few tumors in which well-documented cases of spontaneous tumor regression in the absence of therapy exist, but this occurs very rarely and may not lead to long-term survival. Surgical treatment is the mainstay of treatment of renal cell cancer (NCI '20). The median OS was 38.1 months for patients who underwent nephrectomy compared with 16.4 months for those treated with systemic therapy alone. 5

**Surgery** is the primary treatment for most kidney cancers, although active surveillance (observation) may be an option for some patients with small tumors. Patients who are not surgical candidates may be offered ablation therapy, a procedure that uses extreme temperature to destroy the tumor. Adjuvant treatment (after surgery) with a targeted therapy drug may be an option for certain patients at high risk for cancer recurrence. For metastatic disease, immunotherapy and targeted therapies are typically the main treatment options, sometimes along with removal of the kidney. The 5-year relative survival rate for kidney and renal pelvis cancer is 75%. Two-thirds of cases are diagnosed at a local stage, for which the 5-year relative survival rate is 93% (ACS '20: 15, 16). Radical nephrectomy with lymph node dissection is the only appropriate therapy for locoregional renal cell carcinoma. If there is invasion of the renal vein and inferior vena cava, urologists may consider tumor embolectomy to remove all residual disease. Partial nephrectomy is performed in selected cases presenting with a grade I renal cell carcinoma and patients with a single kidney. When synchronistic or metachronous tumors occur bilaterally, renal transplantation can be considered (Yagoda '90: 246-248).

Pre-operative or postoperative radiation therapy has limited value. Chemotherapy is also ineffective, with transient tumor regression occurring in less than 5% to 10%. The most commonly used agents are vinblastine and a nitrosourea. Progestins produce tumor regression in less than 2% to 8% of cases and should never be employed as surgical adjuvants. Alpha-interferon induces responses in 13% to 20% of cases; however responses have been atrial and of limited duration (Yagoda '90: 246-248). Patients who underwent nephrectomy before receiving interferon-alpha had a median OS of 17 months compared with an OS of 7 months in patients who received interferon-alpha alone (Mathieu et al '15). Cytokine therapy with interferon-alpha or IL-2 has been shown to induce objective responses, and interferon-alpha appears to have a modest impact on survival in selected patients. Interferon-alpha has approximately a 15% objective response rate in appropriately selected individuals. In general, these patients have nonbulky pulmonary or soft tissue metastases with excellent PS ratings of 0 or 1, according to the ECOG rating scale, and the patients show no weight loss (Coppin et al '05). High-dose IL-2 produces an overall response rate similar to that of interferon-alpha, but approximately 5% of the patients have shown durable complete remissions (McDermott et al '15).

The four FDA-approved anti-VEGF agents include three oral tyrosine kinase inhibitors: pazopanib, sorafenib, and sunitinib; and an anti-VEGF monoclonal antibody, bevacizumab. Axitinib is a newer, highly selective, and more potent inhibitor of VEGF receptors 1, 2, and 3 and has been approved by the FDA for the treatment of advanced renal cell carcinoma after the failure of one previously received systemic therapy (Rini et al '11). Sunitinib and the combination of bevacizumab plus interferon-alpha have each been associated with longer PFS than interferon-alpha alone in randomized, controlled trials. Sunitinib is an orally available multikinase inhibitor (VEGFR-1, VEGFR-2, PDGFR, c-Kit). Sunitinib as first-line systemic therapy was associated with a median PFS of 11 months compared with 5 months for interferon-alpha, and nonsignificant trend to longer OS, 26.4 months vs. 21.8 months. Bevacizumab, a monoclonal antibody that binds to and neutralizes circulating VEGF protein, delayed progression of clear-cell renal cell carcinoma when compared with placebo in patients with disease refractory to biological therapy (Yang et al '03). Similarly, bevacizumab plus interferon-alpha as first-line therapy resulted in longer PFS but not OS compared with interferon-alpha alone in two similarly designed, randomized, controlled trials (Escudier et al '07). PFS was significantly prolonged in the pazopanib arm at 9.2 months compared with 4.2 months in the placebo arm. The median PFS time was 8.4 months for those in the pazopanib arm and 9.5 months for those in the sunitinib arm. There was no difference in OS. 70% of the patients preferred pazopanib, and 22% of the patients preferred sunitinib (Escudier et al '14). Cabozantinib is an oral tyrosine kinase inhibitor of the MET, AXL, and VEGF receptors. Median OS was 21.4 months for patients who received cabozantinib and 16.5 months for patients who received everolimus (Choueiri et al '14). Cabozantinib passed the non-inferiority test with sunitinib (Choueiri et al '18). Median PFS was 8.3 months for axitinib and 5.7 months for sorafenib. Median OS was 20.1 months with axitinib compared with 19.2 months with sorafenib. The largest benefit was seen in patients who received cytokines as first-line therapy and whose median PFS was 12.2 months with axitinib compared with 8.2 months with sorafenib, while median OS was 29.4 months with axitinib compared with 27.8 months with sorafenib. The median PFS for patients randomly assigned to sorafenib was 167 days compared with 84 days for patients randomly assigned to placebo (Motzer et al '13). Temsirolimus is an intravenously administered mammalian target of rapamycin (mTOR) inhibitor. Making temsirolimus the only therapy for renal cell carcinoma to clearly show results in longer OS than did interferon-alpha (Escudier et al '09). Median PFS was 4.0 months with everolimus compared with 1.9 months with placebo. No difference in OS was

reported [47] The combination of lenvatinib plus everolimus was compared with each medication as a single agent. Median PFS was significantly longer in the combination arm (14.6 months) than in the everolimus arm (5.5 months). Median OS in the lenvatinib-alone arm was 19.1 months and did not differ significantly from the other two arms (Motzer et al '15).

After immune checkpoint inhibitors and antiangiogenic targeted therapies were found to improve outcomes, the combination of these two approaches has been studied in clinical trials and shown to result in longer OS when compared with monotherapy. Median OS was 18.4 months in the sunitinib-alone arm and 13.9 months in the nephrectomy-followed-by-sunitinib arm (Mégean et al '18). 1-year OS was 90% in the pembrolizumab plus axitinib arm compared with 78% in the sunitinib arm. The objective response rate was 59.3% with combination therapy compared with 35.7% with sunitinib (Rini et al '18). In stage IV patients median PFS was 13.8 months in the combination arm compared with 8.4 months in the sunitinib arm (Motzer et al '19). The combination of ipilimumab and nivolumab was shown to prolong OS when compared with sunitinib as first-line systemic therapy for advanced-stage renal cell carcinoma in a randomized, controlled trial. Both drugs are immune checkpoint inhibitors. Ipilimumab is an antibody that targets CTLA-4. Nivolumab is an antibody that targets PD-1. 18-month OS was 75% in the ipilimumab-nivolumab arm compared with 60% in the sunitinib arm, difference in PFS was not statistically significant (Motzer et al '18).

**First-line treatment:** Radical nephrectomy (for T4, M0 lesions). Cytoreductive nephrectomy (for any T, M1 lesions in patients with good-risk disease). Ipilimumab plus nivolumab for patients with intermediate-risk or poor-risk disease. Pembrolizumab plus axitinib. Cabozantinib for patients with intermediate- or poor-risk disease. Avelumab plus axitinib. Sunitinib. Pazopanib. Temsirolimus. Bevacizumab with or without interferon-alpha. Interferon-alpha. IL-2. Palliative EBRT. **Second-line therapy:** Nivolumab (for patients who have previously been treated with a sunitinib, pazopanib, sorafenib, and/or axitinib). Lenvatinib plus everolimus in patients previously treated with sunitinib, pazopanib, cabozantinib, axitinib, or sorafenib. Cabozantinib (for patients who have previously been treated with sunitinib, pazopanib, sorafenib, or axitinib). Axitinib. Everolimus (for patients who have previously been treated with sunitinib and/or sorafenib). Sorafenib. Palliative EBRT (NCI '20).

In 2020, an estimated 81,400 new cases of **bladder cancer** will be diagnosed in the US and 17,980 people will die from the disease. The incidence rate is about 4 times higher in men than in women and 2 times higher in white men than in black men. Bladder cancer is the sixth most common cancer in the United States after lung cancer, prostate cancer, breast cancer, colon cancer, and lymphoma. It is the third most common cancer in men and the eleventh most common cancer in women. Of the roughly 70,000 new cases annually, about 53,000 are in men and about 18,000 are in women. Of the roughly 15,000 annual deaths, more than 10,000 are in men and fewer than 5,000 are in women. After decades of slowly increasing, bladder cancer incidence rates declined from 2007 to 2016 by about 1% per year. In contrast, the death rate for urinary bladder cancer has generally declined since at least the mid-1970s; from 2008 to 2017, the rate decreased by 0.3% per year. Tumors originating from the urothelial lining of the renal pelvis, ureter, urinary bladder, urethra, and prostatic ducts accounted for 2% of all malignant tumors annually in the United States with approximately 41,000 new cases and 11,000 deaths (2.5% of cancer deaths) in 1990. The mean age for bladder cancer is 68 years, and the incidence rises to 150 per 100,000 at age 70. The male to female ratio is 3:1 – it is the sixth most frequent tumor in males. Cyclophosphamide and phenacetin have been implicated as etiologic agents, as well as calculus disease and chronic infection. Patients surviving a renal pelvis tumor are 21

times more likely to develop another tumor within the urothelial tract than those without such a history (Yagoda '90: 253, 254).

Smoking is the most well-established **risk factor** for bladder cancer, accounting for almost half (47%) of all cases in the US. Risk is also increased among workers in the dye, rubber, leather, and aluminum industries; painters; people who live in communities with high levels of arsenic in the drinking water; and people with certain bladder birth defects or long-term urinary catheters (Yagoda '90: 253, 254). There is strong evidence linking exposure to carcinogens to bladder cancer. The most common risk factor for bladder cancer in the United States is cigarette smoking. It is estimated that up to half of all bladder cancers are caused by cigarette smoking and that smoking increases a person's risk of bladder cancer two to four times above baseline risk. Smokers with less functional polymorphisms of N-acetyltransferase-2 (known as slow acetylators) have a higher risk of bladder cancer than other smokers, presumably because of their reduced ability to detoxify carcinogens. Certain occupational exposures have also been linked to bladder cancer, and higher rates of bladder cancer have been reported in textile dye and rubber tire industries; among painters; leather workers; shoemakers; and aluminum-, iron-, and steelworkers. Specific chemicals linked to bladder carcinogenesis include beta-naphthylamine, 4-aminobiphenyl, and benzidine. Although these chemicals are now generally banned in Western countries, many other chemicals still in use are also suspected of causing bladder cancer (Kirkali et al '05). Exposure to the chemotherapy drug cyclophosphamide has also been associated with an increased risk of bladder cancer. Chronic urinary tract infections and infection with the parasite *S. haematobium* have also been associated with an increased risk of bladder cancer, often squamous cell carcinomas. Chronic inflammation is thought to play a key role in carcinogenesis in these settings (Monach et al '10).

The complete list of bladder cancer risk factors by the National Cancer Institute include the following: Use of tobacco, especially cigarettes. Family history of bladder cancer. Genetic mutations. HRAS mutation (Costello syndrome, facio-cutaneous-skeletal syndrome). Rb1 mutation. PTEN/MMAC1 mutation (Cowden syndrome). NAT2 slow acetylator phenotype. GSTM1 null phenotype. Occupational exposure to chemicals in processed paint, dye, metal, and petroleum products that include: Aluminum production (polycyclic aromatic hydrocarbons, fluorides). Aminobiphenyl and its metabolites. Aromatic amines, benzidine and its derivatives. Certain aldehydes. 2-Naphthylamine, beta-naphthylamine. O-Toluidine. Treatment with cyclophosphamide, ifosfamide, or pelvic radiation for other malignancies. Use of Chinese herbs: aristolochic acid extracted from species of *Aristolochia fangchi*. Exposure to arsenic. Arsenic in well water. Inorganic arsenic compounds (gallium arsenide). Exposure to chlorinated aliphatic hydrocarbons and chlorination by-products in treated water. *Schistosoma haematobium* bladder infections (bilharzial bladder cancer). Neurogenic bladder and associated use of indwelling catheters (NCI '20).

Bladder cancer is usually detected early because of **blood in the urine** or other symptoms, including increased frequency or urgency of urination or pain or irritation during urination. Less commonly, patients may complain of urinary frequency, nocturia, and dysuria, symptoms that are more common in patients with carcinoma *in situ*. Patients with upper urinary tract urothelial carcinomas may present with pain resulting from obstruction by the tumor. In patients with bladder cancer, upper urinary tract imaging is essential for staging and surveillance. This can be accomplished with ureteroscopy, retrograde pyelograms during cystoscopy, intravenous pyelograms, or computed tomography (CT) urograms. When bladder cancer is suspected, the most useful diagnostic test is cystoscopy. Radiological studies such as CT scans or ultrasound do not have sufficient sensitivity to be useful for detecting bladder cancers. Cystoscopy can be

performed in a urology clinic. If cancer is seen on cystoscopy, the patient is typically scheduled for bimanual examination under anesthesia and a repeat cystoscopy in an operating room so that transurethral resection of the tumor(s) and/or biopsies can be performed. If a high-grade cancer (including carcinoma *in situ*) or invasive cancer is seen, the patient is staged with a CT scan of the abdomen and pelvis (or CT urogram) and either a chest x-ray or chest CT scan. Patients with a nonhepatic elevation of alkaline phosphatase or symptoms suggestive of bone metastases undergo a bone scan (NCI '20).

Low-grade bladder cancer often recurs in the bladder after treatment but rarely invades the muscular wall of the bladder or spreads to other parts of the body. Patients rarely die from low-grade bladder cancer. High-grade bladder cancer commonly recurs in the bladder and has a strong tendency to invade the muscular wall of the bladder and spread to other parts of the body. Bladder cancer is also divided into muscle-invasive and nonmuscle-invasive disease, based on invasion of the muscularis propria (also referred to as the detrusor muscle), which is the thick muscle deep in the bladder wall. Under conditions of chronic inflammation, such as infection of the bladder with the *Schistosoma haematobium* parasite, squamous metaplasia may occur in the bladder. In addition to transitional cell carcinomas and squamous cell carcinomas, adenocarcinomas, small cell carcinomas, and sarcomas can form in the bladder. In the United States, transitional cell carcinomas derived of the uro-epithelium represent most (> 90%) bladder cancers About 2% to 7% are squamous cell carcinomas, and 2% are adenocarcinomas (Al-Ahmadie et al '1). However, a significant number of transitional cell carcinomas have areas of squamous or other differentiation. Cysts can occur in the urinary bladder. Embryonal rhabdomyosarcoma tends to occur in children. The majority of epidermoid tumors originate in the lateral and posterior bladder wall, while adenocarcinoma is found in the dome of the bladder and trigone. Tumors can occur within bladder diverticulum. Urachal cancer originates from the urachus, an embryologic remnant of the gut, similar to colonic adenocarcinoma, producing carcinoembryonic antigen (CEA). Beta human chorionic gonadotropin has been found histologically in up to 10% of transitional cell tumors and may be of prognostic significance. Common sites for metastases include lymph nodes, lung, liver and bone. Renal pelvis tumors tend to extend directly into the renal pelvis, down the ureter, and to regional lymph nodes (Yagoda '90: 253-257).

The most frequent sign is gross hematuria in 60% to 75% of cases, usually microscopic at first. Dysuria and increased urinary frequency due to bladder irritability are common signs. Over two-thirds of patients with positive nodes eventually die from disseminated disease (Yagoda '90: 253-257). Patients who die from bladder cancer almost always have disease that has metastasized from the bladder to other organs. Approximately 70% to 80% of patients with newly diagnosed bladder cancer will present with superficial bladder tumors (i.e., stage Ta, Tis, or T1). The prognosis of these patients depends largely on the grade of the tumor. Patients with high-grade tumors have a significant risk of dying of their cancer even if it is not muscle-invasive (Herr et al '00). Among patients with high-grade tumors, those who present with superficial, nonmuscle-invasive bladder cancer can usually be cured, and those with muscle-invasive disease can sometimes be cured. Bladder cancer tends to recur, even when it is noninvasive at the time of diagnosis; therefore, standard practice is to perform surveillance of the urinary tract after a diagnosis of bladder cancer (Manoharan et al '09).

**Cytoscopy** under anesthesia with manual palpation and appropriate biopsies is mandatory for a diagnosis. Urinary cytology is extremely useful and more often is positive after cystoscopy. Additional tests include an intravenous urogram to evaluate the upper tracts and the urinary

bladder, and a pelvic and abdominal CT scan. Prior to surgery, chest film, blood count, 12-channel screen and serum creatinine are needed (Yagoda '90: 253-257). Clinical staging, even when computed tomographic (CT) and/or magnetic resonance imaging (MRI) scans and other imaging modalities are used, often underestimates the extent of tumor, particularly in cancers that are less differentiated and more deeply invasive. CT imaging is the standard staging modality. A clinical benefit from obtaining MRI or positron emission tomography scans instead of CT imaging has not been demonstrated (Cowan et al '10).

### Bladder Cancer Staging System

Stage	Description
T	Primary Tumor
TX	Cannot be assessed.
T0	No tumor clinically detectable.
Tis	Carcinoma in situ (flat (JSM=0))
Ta	Papillary noninvasive tumor (JSM=0)
T1	No microscopic invasion beyond lamina propria, induration on bimanual examination, freely mobile mass which disappears after resection (JSM=0).
T2	Microscopic invasion of superficial bladder muscle, mobile induration of bladder on bimanual examination that disappears after resection (JSM=B1).
T3	Tumor invades into muscle perivesical fat, induration or nodular mobile mass that persists after transurethral resection.
T3a	Deep muscle invasion (JSM=B2).
T3b	Perivesical fat invasion (JSM=C).
T4	Tumor fixed or invades neighboring structures.
T4a	Prostate, uterus, vagina invasion (JSM=D1).
T4b	Tumor fixed to pelvic walls or invades abdominal walls.
N	Regional lymph nodes
NX	Cannot be assessed.
N0	No tumor.
N1	Single homolateral regional lymph node.
N2	Contralateral, bilateral, multiple regional nodes.
N3	Fixed mass on pelvic wall with space between mass and tumor (JSM=D1 for N1-3)
N4	Tumor involves juxtaregional lymph nodes (JSM=D2 for N\$ or M1).
M	Distant metastases
MX	Cannot be assessed.
M0	No known distant metastases.
M1	Distant metastases.

Source: Yagoda '90: Table 31-3, Pg. 255, Amin et al '17

**Surgery**, alone or in combination with other treatments, is used in more than 90% of cases. Early-stage cancers may be treated by removing the tumor and then administering immunotherapy (BCG-bacillus Calmette-Guérin) or chemotherapy drugs directly into the bladder (intravesical therapy). Treatment of nonmuscle-invasive bladder cancers (Ta, Tis, T1) is based on risk stratification. Essentially all patients are initially treated with a transurethral resection (TUR) of the bladder tumor followed by a single immediate instillation of intravesical chemotherapy (mitomycin C is typically used in the United States) (Babjuk et al '11). The relapse rate for TUR alone was 48% and 37% for TUR plus intravesical chemotherapy, including epirubicin, mitomycin C (MMC), thiotepa, and pirarubicin. 7 More advanced cancers may

require removal of the entire bladder (cystectomy). Patient outcomes are improved with the use of chemotherapy before cystectomy. Standard treatment for patients with muscle-invasive bladder cancers whose goal is cure is either neoadjuvant multiagent cisplatin-based chemotherapy followed by radical cystectomy and urinary diversion or radiation therapy with concomitant chemotherapy (James et al '12). Distant-stage cancers are typically treated with chemotherapy, sometimes along with radiation. Immunotherapy and targeted therapy drugs are newer options if chemotherapy cannot be used or is no longer working. Timely follow-up care is extremely important for all patients because of the high likelihood of cancer recurrence, or a subsequent bladder cancer. The 5-year relative survival rate for bladder cancer is 77%. Half (51%) of all cases are diagnosed before the tumor has spread beyond the layer of cells in which it developed (in situ), for which the 5-year survival is 96% (ACS '20: 26). Reconstructive techniques that fashion low-pressure storage reservoirs from the reconfigured small and large bowel eliminate the need for external drainage devices and, in many patients, allow voiding per urethra. These techniques are designed to improve the quality of life for patients who require cystectomy (Hautmann et al '93).

Therapy for superficial lesions (Stages 0, A and sometimes B1) is **endoscopic resection** and fulguration with cystoscopy repeated every 3 months. When lesions recur frequently or are diffuse, the standard therapy is thiophosphoramide (thiotepa) 60 mg/60 ml normal saline IV for 2 hours, weekly for 6 consecutive weeks. Approximately 30% to 40% of patients will respond, particularly those with low-grade lesions, but severe myelo-suppression may occur. BCG 120 mg/50 ml of normal saline has also been found to be extremely efficacious when given weekly for 6 weeks, resulting in 60% of cases achieving complete remission. Other agents include mitomycin-C, 20 mg to 60 mg/20 ml to 40 ml, and doxorubicin 20 mg to 60 mg; however both of these agents cause severe bladder irritation. Radical cystectomy is considered for diffuse or recurrent Tis lesions, a procedure resulting in a 5 year survival rate of more than 90%. Standard therapy for Stages B-C disease is radical cystectomy with resection of local pelvic nodes. Overall 5 year survival rates for Stages B-C range from 30% to 50% in patients presenting with papillary low-grade lesions, survival is 60% to 75%. When surgery is medically contraindicated, supervoltage irradiation, 6000 cGy to 7000 cGy in 6 to 8 weeks, can produce 5 year survival rates of approximately 20% to 30% or higher for B1-2 and C disease (Yagoda '90: 254-257).

The most active single **chemotherapeutic agents** are cisplatin and methotrexate, and to a lesser extent, doxorubicin, vinblastine and mitomycin-C. Single agents induce response in 15% to 30% of cases; few responses are complete. Combination chemotherapy programs have reported complete remission in 16% to 40% of cases, and partial response in an additional 15% to 30%. Most combinations employ cisplatin and doxorubicin, frequently with cyclophosphamide (CISCA), cisplatin and methotrexate together and with vinblastine (CMV) and doxorubicin (M-VAC). Such regimens seem to be efficacious against transitional cell carcinoma but not for Tis, squamous cell, or adenocarcinoma. Long-term remission has been reported in patients with metastatic disease. CMV induces a 28% complete remission rate leading to a 1 month median survival for patients with complete remission; a few are surviving more than 2 years. M-VAC has induced complete remission in 39% of patients with 58% surviving 22 to 47 months or more. Estimated median survival is 36 months. Prolongation of survival increased incidence of central nervous system metastasis with most patients dying from disseminated disease. Lymph node involvement (Stage D2, N1-4) is an extremely poor prognostic sign, with 50% of patients undergoing radical cystectomy and lymph node dissection dying in less than 1 year, and 87% in less than 2 years. The 5 year survival rate is 0% to 7% with most patients dying from disseminated disease (Yagoda '90: 254-257).

**Intravesical therapy** with thiotepa, MMC, doxorubicin, or BCG is most often used in patients with multiple tumors or recurrent tumors or as a prophylactic measure in high-risk patients after TUR (Igawa et al '96). Intravesical BCG is the treatment of choice for reducing the risk of cancer progression by 32% and is mainly used for cancers with an intermediate or high risk of progressing (Babju et al '11). With a median follow-up of 3.6 years, 47% of the BCG group had no evidence of disease and 26% of the chemotherapy group had no evidence of disease (Sylester et al '05). A study of three cycles of neoadjuvant cisplatin, methotrexate, vinblastine, and doxorubicin administered before cystectomy compared with cystectomy alone in 317 patients with stage T2 to stage T4a bladder cancer, showed that 5-year survival was 57% in the group that received neoadjuvant chemotherapy and 43% in the group treated with cystectomy alone (Grossman et al '03).

Definitive **radiation therapy** is a standard option that yields a 5-year survival of approximately 30% to 40%. When radiation therapy and chemotherapy are administered concomitantly, the results are better. Five-year OS was 48% in the chemoradiation therapy group and 35% in the radiation therapy group (James et al '12). Synchronous chemoradiation therapy using other chemotherapy regimens, such as cisplatin alone or combined with fluorouracil, have reported 5-year OS rates of 50% to 60% and survival with an intact bladder in 40% to 45% of patients (Efstathiou et al '06). Cisplatin-based combination chemotherapy regimens are the standard of care for stage IV bladder cancer (Kachnic et al '97). The only chemotherapy regimens that have been shown to result in longer survival in randomized controlled trials are methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); high-dose MVAC; and cisplatin, methotrexate, and vinblastine (CMV)(von der Maase et al '05). A comparison of MVAC with cisplatin, cyclophosphamide, and doxorubicin demonstrated improved response rate and longer median survival (48 weeks vs. 36 weeks) with the MVAC regimen (Logothetis et al '90). A comparison of MVAC with single-agent cisplatin in advanced bladder cancer also showed a significant advantage with MVAC in both response rate and median survival (12.5 months vs. 8.2 months (Loehrer et al '92). The median survival was 7 months with CMV compared with 4.5 months for methotrexate plus vinblastine (Meade et al '98).

Pembrolizumab is a humanized monoclonal antibody that binds to PD-1. In patients previously treated with platinum-based chemotherapy, pembrolizumab has been shown to prolong OS compared with second-line chemotherapy. As a result, pembrolizumab has been approved by the U.S. Food and Drug Administration (FDA) for patients with locally advanced or metastatic urothelial carcinoma who fall into one of the following three categories: Cisplatin-ineligible and have tumors that express PD-L1 (combined positive score [CPS] of at least 10%). Cisplatin- and carboplatin-ineligible. Progression of disease after treatment with platinum-based chemotherapy. OS was longer with pembrolizumab (10.3 months vs. 7.4 months. In patients with a PD-L1 CPS of at least 10%, median OS was 8.0 months with pembrolizumab compared with 5.2 months of chemotherapy. The PFS rate at 12 months was 16.8% in the pembrolizumab arm and 6.2%. The objective response rate was 21.1% in the pembrolizumab arm and 11.4% in the chemotherapy arm. Among those who responded, the median duration of response was longer than 18 months with pembrolizumab compared with a response of 4.3 months with chemotherapy. Pembrolizumab was associated with a lower rate of treatment-related adverse events than was chemotherapy (60.9% vs. 90.2%) and a lower rate of high-grade adverse events (15.0% vs. 49.4%). The most common adverse events with pembrolizumab were pruritus, fatigue, nausea, diarrhea, and decreased appetite. 55 In cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma, the overall response rate was 29%. In patients with a PD-L1

CPS of at least 10%, the overall response rate was 51% (Bellmunt et al '17). It is important to note that in 2018, the FDA issued an alert that preliminary data from two ongoing trials showed shorter survival in first-line therapy trials comparing pembrolizumab or atezolizumab with cisplatin or carboplatin-based therapy (Ballar et al '17).

Atezolizumab has been approved by the FDA for patients with locally advanced or metastatic urothelial carcinoma who fall into one of the following three categories: Cisplatin-ineligible and have tumors that express PD-L1 (at least 5% of the tumor area covered by tumor-infiltrating immune cells that stain for PD-L1). Cisplatin- and carboplatin-ineligible. Progression of disease after treatment with platinum-based chemotherapy. Median OS was 11.1 months for atezolizumab versus 10.6 months for chemotherapy in patients with at least 5% of tumor cells staining for PD-L1 (Powles et al '18). Response rates were also similar: 23% with atezolizumab and 22% with chemotherapy. Patients receiving atezolizumab had a lower rate of high-grade toxicity (20% vs. 43%) and a lower rate of treatment discontinuation resulting from adverse events (7% vs. 18%). A median follow-up of Nivolumab 15 months, 24% had an objective response, and 22% had grade 3 or 4 adverse events (Sharma et al '16). The overall response rate to Avelumab was 25.0% in patients with at least 5% of tumor cells staining for PD-L1 and 14.7% for those with less than 5% PD-L1 positivity. Median PFS was 6.3 weeks; 23% of the patients were progression free at 24 weeks. The overall response rate to Durvalumab was 17.8%. The response rate was 27.6% in patients with high expression of PD-L1 compared with 5.1% in patients with low or no PD-L1 expression. High-grade adverse events were reported in 6.8% of patients, including 2.1% with high-grade immune-mediated adverse events (Patel et al '18).

Enfortumab vedotin is a type of targeted therapy called an antibody-drug conjugate. Antibody-drug conjugates consist of a monoclonal antibody chemically linked to a drug. The monoclonal antibody part of enfortumab vedotin binds to a protein called nectin-4, which is found on the surface of most bladder cancer cells. The antibody is chemically linked to monomethyl auristatin E, or MMAE, a type of chemotherapy drug called a microtubule inhibitor. Once the conjugate is taken up by cells, the drug stops them from dividing and leads to their death. Enfortumab vedotin has been approved by the FDA for patients with metastatic urothelial carcinoma that has progressed after treatment with both platinum-based first-line chemotherapy and second-line therapy with an immune checkpoint inhibitor. The approval was based on a single-arm trial of 125 patients with metastatic urothelial carcinoma. There was a 44% overall response rate and a 12% complete response rate. The median duration of response was 7.6 months. Adverse events included fatigue (50%), peripheral neuropathy (50%), alopecia (49%), rash (48%), decreased appetite (44%), and dysgeusia (40%) (Rosenberg et al '19). Erdafitinib (JNJ-42756493) is a potent tyrosine kinase inhibitor of fibroblast growth factor receptors 1–4. It has been approved by the FDA for patients with urothelial carcinoma that has a mutation in one of the four fibroblast growth factor receptor genes and that has progressed after receiving chemotherapy. Roughly 20% of metastatic urothelial carcinomas of the bladder have mutations of *FGFR*, as do 35% of urothelial carcinomas of the ureters and renal pelvis. The response rate by independent radiologic review was 34%. The response rate was higher among the subjects with *FGFR3* mutations than among the subjects with *FGFR2/FGFR3* fusions. Grade 3 adverse events that affected at least 10% of subjects included stomatitis and hyponatremia. The most common adverse events of any grade were hypophosphatemia (77%), stomatitis (58%), diarrhea (51%), dry mouth (46%), decreased appetite (38%), and dysgeusia (37%) (Loriot et al '19).

Urethral cancer is rare. The annual incidence rate for urethral cancer in the Surveillance, Epidemiology, and End Results (SEER) database during the period from 1973 to 2002 in the United States for men was 4.3 per million and for women was 1.5 per million, with downward trends over the three decades (Swartz et al '06). The incidence was twice as high in African Americans as in whites (5 per million vs. 2.5 per million). Urethral cancers appear to be associated with infection with human papillomavirus (HPV), particularly HPV16, a strain of HPV known to be causative for cervical cancer (Wiener et al '94). The female urethra is largely contained within the anterior vaginal wall. In adults, it is about 4 cm in length. The male urethra, which averages about 20 cm in length, is divided into distal and proximal portions. The distal urethra, which extends distally to proximally from the tip of the penis to just before the prostate, includes the meatus, the fossa navicularis, the penile or pendulous urethra, and the bulbar urethra. The proximal urethra, which extends from the bulbar urethra to the bladder neck, includes distally to proximally the membranous urethra and the prostatic urethra. Superficial tumors located in the distal urethra of both the female and male are generally curable. However, deeply invasive lesions are rarely curable by any combination of therapies. In men, the prognosis of tumors in the distal (pendulous) urethra is better than for tumors of the proximal (bulbomembranous) and prostatic urethra, which tend to present at more advanced stages (Dalbagni et al '99). Likewise, distal urethral tumors tend to occur at earlier stages in women, and they appear to have a better prognosis than proximal tumors (Gheiler et al '98).

The most common histologic types of urethral cancer were the following: Transitional cell (55%). Squamous cell (21.5%). Adenocarcinoma (16.4%). Other cell types, such as melanoma, were extremely rare. The female urethra is lined by transitional cell mucosa proximally and stratified squamous cells distally. Therefore, transitional cell carcinoma is most common in the proximal urethra and squamous cell carcinoma predominates in the distal urethra. Adenocarcinoma may occur in both locations and arises from metaplasia of the numerous periurethral glands. The male urethra is lined by transitional cells in its prostatic and membranous portion and stratified columnar epithelium to stratified squamous epithelium in the bulbous and penile portions. The submucosa of the urethra contains numerous glands. Therefore, urethral cancer in the male can manifest the histological characteristics of transitional cell carcinoma, squamous cell carcinoma, or adenocarcinoma. Except for the prostatic urethra, where transitional cell carcinoma is most common, squamous cell carcinoma is the predominant histology of urethral neoplasms. Because transitional cell carcinoma of the prostatic urethra may be associated with transitional cell carcinoma of the bladder and/or transitional cell carcinoma arising in prostatic ducts, it is often treated similarly to these primaries and should be separated from the more distal carcinomas of the urethra (Swartz et al '06). Approximately 5% to 10% of men with cystectomy for bladder cancer may have or may develop urethral cancer distal to the urogenital diaphragm (Mark et al '19). Endoscopic examination, urethrography, and magnetic resonance imaging are useful in determining the local extent of the tumor (Ryu et al '01). The AJCC has designated staging by TNM (tumor, node, metastasis) classification to define urethral cancer (Amin et al '17).

Surgery is the mainstay of therapy for urethral cancers in both women and men. The surgical approach depends on tumor stage and anatomic location, and tumor grade plays a less important role in treatment decisions. Although the traditional recommendation has been to achieve a 2-cm tumor-free margin, the optimal surgical margin has not been rigorously studied and is not well defined. The role of lymph node dissection is not clear in the absence of clinical involvement, and the role of prophylactic dissection is controversial. Radiation therapy and/or chemotherapy may be added in some cases in patients with extensive disease or in an attempt at organ

preservation; but there are no clear guidelines for patient selection, and the low level of evidence precludes confident conclusions about their incremental benefit. Ablative techniques, such as transurethral resection, electroresection and fulguration, or laser vaporization-coagulation, are used to preserve organ function in cases of superficial anterior tumors, although the supporting literature is scant (Karnes et al '10). Radiation therapy with external beam, brachytherapy, or a combination is sometimes used for the primary therapy of early-stage proximal urethral cancers, particularly in women. Brachytherapy may be delivered with low-dose-rate iridium Ir 192 sources using a template or urethral catheter. Definitive radiation is also sometimes used for advanced-stage tumors, but because monotherapy of large tumors has shown poor tumor control, it is more frequently incorporated into combined modality therapy after surgery or with chemotherapy. The most commonly used tumor doses are in the range of 60 Gy to 70 Gy. Severe complication rates for definitive radiation are about 16% to 20% and include fistula development, especially for large tumors invading the vagina, bladder, or rectum. Urethral strictures also occur in the setting of urethral-sparing treatment. Toxicity rates increase at doses greater than 65 Gy to 70 Gy. Intensity-modulated radiation therapy has come into more common use in an attempt to decrease local morbidity of the radiation (Koontz et al '10).

The literature on chemotherapy for urethral carcinoma is anecdotal in nature and restricted to retrospective, single-center case series or case reports. A wide variety of agents used alone or in combination have been reported over the years, and their use has largely been extrapolated from experience with other urinary tract tumors. For squamous cell cancers, agents that have been used in penile cancer or anal carcinoma include: Cisplatin. Fluorouracil. Bleomycin. Methotrexate. Irinotecan. Gemcitabine. Paclitaxel. Docetaxel. Mitomycin-C (Trabulsi et al '10). Chemotherapy for transitional cell urethral tumors is extrapolated from experience with transitional cell bladder tumors and, therefore, usually contains the following: Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Paclitaxel. Carboplatin. Ifosfamide, with occasional complete responses. Chemotherapy has been used alone for metastatic disease or in combination with radiation therapy and/or surgery for locally advanced urethral cancer. It may be used in the neoadjuvant setting with radiation therapy in an attempt to increase the resectability rate or in an attempt at organ preservation (Mark et al '19). However, the impact of any of these regimens on survival is not known for any stage or setting.

## 15. Myeloma

Bone pain, known as **myeloma**, or multiple myeloma if there are multiple bone infections, is an extremely common serious complication because it is crippling and untreated infections can break through the bone to marrow causing leukemia or through soft tissue to the lymphatic system, causing lymphomas. Bone pain is the primary physical symptom of leukemia and is the most painful symptom in lymphoma. **Multiple myeloma** is plasma cell cancer that originates in the bone marrow and is characterized by involvement of the skeleton at multiple sites with peak incidence between 50 and 60 years. Infiltration of bone is manifested by pain and stress fractures. Multiple myeloma presents most often as multifocal destructive bone lesions throughout the skeletal system vertebral column 66%, ribs 44%, skull 41%, pelvis 28%, femur 24% clavicle 10% and scapula 10%. Focal lesions begin in the medullary cavity, erode the calcareous bone and progressively destroy the cortical bone. Fractures are often produced by plasma cell lesions. On section, the bony defects are typically filled with soft, red, gelatinous tissue. Most commonly the lesions appear radiographically as punched out defects, usually 1 to 4 cm in diameter. Increased numbers of plasma cells in the marrow constitute 10 to 90% of total.

Renal involvement, generally called **myeloma nephrosis**, causes abnormal plasma cells to be encountered or at least proteinaceous casts surrounded by giant cells, and hypercalcemia and pyelonephritis may occur. **Hypercalcemia** resulting from bone reabsorption may give rise to neurologic manifestations such as confusion, weakness, lethargy, constipation and polyuria. Recurrent infections with bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *E. coli* resulting from severe suppression of normal immunoglobulins, also pose a major clinical problem. In 99% of patients with multiple myeloma, electrophoretic analysis reveals increases levels of immunoglobulins in the blood and/or light chains (**Bence Jones proteins**) in the urine. It may also spread to extra-osseous sites. Renal insufficiency is the second leading cause of death after infection. The neoplastic plasma cells synthesize complete or incomplete immunoglobulins.

**Diagnosis** rests on radiographic and laboratory findings. The lesions appear as sharply punched out defects having a rounded soap-bubble appearance on x-ray film, but generalized osteoporosis may be seen. Marrow examination reveals aggregates of plasma cells that suppress and replace normal hematopoietic elements. The resultant marrow failure gives rise to a normocytic normochromic anemia, sometimes accompanied by moderate leukopenia and thrombocytopenia. Rarely plasma cells flood the peripheral blood, giving rise to plasma cell leukemia. Prognosis depends on the stage at the time of diagnosis. Patients with multiple bony lesions, if untreated, rarely survive for more than 6 to 12 months. Chemotherapy in the form of alkylating agents induces remission in 50 to 70% of patients, but the median survival is still a dismal 3 years. Autologous and allogeneic bone marrow transplantation after intensive chemotherapy offers the promise of cure. High serum levels of cytokine IL-6 is associated with a poor prognosis. Loss of bone is in large part due to osteoclastic reabsorption induced by the tumor.

Malignant proliferative disorders constitute the most important part of white cell disorders.

**Malignant lymphomas** take the form of cohesive tumorous lesions, composed mainly of lymphocytes and rarely of histiocytes, that arise in lymphoid tissue anywhere in the body, most commonly within lymph nodes. **Leukemias** and myeloproliferative disorders are neoplasms of the hematopoietic stem cells arising in the bone marrow that secondarily flood the circulating blood or other organs with transformed cells. **Plasma cells dyscrasias** and related disorders usually arising in the bones, take the form of localized or disseminated proliferations of antibody forming cells. Thus, this category is marked by the appearance in the peripheral blood of abnormal levels of complete immunoglobulins or the light or heavy chains of the immunoglobulins. The histiocytoses represent proliferative lesions of histiocytes that include rare histiocytic neoplasms that present as malignant lymphomas,. A special category of histiocytes referred to as **Langerhans' cell histiocytes** gives rise to a spectrum of disorders, some of which behave disseminated malignant tumors and others as localized benign proliferations (Saunders '94: 633, 634).

**Solitary myeloma (plasmacytoma)** lesion occurs in 3 to 5% of monoclonal gammopathies. Extraosseous lesions are often located in the lungs, oronasopharynx, or nasal sinuses. Progression to classic multiple myeloma becomes manifest in most patients with osseous plasmacytoma, whereas extraosseous primaries rarely disseminate. Solitary plasmacytoma involving the bones is an early stage of multiple myeloma, but in some individual sites may be present for 10 to 20 years without progression. Extraosseous plasmacytomas, particularly involving the upper respiratory tract, are limited disease that can usually be cured by local resection (Saunders '94: 663-665). **Plasma cell dyscrasias** account for 15% of all deaths from malignant white cell disease. Plasma cell myeloma is the most important and most common syndrome characterized

by multiple neoplastic tumorous masses of plasma cells scattered throughout the skeletal system. Waldenström's macroglobulinemia associated with lymphadenopathy and hepatosplenomegaly, but the lytic bone lesions are not present. **Heavy-chain disease** is rare gammopathy infiltrating plasma cells and precursors that synthesize only heavy chains. Primary or immunocyte associated amyloidosis is a monoclonal proliferation of plasma cells, with excessive production of free light chains that are deposited as amyloid. **Monoclonal gammopathy** of undetermined significant. Expansion of incomplete monoclonal immunoglobulin secreting cells in the plasma and/or urine called dyscracias, gammopathies, monoclonal gammopathies, dysproteinemias, and paraproteinemias (Saunders '94: 662, 663). Distinctly affiliated with **monoclonal antibodies** diverted from oncology to afflict pain and methicillin resistant Staphylococcus aureus (MRSA) to specific locations in the anatomy.

Normocytic, **normochromic anemia** is present in 60% of patients at diagnosis. It is due primarily to the decreased production of red blood cells by marrow, infiltration with plasma cells, and the suppressive effect of various cytokines. Patients with renal failure may also have decreased levels of erythropoietin, which can worsen the degree of anemia. Among newly diagnosed patients, up to 20% have hypercalcemia (corrected serum calcium level > 11.5 mg/dL) secondary to progressive bone destruction, which may be exacerbated by prolonged immobility, especially in the context of fracture. **Hypercalcemia** should be suspected in patients with myeloma who have nausea, fatigue, confusion, polyuria, or constipation. It may also suggest high tumor burden. It should be considered an oncologic emergency and requires prompt treatment with aggressive hydration, use of bisphosphonates, calcitonin, and antimyeloma therapy, including steroids. Approximately 20% of patients present with renal insufficiency and at least another 20% to 40% develop this complication in later phases of the disease. Light-chain cast nephropathy is the most common cause of renal failure. Additional causes include hypercalcemia, dehydration, and hyperuricemia. Less commonly, amyloidosis, light-chain deposition disease, non-steroidal anti-inflammatory agents taken for pain control, intravenous radiographic contrast administration, and calcium stones may contribute to renal failure. Bisphosphonate therapy has been associated with the kidney problem azotemia, which is usually reversible with treatment cessation.

### Common Laboratory Features of Plasma Cell Dyscracias and Myeloma

Disease	Laboratory Features
Multiple Myeloma	Marrow plasmacytosis >10% Clonal immunoglobulin peak > 3.0 g/dL Presence of Bence-Jones protein Lytic bone lesions and/or diffuse osteopenia Related organ or tissue impairment
Smoldering myeloma	Monoclonal immunoglobulin level > 3.0 g/dL No symptoms due to plasma cell dyscracia No lytic bone disease Normal calcium and renal function No anemia
Solitary plasmacytoma of bone	Solitary lesion due to plasma cell tumor Normal skeletal survey and MRI of skull, spine and pelvis Normal bone marrow plasmacytosis No anemia, hypercalcemia or renal disease Preserved levels of uninvolved immunoglobulins

Monoclonal gammopathy of unknown significance (MGUS)	Monoclonal immunoglobulin level < 3.0 g/dL Bone marrow plasma cells < 10% No bone lesions No symptoms due to plasma cell dyscrasia Usually preserved levels of uninvolved immunoglobulins No related organ or tissue impairment
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Source: Jagannath. Cancernetwork '11

**Waldenström macroglobulinemia**, constituting about 5% of monoclonal gammopathies, is a disease of old age, usually the sixth and seventh decades. Half of patients have lymphadenopathy, hepatomegaly and splenomegaly. Visual impairment from distention and hemorrhage of retinal veins, neurologic problems such as headaches, dizziness, deafness and stupor, from sluggish blood flow; bleeding, cryoglobulinemia from precipitation of macroglobulins at low temperatures produces symptoms such as Raynaud's phenomenon and cold urticarial. It is marked by a diffuse, leukemia-like infiltration of the bone marrow by lymphocytes, plasma cells and hybrid forms that synthesize a monoclonal IgM immunoglobulin, leading to macroglobulinemia. The tumor cells diffusely infiltrate the lymphoid tissues, including bone marrow, spleen and lymph nodes.

**Heavy chain disease** is an extremely rare monoclonal gammopathy characterized by elevated levels in the blood or urine of specific heavy chain immunoglobulins. Gamma-chain disease is found most often in the elderly, and resembles malignant lymphoma, manifesting in lymphadenopathy, anemia, and fever, often accompanied by malaise, weakness and hepatomegaly or splenomegaly. The course can be rapidly downhill to death within a few months or protracted for years. Alpha-chain disease is most common occurring mostly in young adults in the Mediterranean area. Mu-chain disease is the rarest, most often encountered in patients with chronic lymphocytic leukemia, hepatomegaly and splenomegaly are usually present but peripheral lymphadenopathy is inconspicuous. M proteins can be identified in the serum of 1% of asymptomatic healthy persons older than 50 years of age and in 3% older than 70 years.

To this dysproteinemia without associated disease, the term "monoclonal gammopathy of undetermined significance (MGUS) is applied. MGUS is the most common monoclonal gammopathy. Beware of **Monoclonal antibodies** diverted from oncology to afflict pain and methicillin resistant Staphylococcus aureus (MRSA) to specific locations in the anatomy. Approximately 20% of patients develop well-defined plasma cell dyscrasia (myeloma, Waldenström's macroglobulinemia or amyloidosis) over a period of 10 to 15 years. In general patients with MGUS have less than 3 gm/dl of monoclonal protein in the serum and no Bence Jones proteinuria. Whether a given patient will follow a benign course, as most do, or develop well-defined plasma cell neoplasm cannot be predicted wherefore periodic assessment of serum M component levels and Bence Jones proteinuria is warranted (Saunders '94: 665, 666). In recent years, the drugs Fludara (fludarabine) and Leustatin (cladribine) have become the first chemotherapy drugs given to people with Waldenstrom's macroglobulinemia. Sometimes Cytosan (cyclophosphamide) is added. Other commonly used chemotherapy drugs are Luekeran (chlorambucil) and prednisone, usually given together, or Adriamycin (doxorubicin). Sometimes an individual may start with one combination of drugs, then switch to another combination that is more effective. Another drug used to treat Waldenstrom's macroglobulinemia is Rituxan (rituximab). Some doctors may use this drug for hard-to-treat disease; others may combine it with chemotherapy drugs at the start of treatment. Campath (alemtuzumab) has also been an effective treatment, as has Velcade (bortezomib).

The term **histiocytosis** is an umbrella designation for a variety of proliferative disorders of histiocytes of macrophages. The histiocytic diseases in children and adults are caused by an abnormal accumulation of cells of the mononuclear phagocytic system. Some histiocytic lymphomas are clearly malignant but reactive histiocytic proliferations in the lymph nodes are benign. The **Langerhans' cell histiocytoses** are associated with tumor like proliferations, but they are not truly neoplastic. The proliferating cell is the Langerhans' cell of marrow origin which is normally found in the epidermis. LCH results from the clonal proliferation of immunophenotypically and functionally immature, morphologically rounded LCH cells found in relevant lesions along with eosinophils, macrophages, lymphocytes, and, occasionally, multinucleated giant cells. The pathologic histiocyte or LCH cell has a gene expression profile closely resembling that of a myeloid dendritic cell. Studies have also demonstrated that the BRAF V600E mutation can be identified in mononuclear cells in peripheral blood and cell-free DNA, usually in patients with disseminated disease. This shows that multisystem LCH arises from a somatic mutation within a marrow or circulating precursor cell, while localized disease arises from the mutation occurring in a precursor cell at the local site (Berres et al '14). The same BRAF V600E mutation has been found in many cancers; however, V600E-mutated BRAF is also present in benign nevi, possibly indicating the need for additional mutations for malignant transformation (Badalian-Very et al '13).

The annual incidence of Langerhans cell histiocytosis (LCH) has been estimated to be between 2 and 10 cases per 1 million children aged 15 years or younger (Stålemark et al '08). The male-to-female ratio (M:F) is close to one, and the median age of presentation is 30 months. LCH most commonly presents with a painful bone lesion, with skin being the second most commonly involved organ. Systemic symptoms of fever, weight loss, diarrhea, edema, dyspnea, polydipsia, and polyuria relate to specific organ involvement. Data showed an overall survival (OS) rate of 84% for patients treated for 12 months with systemic chemotherapy. Overall, recurrences have been found in 10% of patients with single-system unifocal disease, 25% of patients with single-system multifocal bone LCH, and 50% of both low-risk multisystem patients and high-risk multisystem patients who achieve nonactive disease status with chemotherapy. HISTSOC-LCH-III data showed a significant difference in reactivation rate for low-risk organ patients randomly assigned to receive 6 months of treatment (54%) versus 12 months of treatment (37%) (Gadner et al '13).

Langerhans' cell histiocytosis presents as three clinicopathologic entities. Acute disseminated Langerhans' cell histiocytosis (Letterer-Siwe disease) occurs most frequently before two years of age but occasionally may affect adults. Cutaneous lesions resemble a seborrheic eruption secondary to infiltration of Langerhans' histiocytes over the front and back of the trunk and on the scalp. Most patients have hepatosplenomegaly, lymphadenopathy, pulmonary lesions and eventually destructive osteolytic bone lesions. Extensive infiltration of the marrow often leads to anemia, thrombocytopenia, and predisposition to recurrent infections such as otitis media and mastoiditis. The course of untreated disease is rapidly fatal, with intensive chemotherapy 50% of patients survive 5 years. Unifocal lesions usually affect the skeletal system, they may be asymptomatic or cause pain and tenderness predisposing to stress fracture. It may heal spontaneously or be cured by local excision or irradiation. Multifocal Langerhans' cell histiocytosis usually affects children who present with fever, diffuse eruptions, particularly on the scalp and in the ear canals, and frequent bouts of otitis media, mastoiditis and upper respiratory tract infections. An infiltrate of Langerhans' cells may lead to mild lymphadenopathy, hepatomegaly, and splenomegaly. In about 50% of patients, involvement of

the posterior pituitary stalk of the hypothalamus leads to diabetes insipidus, which does not seem to be treated with chemotherapy. The combination of calvarial bone defects, diabetes insipidus and exophthalmos is referred to as the **Hand-Schüller-Christain triad**. Many patients experience spontaneous regression, others can be treated with chemotherapy (Saunders '94: 666, 667).

Childhood LCH is treated with medium- to high-potency topical steroids are effective, but recurrence after discontinuation is common and osteonecrosis from Cushing's disease is a threat (Lau et al '06). Oral methotrexate (20 mg/m<sup>2</sup>) weekly for 6 to 12 months (Steen et al '01). Oral hydroxyurea (20 mg/kg) daily for at least 12 months (Zinn et al '16). Oral thalidomide 50 mg to 200 mg nightly (McClain et al '07). Oral thalidomide may be effective for both pediatric and adult patients. Curettage is used for isolated bone lesions. Low-dose radiation therapy (7–10 Gy) is effective (Selch et al '90). The current treatment for CNS-risk bones is 12 months of vinblastine/prednisone therapy. Weekly vinblastine (6 mg/m<sup>2</sup>) for 7 weeks for good response. Daily prednisone (40 mg/m<sup>2</sup>) for 4 weeks, then tapered over 2 weeks. Afterward, prednisone is given for 5 days at 40 mg/m<sup>2</sup> every 3 weeks with the vinblastine injections (Gadner et al '13). Treatment included a 6-week induction regimen of cytarabine, vincristine, and prednisolone followed by 6 months of maintenance therapy with cytarabine, vincristine, prednisolone, and low-dose intravenous methotrexate. If patients had a poor response to the initial regimen, they were switched to a salvage regimen of intensive combination doxorubicin, cyclophosphamide, methotrexate, vincristine, and prednisolone. The 5-year response rate was 78%, and the OS rate was 95% for patients with multisystem disease. Diabetes insipidus occurred in 8.9% of patients with multisystem disease (Morimoto et al '06). Intensive acute myeloid leukemia–like protocol consisting of cladribine and cytarabine showed a progression-free survival rate of 63% and a 5-year overall survival (OS) rate of 85% in this refractory high-risk patient population (Donadieu et al '15). Eleven patients with recurrent multisystem high-risk and low-risk disease treated with clofarabine had an OS rate of 90% (Simko et al '14). Bisphosphonate therapy can also be effective for treating LCH bone lesions (Chellapandian et al '16). A nationwide survey from Japan described 16 children treated with bisphosphonates for bone LCH. All of the children had bone disease; none had risk-organ disease. Most patients received six cycles of pamidronate at 1 mg/kg per course given at 4-week intervals. In 12 of 16 patients, all active lesions including skin (n = 3) and soft tissues (n = 3) resolved. Eight patients remained disease free at a median of 3.3 years (Morimoto et al '11). Other bisphosphonates such as zoledronate have been used to successfully treat bone LCH (Sivendran et al '11).

It is estimated that one to two adult cases of LCH occur per 1 million population (Baumgartner et al '97). A German registry with 121 registrants showed that 62% had single-organ involvement and 38% had multisystem involvement, while 34% of the total study population had lung involvement. The median age at diagnosis was 44 years (±12.8 years). The most common organ involved was lung, followed by bone and skin. Presenting symptoms from published studies are (in order of decreasing frequency) dyspnea or tachypnea, polydipsia and polyuria, bone pain, lymphadenopathy, weight loss, fever, gingival hypertrophy, ataxia, and memory problems. The signs of LCH are skin rash, scalp nodules, soft tissue swelling near bone lesions, lymphadenopathy, gingival hypertrophy, and hepatosplenomegaly (Kaltsas et al '00). Fifty-nine percent of patients do well with either spontaneous remission with cessation of smoking, or with some form of therapy.[8] Patients receiving lung transplants for the treatment of pulmonary LCH have a 77% survival rate at 1 year and a 54% survival rate at 10 years, with a 20% chance of LCH recurrence (Dauriat et al '06). Single-bone lesions should undergo curettage of the lesion followed by observation, with or without intralesional corticosteroids. Skin lesions should

be surgically removed. Chemotherapy regimens, including cladribine, have been published. A retrospective analysis of 80 patients treated with radiation therapy alone reported a 77% complete remission rate and a 12.5% partial remission rate, with 80% long-term control noted in adults (Kriz et al '13). Case reports and case series have described the successful use of bisphosphonates, both intravenous pamidronate and oral zoledronate, in controlling severe bone pain in patients with multiple osteolytic LCH bone lesions (Brown et al '01). Another approach using anti-inflammatory agents (pioglitazone and rofecoxib) coupled with trofosfamide in a specific timed sequence was successful in two patients who had disease resistant to standard chemotherapy treatment (Reichle et al '05). Topical or intralesional corticosteroid. Topical tacrolimus. Topical imiquimod (O'Kane et al '09). Psoralen and long-wave ultraviolet A radiation (PUVA) and UVB. Therapies such as PUVA/UVB may be more useful in adults because long-term toxicity may be reduced (Vogel et al '08). Systemic therapy for severe skin LCH includes oral methotrexate, hydroxyurea, oral thalidomide, oral interferon-alpha, or combinations of interferon and thalidomide (Zinn et al '16). In a series of five adults treated with cladribine three patients achieved complete remissions and two patients achieved partial remissions (Pardani et al '03). Methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) was used in seven patients for 12 weeks, responses were seen in all patients, two with partial responses and five with complete responses (Derenzini et al '10). Imatinib mesylate was effective in the treatment of four out of five adult patients with LCH who had skin, lung, bone, and/or CNS involvement (Janku et al '10).

**Chemotherapy for Multiple Myeloma, Plasma Cell Dyscracias, Waldenström macroglobulinemia and Langerhans' cell histiocytoses**

Multiple Myeloma and Plasma Cell Dyscracias	Oral Thalidomide, with dexamethasone, a corticosteroid. Others: Bortezomib, Carfilzomib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytosan (Cyclophosphamide), Doxil (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride Liposome, Dox-SL (Doxorubicin Hydrochloride Liposome), Evacet (Doxorubicin Hydrochloride Liposome), Kyprolis (Carfilzomib), Lenalidomide, LipoDox (Doxorubicin Hydrochloride Liposome), Mozobil (Plerixafor), Neosar (Cyclophosphamide), Plerixafor Pomalidomide (Pomalyst), Pomalyst, Revlimid (Lenalidomide), Synovir (Thalidomide), Thalidomide, Thalomid (Thalidomide), Velcade (Bortezomib), Zoledronic Acid Zometa (Zoledronic Acid).
Waldenström macroglobulinemia	Fludara (fludarabine) and Leustatin (cladribine) first to try. Cytosan (cyclophosphamide) may be added. Other commonly used chemotherapy drugs are Luekeran (chlorambucil) and prednisone, usually given together, or Adriamycin (doxorubicin). Rituxan (rituximab). Campath (alemtuzumab) has also been an effective treatment, as has Velcade (bortezomib).
Langerhans' cell histiocytoses	Oral methotrexate (20 mg/m <sup>2</sup> ) weekly for 6 months or Oral thalidomide 50 mg to 200 mg nightly, with prednisone are taken for low risk disease or vinblastine IV and prednisone for patients with more complicated cases requiring radiation and surgery

Source: FDA

Oral Thalidomide, used in conjunction with dexamethasone, a corticosteroid, are the first FDA approved drugs usually taken by people diagnosed with multiple myeloma and plasma cell dyscrasias. Others include: Bortezomib, Carfilzomib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Doxil (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride Liposome, Dox-SL (Doxorubicin Hydrochloride Liposome), Evacet (Doxorubicin Hydrochloride Liposome), Kyprolis (Carfilzomib), Lenalidomide, LipoDox (Doxorubicin Hydrochloride Liposome), Mozobil (Plerixafor), Neosar (Cyclophosphamide), Plerixafor Pomalidomide (Pomalyst), Pomalyst, Revlimid (Lenalidomide), Synovir (Thalidomide), Thalidomide, Thalomid (Thalidomide), Velcade (Bortezomib), Zoledronic Acid Zometa (Zoledronic Acid). Radiation therapy may be done to relieve bone pain or treat a bone tumor.

Two types of **bone marrow transplantation** may be tried: Autologous bone marrow or stem cell transplantation makes use of one's own stem cells. Allogeneic transplant makes use of someone else's stem cells. This treatment carries serious risks but offers the chance of improved survival. Many patients with myeloma develop bacterial infections that may be serious, and infectious complications remain the most common cause of death in myeloma patients. In the past, gram-positive organisms (eg, *Streptococcus pneumoniae*, *Staphylococcus aureus*) and *Haemophilus influenzae* were the most common pathogens. More recently, however, infections with gram-negative organisms, anaerobes, and fungi have become frequent. The increased susceptibility of patients with multiple myeloma to bacterial infections, specifically with encapsulated organisms, has been attributed to impairments of host-defense mechanisms, such as hypogammaglobulinemia, qualitative deficiency in immunoglobulin function, granulocytopenia, decreased cell-mediated immunity, and the prolonged use of steroids.

**Fungal infections** often cause excruciating bone pain and can theoretically lead to white cell disease if the infection breaks through the bone and eats the marrow. Athletes foot crème (clotrimazole) is generally effective. Another antifungal foot powder spray (toftate), powder being prescribed for elders, however caused a diffuse pain to occur, and elders are definitely recommended to use clotrimazole (athlete's foot cream) as their basic antifungal, Athlete's foot cream (clotrimazole) can be purchased for \$1 and lasts about one of three weeks recommended for the treatment of athlete's foot, jock itch and bone pain. Make no mistake, cancer is not a fungal infection, but some fungi, such as *Aspergillus* are highly carcinogenic, underdiagnosed and potentially untreated in leukemia and myeloma patients with hydrocortisone crème wherever it hurts above the shin. There are several oral antifungal drugs such as Lamisil and Grifulvin V available for the treatment of athlete's foot and toenail and fingernail onychomycosis. *Aspergillois niger*, and other insidious fungal pathogens are treated to a fingernail pulse of SporanoX (itraconazole), a highly effective broad spectrum oral antifungal used in the treatment of both pulmonary and extra pulmonary invasive aspergillus as well as the common onychomycosis and histoplasmosis - 200 mg 3 times daily for 3 days, then 200 mg twice daily until no longer immune-compromised. For primary prophylaxis of aspergillois in immunocompromised individuals at high risk of invasive disease such as neutropenic patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) or hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD). IDSA considers posaconazole the drug of choice; alternatives are itraconazole or micafungin. The prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy and also for oropharyngeal

candidiasis. Sporanox is hepatotoxic and liver enzymes must be monitored on a monthly basis and is highly contraindicated in heart failure due to adverse drug reactions with antihypertensive drugs. IV amphotericin B is the preferred alternative to oral Sporanox (itraconazole). The effectiveness of oral antifungals is 60-80%. There is still a chance of re-infection after finishing the course of the medication. The re-infection rate is 15% but can be as high as 25% in diabetics. Hygiene is important. Serious adverse reactions are less than 0.5%. There are some interactions between these medication and other drugs such as cyclosporine, cimetidine, rifampin, terfenadine, and caffeine (Debrowolski '04: 14-16).

## 16. Leukemia

There were 48,610 new cases and 23,720 deaths from **leukemia** estimated in the United States in 2013. In 2020, an estimated 60,530 new cases of leukemia will be diagnosed in the US and 23,100 people will die from the disease. The leukemias are malignant neoplasms of the hematopoietic stem cells characterized by diffuse replacement of the bone marrow by neoplastic cells. These cells may also infiltrate the liver, spleen, lymph nodes and other tissues throughout the body. Although the presence of excessive numbers of abnormal cells in the peripheral blood is the most dramatic manifestation of leukemia, it should be remembered that the leukemias are primary disorders of the bone marrow although some patients with a diffusely infiltrated bone marrow may present with leukopenia. Two major variants of acute and chronic leukemias are recognized: lymphocytic and myelocytic (myelogenous). Thus, a simple classification would have four patterns of leukemia: acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelocytic (myeloblastic) leukemia (AML), and chronic myelocytic leukemia (CML). Among adults (20 years of age and older), the most common types of leukemia are CLL (37%) and AML (32%), whereas in children and adolescents (ages 0 to 19 years), ALL is most common, accounting for 74% of cases. From 2007 to 2016, the incidence rate was stable for CLL and increased by about 1% per year for ALL and 2% per year for CML and AML. In contrast to incidence trends, the death rate from 2008 to 2017 was stable for AML and decreased by 1% per year for ALL and CML and by about 3% per year for CLL (ACS '20: 16).

**Symptoms** of leukemia, which can appear suddenly for acute subtypes, include fatigue, paleness, weight loss, repeated infections, fever, bleeding or bruising easily, bone or joint pain, and swelling in the lymph nodes or abdomen. Chronic leukemia typically progresses slowly with few symptoms during early stages. Risk of most types of leukemia is increased among individuals exposed to high-level ionizing radiation, most commonly from cancer treatment. Certain types of chemotherapy also increase risk of some types of leukemia. In addition, risk is increased in people with certain genetic abnormalities and in workers exposed to some chemicals, such as benzene (e.g., during oil refining or rubber manufacturing). Cigarette smoking is a risk factor for AML in adults, and there is accumulating evidence that parental smoking before and after childbirth may increase acute leukemia risk in children. Excess body weight may increase risk of some leukemia subtypes (ACS '20: 16).

The concept that myeloproliferative disorders result from clonal neoplastic proliferations of the multipotent myeloid stem cells is well established. Several **environmental factors** have been implicated in the causation of leukemias and lymphomas. Well-established influences include ionizing radiation, chemicals and alkylating agents used in chemotherapy. Two viruses, HTLV-2 and EBV, have been associated with acute T-cell leukemia/lymphoma and Burkitt's lymphoma respectively. Recent studies have implicated HTLV-1 and HTLV-2 in the causation of mycosis

fungoides as well (Saunders '94: 648, 649, 658, 656). The human retrovirus HTLV-1 causes an aggressive form of leukemia in adults in Japan and the Caribbean. It is transmitted primarily via infected cells in human fluid (like HIV) – maternal milk, blood and seminal fluid (Greaves '00:257). 80% of bone infections, **osteomyelitis** are caused by methicillin resistant *Staphylococcus aureus* (MRSA) and *S. dermitidis*, best treated with Epsom salt bath or saline debridement. Bone marrow transplant, if complicated, may be necessary. Common water molds and other molds can cause osteomyelitis are highly suspected of infecting the bone and sending spores through the bloodstream causing acute blast crisis and may be mistaken for overgrown immature white cells. Hydrocortisone crème, and anti-fungals might be curative. For primary prophylaxis of aspergillosis in immunocompromised individuals at high risk of invasive disease such as neutropenic patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) or hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) posaconazole is the drug of choice; alternatives are itraconazole or micafungin. Hydrocortisone crème is not so effective because corticosteroids cause osteonecrosis (Bernatsky & Senécal '05: 38).

**Disorders of white cells** may be classified into two broad categories, proliferative and leukopenias characterized by a deficiency of leukocytes. Proliferations of white cells and lymph nodes can be reactive or neoplastic. Reactive proliferation in response to an underlying microbial disease is fairly common. Neoplastic disorders, although less frequent, are much more severe. **Leukopenia** is an abnormally low white cell count usually resulting from reduced numbers of neutrophils (neutropenia, granulocytopenia). **Lymphopenias** are much less common, and in addition to the congenital immunodeficiency diseases, they are associated with specific clinical syndromes (e.g Hodgkin's disease, nonlymphocytic leukemias, following corticosteroid therapy and occasionally in chronic diseases). **Neutropenia**, a reduction in the number of granulocytes in the peripheral blood may be seen in a wide variety of circumstance. A marked reduction in neutrophil count predisposes to infection. The symptoms and signs of neutropenias are those of bacterial infections – malaise, chills, and fever, followed by weakness and fatigue-ability. In severe agranulocytosis with virtual absence of neutrophils, these infections may become so overwhelming as to cause death within a few days. Characteristically the total white cells count is reduce to 1000 cells per mm<sup>3</sup> of blood, and when counts fall below 500 per mm<sup>3</sup> serious infections tend to occur. In addition to control of bacterial infections with antibiotics, treatment efforts are aimed toward increasing the production of neutrophils by administration of recombinant human granulopoietic factors such as granulocyte-macrophage colony stimulating factor (GM-CSF) and G-CSF (Saunders '94: 630, 631).

Inadequate or ineffective **granulopoiesis** may be encountered with (1) suppression of myeloid stem cells as occurs in aplastic anemia, a variety of leukemias and lymphomas, where granulocytopenia is accompanied by anemia and thrombocytopenia; (2) suppression of the committed granulocytic precursors, which occurs after exposure to certain drugs such as alkylating agents and antimetabolites used in cancer treatment which produce neutropenias in a dose-related fashion and other drugs in an idiosyncratic reaction with aminopyrine, chloramphenicol, sulfonamides, chlorpromazine, thiouracila and phenylbutazone; (3) megaloblastic anemias due to vitamin B<sub>12</sub> or folate deficiency and (4) monoclonal proliferations of CD8+ large granular lymphocytes. Ulcerating necrotizing lesions of the gingiva, floor of the mouth, buccal mucosa, pharynx, or anywhere within the oral cavity (agranulocytic angina) are characteristic of agranulocytosis. The ulcers are typically deep, undermined and covered by gray to green black necrotic membranes for which numerous bacteria or fungi can be isolated. Similar ulcerations may occur less frequently in the skin, vagina, anus, or gastrointestinal tract.

In many instances the bacteria and fungi grow in colony formations. The regional lymph nodes draining these infections are enlarged and inflamed but the spleen and liver are rarely enlarged (Saunders '94: 630, 631).

**Leukocytosis** is a common reaction to a variety of inflammatory states. Pyogenic infections are common causes of neutrophilic leukocytosis, but it may also result from non-microbial stimuli, such as tissue necrosis caused by burns or myocardial infarctions. In patients with severe, life-threatening sepsis, in addition to leukocytosis there may be morphologic changes in the neutrophils, such as toxic granulations and cytoplasmic vacuoles. **Eosinophilic leukocytosis** is characteristic of allergic disorders, such as bronchial asthma, hay fever, parasitic infections and some diseases of the skin. The skin diseases include pemphigus, eczema and dermatitis herpetiformis. In hospitalized adult patients the most likely cause of eosinophilia is an allergic drug reaction. Elevations in monocyte may be seen in several chronic infections including tuberculosis, bacterial endocarditis, brucellosis, rickettsiosis, and malaria. Certain collagen vascular diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis are associated with monocytosis, as are inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. **Lymphocytosis** may accompany monocytosis in chronic inflammatory states such as brucellosis and tuberculosis. The lymphocyte count may also be increased in acute viral infections such as viral hepatitis, in cytomegalovirus infections and particularly infectious mononucleosis. In most instances, reactive leukocytosis is easy to distinguish from neoplastic proliferation of the white cells (i.e. leukemias) by the rarity of immature cells in the blood. However, in some inflammatory states, many immature white cells may appear in the blood and a picture of leukemia may be simulated (leukemoid reaction). Infections and other inflammatory stimuli may not only cause leukocytosis but also involve the lymph nodes, which act as defensive barriers (Saunders '94: 63, 632).

**Chemotherapy**, sometimes in combination with targeted drugs, is used to treat most acute leukemias. Several targeted drugs are effective for treating CML because they attack cells with the Philadelphia chromosome, an acquired genetic abnormality that is the hallmark of the disease. Some of these drugs are also used to treat a type of ALL involving a similar genetic defect. CLL that is not progressing or causing symptoms may not require treatment right away, but these patients need to be closely monitored. More aggressive CLL is treated with targeted drugs and/or chemotherapy. Certain types of leukemia may be treated with high-dose chemotherapy, followed by stem cell transplantation under appropriate conditions. Newer experimental treatments that boost the body's immune system, such as CAR T-cell therapy, have shown much promise, even against some hard-to-treat leukemias. **Survival varies** substantially by age and leukemia subtype. The current 5-year relative survival rate for adults (ages 20 and older) is 25% for AML; 37% for ALL; 69% for CML; and 85% for CLL. For patients ages 0-19 years, it is 67% for AML and 89% for ALL. Advances in treatment have resulted in large improvements in survival for most types of leukemia. For example, 5-year relative survival for CML has more than tripled, up from 22% in the mid-1970s, largely due to the development of targeted drugs.

### Chemotherapy for Leukemia

White Cell Disease	FDA Approved Drug
Acute Leukemias	

Acute lymphoblastic leukemia (ALL)	Abitrexate (Methotrexate), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Arranon (Nelarabine), Asparaginase Erwinia chrysanthemi, Cerubidine (Daunorubicin Hydrochloride), Clafen (Cyclophosphamide), Clofarabine, Clofarex (Clofarabine), Clolar (Clofarabine), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine), Cytoxan (Cyclophosphamide), Dasatinib, Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Erwinaze Asparaginase Erwinia Chrysanthemi), Folex (Methotrexate), Folex PFS (Methotrexate), Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Imatinib Mesylate, Marqibo (Vincristine Sulfate Liposome), Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Nelarabine, Neosar (Cyclophosphamide), Oncaspar (Pegaspargase), Pegaspargase, Ponatinib Hydrochloride, Rubidomycin (Daunorubicin Hydrochloride), Sprycel (Dasatinib), Tarabine PFS (Cytarabine), Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, Vincristine Sulfate Liposome
Acute myeloblastic leukemia (AML)	Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Arsenic Trioxide, Cerubidine (Daunorubicin Hydrochloride), Clafen (Cyclophosphamide), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine), Cytoxan (Cyclophosphamide), Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Neosar (Cyclophosphamide), Rubidomycin (Daunorubicin Hydrochloride), Tarabine PFS (Cytarabine), Trisenox (Arsenic Trioxide), Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, combination; ADE
Myelodysplastic syndromes	
Chronic myeloid leukemia (CML)	Bosulif (Bosutinib), Bosutinib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine), Cytoxan (Cyclophosphamide), Dasatinib, Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Imatinib Mesylate, Neosar (Cyclophosphamide), Nilotinib, Omacetaxine Mepesuccinate, Ponatinib Hydrochloride, Sprycel (Dasatinib), Synribo (Omacetaxine Mepesuccinate), Tarabine PFS (Cytarabine), Tassigna (Nilotinib)
Chronic lymphocytic leukemia (CLL)	Alemtuzumab, Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Arzerra (Ofatumumab), Bendamustine Hydrochloride, Campath (Alemtuzumab), Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Fludara (Fludarabine Phosphate), Fludarabine Phosphate, Leukeran (Chlorambucil), Linfovizin (Chlorambucil), Neosar (Cyclophosphamide), Ofatumumab, Treanda (Bendamustine Hydrochloride), combinations CHLORAMBUCIL-PREDNISONE, CVP
Meningeal Leukemia	Cytarabine, Cytosar-U (Cytarabine), Tarabine PFS (Cytarabine), Methotrexate
Hairy cell leukemia	Cladribine (2-chlorodeoxyadenosine, 2-CdA), Pentostatin
Polycythemia vera	Anagrelide (Agrylin), Ruxolitinib (Jakafi)

Source: FDA

In 1960, Peter Nowell and David Hungerford, working in Philadelphia, described a shortened chromosome in the blood and bone marrow of patients with CML. This was the first consistent chromosomal abnormality associated with a human cancer. Then, in 1973, Janet Rowley showed that this abnormal chromosome, now called the Philadelphia chromosome, came about because of an exchange of genetic material between two chromosomes. In the 1980s, it was demonstrated that the consequence of this chromosome exchange was the production of an abnormal gene called *BCR-ABL* fueling the excess growth of white blood cells in CML. With the target identified, a drug discovery program was started, aimed at developing a drug to shut down the activity of *BCR-ABL*. The compound that became known as imatinib (Gleevec) was developed in 1992, and studies showed that this compound killed CML cells without harming normal cells. In 1998, the drug was tested in patients with CML who had exhausted standard treatment options and whose life expectancy was limited. Within six months of starting the clinical trials of imatinib, all of the patients had their blood counts return to normal. Remarkably, this once-a-day pill had minimal side effects. These unprecedented results were confirmed in much larger clinical trials, and imatinib was approved by the U.S. Food and Drug Administration (FDA) in 2001, less than three years from the start of the clinical trials. With longer follow-up, this once routinely fatal leukemia now has a five-year survival rate of 95 percent. Newer drugs (dasatinib and nilotinib) have been developed that can shut down most of the mutated forms of *BCR-ABL*, and have significant activity in patients with resistance to imatinib; these drugs are also FDA-approved (Druker '08). Imatinib treatment costs around \$20,000.

**Acute leukemias** are associated with replacement of normal marrow elements by a sea of proliferating “blast cells” that do not seem to undergo normal maturation, possibly common water mold rather than human. Consequently, there is a loss of mature myeloid elements such as red cells, granulocytes, and platelets, and hence clinical features of acute leukemias are dominated by anemia, infections and hemorrhages. In **chronic leukemia** the grouping together of chronic lymphocytic and myelogenous leukemias is problematic. Neither of these disorders is rapidly fatal, but the clinical and morphological features that seem to unite the acute leukemias are lacking. In chronic myelogenous leukemia (CML), polycythemia vera, essential thrombocytopenia, and myeloid metaplasia are related disorders that represent clonal, neoplastic proliferations of the multipotent myeloid stem cells. The term **chronic myeloproliferative disorders**, best describes these neoplasms of the myeloid stem cell (Saunders '94: 648, 649).

### Differential Diagnosis of Leukemias

Type of Leukemia	Diagnosis	Comments
Acute Leukemias	Anemia almost always present. White cell count elevated as high as 100,000 cells per $\mu\text{L}$ but in 50% is less than 10,000 cells per $\mu\text{L}$ . Immature white cells, including blast forms, make up 60 to 100% of all blood and marrow cells. Platelet count usually depressed to less than 100,000 per $\mu\text{L}$	Presents within 3 months of onset of fatigue due to anemia, fever reflecting an infection due to absence of mature leukocytes, bleeding (petechiae, ecchymoses, epistaxis gum bleeding secondary to thrombocytopenia; bone pain and tenderness, lymphadenopathy, splenomegaly and hepatomegaly; Central nervous system manifestations, such as headache, vomiting and nerve palsies resulting from meningeal spread.

Acute lymphoblastic leukemia (ALL)	90% of patients have numerical or structural changes to chromosomes of the leukemia cells hyperdiploidy >50 chromosomes is a good indicator, pseudoploidy of 46 structurally rearranged chromosomes, or translocations come with a poor prognosis for which allogeneic bone marrow transplantation offers hope.	2500 new cases per year. Primarily disease of children and young adults. 80% of childhood leukemias. Twice as common in whites as in nonwhites and more frequent in boys than in girls. Testicular involvement is common. More than 90% remission and two-thirds cure rate with modern chemotherapy. 90% of patients have chromosomal changes
Acute myeloblastic leukemia (AML)	Diagnosed if bone marrow contains more than 30% myeloblasts. Chromosomal abnormalities in 90% of patients. 50 to 70% of cases karyotypic changes can be detected by standard cytogenetic techniques. AML divided into eight categories depending on the degree of maturation (1) minimally differentiated AML, (2) AML without differentiation, (3) AML with maturation, (4) Acute promyelocytic leukemia, (5) acute myelomonocytic leukemia, (6) acute monocytic leukemia, (7) acute erytroleukemia, (8) acute megakaryocytic leukemia	Affects adults from ages 15 to 39 years. 20% of childhood leukemias. Diverse origin transformation of multipotent (trilineage) myeloid stem cells as evidenced by common cytogenetic abnormalities in granulocytic and erythroid precursors, though myeloblasts dominate the blood and bone marrow. Or common granulocyte monocyte precursor involvement gives rise to myelomonocytic disease. Difficult to treat, 60% achieve remission but only 15 to 30% remain free for five years. 50 to 60% of those who undergo allogeneic bone marrow transplantation at first remission appeared cured.
Myelodysplastic syndromes	Group of clonal stem cell disorders with maturation defects resulting in ineffective hematopoiesis and an increased risk of transformation to acute myeloblastic leukemias. Bone marrow is partly or wholly replaced by the clonal progeny of a mutant pluripotent stem cell that retains the capacity to differentiate into red cells, granulocytes and platelets, but in a manner that is both ineffective and disordered resulting in bone marrow that is usually hypercellular or normocellular, but the peripheral blood shows pancytopenia. The abnormal stem cell clone is unstable and prone to acute leukemia.	Pre-leukemic condition affecting older people between 60 and 70 years of age. Patients present with weakness, infections and hemorrhages, all due to pancytopenia. Approximately half of the patients are asymptomatic, and the disease is discovered incidentally to blood tests. Ten to forty percent progress to frank AML. Median survival varies from 9 to 29 months.
Chronic myeloid leukemia (CML)	Neoplastic cloned pluripotent stem cell affecting virtually all hematopoietic lineages. Distinctive cytogenetic and molecular	15 to 20% of all cases of leukemia. Primarily affects adults between the ages of 25 and 60 years, with the peak incidence in the fourth and fifth

	<p>abnormality. &gt;90% Ph chromosome reciprocal translocation t(9;22) (q34;q11). 10-20 fold increase in the mass of granulocytic precursor cells with smaller number of normal progenitor cells in the marrow. Usually elevated leukocyte count commonly exceeding 100,000 cell per mm<sup>3</sup> circulating cells predominantly neutrophils and metamyelocytes, but basophils and eosinophils are also prominent. A small number of myeloblasts (&lt;10%) can be found in peripheral blood. Up to 50% have thrombocytosis early in the course of disease. Almost total lack of alkaline phosphatase in granulocytes. The diagnostic feature is the presence of Ph chromosome and <i>bcr-c-abl</i> rearrangements.</p>	<p>decades of life. Initial symptoms are anemia or hyper-metabolism due to increased cell turnover and include easy fatiguability, weakness, weight loss and anorexia. Slow progression, without treatment a median survival of 3 years can be expected. After a variable period averaging 3 years, about 50% of patients have a leukemic "blast crisis". In 70% the blasts have the features of myeloblasts, whereas the remaining 30% contain the enzyme TdT and express B-lineage antigens. Treatment is unsatisfactory. Although it is possible to induce remissions with chemotherapy, the median survival of 3 to 4 years is unaltered. Bone marrow transplantation is the only curative treatment. After the development of blast crisis all forms of treatment become virtually ineffective.</p>
Chronic lymphocytic leukemia (CLL)	<p>Lymphoid malignancy of B cells, T cells rare &lt;5%. 50% of patients will CLL have abnormal karyotypes, Trisomy 2 is most common, in one-third of patients, with a poor prognosis. Total leukocyte count may be increased slightly or can reach 200,000 per mm<sup>3</sup>. Smudge cells with crushed nuclei of lymphocytes are common in peripheral blood smears.</p>	<p>25% of all leukemias in the US and Europe. Typically occurs in persons over 50, median 60 years, males twice as often as females. Uncommon in Japan and other Asian countries. Often asymptomatic, easy fatiguability, loss of weight and anorexia. Generalized lymphadenopathy and hepatosplenomegaly are present in 50 to 60% of cases. Median survival is 4 to 6 years and blast crisis are uncommon.</p>
Hairy cell leukemia	<p>Fine hairlike projections on leukemic cells. Tartrate resistant acid phosphatase (TRAP) in neoplastic B cells. Pancytopenia, resulting from marrow failure and splenic sequestration, is seen in more than half the cases. Leukocytosis present in only 25% of patients. Hairy cells can be identified in the peripheral blood smear in most cases.</p>	<p>Hairy cell leukemia occurs mainly in older males and its manifestations result largely from infiltration of bone marrow, liver and spleen. Splenomegaly is more common than hepatomegaly. Lymphadenopathy is rare. Splenectomy is of benefit in two-thirds of patients. With old treatment median survival was less than 5 years, however, treatment with interferon-<math>\alpha</math> and newer chemotherapeutic agents has led to lasting remissions and possibly cures.</p>
Polycythemia vera	<p>Proliferation of erythroid, granulocytic and megakaryocytic</p>	<p>Appears insidiously in late middle age ~60 years. Blood is deoxygenated,</p>

	<p>elements, all derived from clonal expansion of a pluripotent stem cell. Absolute increase in red cell mass due to domination of erythroid precursors. Associated with virtually undetectable levels of serum erythropoietin. Hemoglobin concentration ranges from 14 to 28 gm/dl with hematocrit values of 60% or more. The white cell count is elevated, ranging between 12,000 and 50,000 cells per mm<sup>3</sup>. The major anatomic changes stem from the increase in blood volume and viscosity brought about by the erythrocytosis. Plethoric congestion of all tissues and organs. The bone marrow is hypercellular. Hematopoiesis expands markedly to replace fatty marrow. As the disease progresses the marrow becomes fibrotic (myelofibrosis) or may be replaced by blasts (leukemic transformation). The liver is enlarged and frequently contains foci of myeloid metaplasia. The spleen is also slightly enlarged, up to 250 to 300 gm.</p>	<p>patient has headache, dizziness, gastrointestinal symptoms, hematemesis, and melena common, 30% develop thrombotic complications affecting the brain and heart. Hemorrhages occur in a third of patients. Life threatening hemorrhages occur in 5 to 10% of cases. In patients who receive no treatment, death from vascular episodes occurs within months, however if that red cell mass can be maintained at nearly normal levels by phlebotomies, median survival of 10 years can be achieved.</p>
<p>Myeloid metaplasia with myelofibrosis</p>	<p>Proliferation of neoplastic myeloid stem cells occurs principally in the spleen (myeloid metaplasia) and in the fully developed syndrome the bone marrow is hypercellular and fibrotic (myelofibrosis). Spleen is sometimes as large as 4000gm. Moderate to severe normochromic normocytic anemia. Red cells show all manner of variation in size and shape, but characteristic are teardrop-shaped erythrocytes (poikilocytes). The white cell count may be normal, reduced or elevated to 80,000 to 100,000 cells per mm<sup>3</sup> basophils are usually prominent. Platelet count is normal or elevated at time of diagnosis but thrombocytopenia supervenes. Biopsy of the marrow to detect the early deposition of reticulin or the</p>	<p>Uncommon in individuals younger than 60 years. Usually begins with progressive anemia or marked splenic enlargement, producing a dragging sensation in the left upper quadrant. Fatigue, weight loss and night sweats from increased metabolism from expanded mass of myeloid cells. Hyperuricemia and secondary gout may complicate the picture. Median survival time varies from 1 to 5 years. Threats to life are recurrent infections, thrombotic episodes or bleeding related to platelet abnormalities and in 5 to 20% of cases, transformation to acute myeloid leukemia.</p>

	more advanced fibrosis is essential for diagnosis.	
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Source: Saunders '94: 648-662

In **acute leukemias**, anemia almost always present. White cell count elevated as high as 100,000 cells per  $\mu\text{L}$  but in 50% is less than 10,000 cells per  $\mu\text{L}$ . Immature white cells, including blast forms, make up 60 to 100% of all blood and marrow cells. Platelet count usually depressed to less than 100,000 per  $\mu\text{L}$ . Acute leukemia presents within 3 months of onset of fatigue due to anemia, fever reflecting an infection due to absence of mature leukocytes, bleeding (petechiae, ecchymoses, epistaxis gum bleeding secondary to thrombocytopenia; bone pain and tenderness, lymphadenopathy, splenomegaly and hepatomegaly; Central nervous system manifestations, such as headache, vomiting and nerve palsies resulting from meningeal spread (Saunders '94: 648-662).

In **Acute lymphoblastic leukemia (ALL)** 90% of patients have numerical or structural changes to chromosomes of the leukemia cells hyperdiploidy  $>50$  chromosomes is a good indicator, pseudodiploidy of 46 structurally rearranged chromosomes, or translocations come with a poor prognosis for which allogeneic bone marrow transplantation offers hope. There are some 2500 new cases of ALL per year. Primarily disease of children and young adults. 80% of childhood leukemias. Twice as common in whites as in nonwhites and more frequent in boys than in girls. Testicular involvement is common. More than 90% remission and two-thirds cure rate with modern chemotherapy. 90% of patients have chromosomal changes (Saunders '94: 648-662). Between 1949 and 1954, the first clinical trials that tested combinations of chemotherapy drugs methotrexate and corticosteroids, (and unfortunately 6-MP) for childhood **acute lymphoblastic leukemia (ALL)** were carried out. Patients lived longer with these new combinations of chemotherapy drugs, but all still died, usually within a year. Because ALL tended to come back in the central nervous system, a major advance was made by aggressively treating the brain and spinal fluid with radiation and drugs that markedly decreased this form of relapse so, one-half of the patients were cured of leukemia. The cure rate now approximates 80 percent and methotrexate is available by prescription for oral consumption (Simone '08).

ALL (also called **acute lymphocytic leukemia**) is an aggressive type of leukemia characterized by the presence of too many lymphoblasts or lymphocytes in the bone marrow and peripheral blood. It can spread to the lymph nodes, spleen, liver, central nervous system (CNS), and other organs. Without treatment, ALL usually progresses quickly. ALL is the most common type of cancer in children, and treatment results in a good chance for a cure. In 2020 there were an estimated 6,150 new cases and 1,520 death from ALL (ACS '20). 80 percent of case have early B-cell lineage, 10-15 percent T cell and  $<5$  percent B cells with surface immunoglobulins. In adults, French-American-British (FAB) L1 morphology (more mature-appearing lymphoblasts) is present in fewer than 50% of patients, and L2 morphology (more immature and pleomorphic) predominates (Brearly et al '79). L3 (Burkitt) acute lymphoblastic leukemia (ALL) is much less common than the other two FAB subtypes. It is characterized by blasts with cytoplasmic vacuolizations and surface expression of immunoglobulin, and the bone marrow often has an appearance described as a starry sky owing to the presence of numerous apoptotic cells. L3 ALL is associated with a variety of translocations that involve translocation of the c-myc proto-oncogene to the immunoglobulin gene locus  $t(2;8)$ ,  $t(8;12)$ , and  $t(8;22)$ . Some patients presenting with acute leukemia may have a cytogenetic abnormality that is morphologically indistinguishable from the Philadelphia chromosome (Ph1) (Peterson et al '76). The Ph1 occurs in only 1% to 2% of patients with acute myeloid leukemia (AML), but it occurs in about 20% of

adults and a small percentage of children with ALL . Many patients who have molecular evidence of the *BCR-ABL* fusion gene, which characterizes the Ph1, have no evidence of the abnormal chromosome by cytogenetics (Secker-Walker et al '88).

There is no clear-cut **staging system** for ALL, it is classified as untreated, in remission, or recurrent. For a newly diagnosed patient with no prior treatment, untreated adult acute lymphoblastic leukemia (ALL) is defined by the following: Abnormal white blood cell count and differential. Abnormal hematocrit/hemoglobin and platelet counts. Abnormal bone marrow with more than 5% blasts. Signs and symptoms of the disease. A patient who has received remission-induction treatment of ALL is in remission if all of the following criteria are met: Bone marrow is normocellular with no more than 5% blasts. There are no signs or symptoms of the disease. There are no signs or symptoms of central nervous system leukemia or other extramedullary infiltration. All of the following laboratory values are within normal limits: White blood cell count and differential. Hematocrit/hemoglobin level. Platelet count. Successful treatment of acute lymphoblastic leukemia (ALL) consists of the control of bone marrow and systemic disease and the treatment (or prevention) of sanctuary-site disease, particularly the central nervous system (CNS).[1,2] The cornerstone of this strategy includes systemically administered combination chemotherapy with CNS preventive therapy. CNS prophylaxis is achieved with chemotherapy (intrathecal and/or high-dose systemic therapy) and, in some cases, cranial radiation therapy. The average length of treatment for ALL varies between 1.5 and 3 years in the effort to eradicate the leukemic cell population (Hoelzer et al '87).

Sixty percent to 80% of adults with ALL usually achieve a complete **remission** status following appropriate induction therapy. In patients with Ph1-positive ALL, the remission rate is generally greater than 90% when standard induction regimens are combined with BCR-ABL tyrosine kinase inhibitors. In the largest study published to date of Ph1-positive ALL patients, overall survival (OS) for 1,913 adult ALL patients was 39% at 5 years (Goldstone et al '08). Patients who experience a relapse after remission usually die within 1 year, even if a second complete remission is achieved. If there are appropriate available donors and if the patient is younger than 55 years, bone marrow transplantation may be a consideration in the management of this disease (Bortin et al '92). Most current induction regimens for patients with adult ALL include combination chemotherapy with prednisone, vincristine, and an anthracycline, other drugs, such as asparaginase or cyclophosphamide, can be added. Current multiagent induction regimens result in complete response rates that range from 60% to 90% (Kantarjian et al '04). Imatinib mesylate, an orally available inhibitor of the BCR-ABL tyrosine kinase, has been shown to have clinical activity as a single agent in Ph1-positive AL(Ottman et al '02). For patients treated with imatinib, OS probability was 38% at 5 years (median, 3.1 year) versus 23% in the imatinib-free group (Bassan et al '10). B-cell ALL, which expresses surface immunoglobulin and cytogenetic abnormalities such as t(8;14), t(2;8), and t(8;22), is not usually cured with typical ALL regimens. Aggressive brief-duration high-intensity regimens, including those previously used in CLB-9251 (NCT00002494), that are similar to those used in aggressive non-Hodgkin lymphoma have shown high response rates and cure rates (75% complete response; 40% failure-free survival) (Lee et al '01). Similarly, T-cell ALL, including lymphoblastic lymphoma, has shown high cure rates when treated with cyclophosphamide-containing regimens (Larsen et al '95).

Standard treatment options for adult acute lymphoblastic leukemia (ALL) in remission include the following: Postremission therapy, including the following: Chemotherapy. Ongoing treatment with a BCR-ABL tyrosine kinase inhibitor, such as imatinib, nilotinib, or dasatinib. Autologous or allogeneic bone marrow transplant (BMT). Central nervous system (CNS)

prophylaxis therapy, including the following: Cranial radiation therapy plus intrathecal (IT) methotrexate. High-dose systemic methotrexate and IT methotrexate without cranial radiation therapy. IT chemotherapy alone. By donor-to-no-donor analysis, standard-risk ALL patients with an HLA-identical sibling had a 5-year OS of 53% compared with 45% for patients lacking a donor (Sebban et al '94). Blinatumomab is a bispecific antibody targeting CD19 and CD3 with approval by the U.S. Food and Drug Administration (FDA) for use in patients with relapsed or refractory B-cell ALL. Remission rates were 43.9% for the blinatumomab-treated group versus 24.6% in the standard-treatment group. Overall survival (OS) was superior in the blinatumomab-treated group (7.7 months vs. 4.0 months in the standard-treatment group) (Kantarjian et al '17). Inotuzumab ozogamicin is an antibody-drug conjugate targeting CD22, which contains a conjugated toxin, calicheamicin. Inotuzumab ozogamicin is approved by the FDA for use in patients with relapsed or refractory B-cell ALL with CD22 expression. Complete remission or complete remission with incomplete count recovery rates were 80.7% for the inotuzumab group versus 29.4% in the standard-treatment group. Progression-free survival was superior in the inotuzumab-treated group (5.0 months vs. 1.8 months in the standard-treatment group). OS was not statistically prolonged in the inotuzumab group (7.7 months in the inotuzumab group vs. 6.7 months in the standard-treatment group). Adverse events involving the liver were found in the inotuzumab group (Kantarjian et al '16). Patients with Ph1-positive ALL will often be taking imatinib at the time of relapse and thus will have imatinib-resistant disease. Dasatinib, a novel tyrosine kinase inhibitor with efficacy against several different imatinib-resistant *BCR-ABL* mutations, has been approved for use in Ph1-positive ALL patients who are resistant to or intolerant of imatinib. 70 percent of patients had a complete response, all relapsed within 6 months (Talaz et al '06).

The diagnosis of **Acute myeloblastic leukemia** (AML) is uncommon before age 45 years; the median age at diagnosis is 68 years (SEER '20). AML also affects adults from ages 15 to 39 years and comprises 20% of childhood leukemias. AML is a heterogenous group of blood cancers that arise as a result of clonal expansion of myeloid hematopoietic precursors in the bone marrow. Not only are circulating leukemia cells (also called blasts) seen in the peripheral blood, but granulocytopenia, anemia, and thrombocytopenia are also common as proliferating leukemia cells interfere with normal hematopoiesis (Sekeres et al '15). A peripheral blood or bone marrow blast count of 20% or greater is required to make the diagnosis, except for cases with certain chromosomal abnormalities (Swerdlow et al '17). Approximately half of the patients with AML will harbor chromosomal abnormalities; therefore, conventional cytogenetic analysis remains mandatory in the evaluation of suspected AML (Slovak et al '00). With the routine use of molecular diagnostics, the identification of recurrent somatic mutations in *NPM1*, *FLT3*, *CEPBA*, and *RUNX1*, among other genes, has become a routine part of determining prognosis. Cytogenetic and molecular analyses provide the strongest prognostic information available, predicting outcome of both remission induction and postremission therapy (Döhner et al '17). In AML the bone marrow contains more than 30% myeloblasts. Chromosomal abnormalities exist in 90% of patients. 50 to 70% of cases karyotypic changes can be detected by standard cytogenetic techniques. AML is divided into eight categories depending on the degree of maturation (1) minimally differentiated AML, (2) AML without differentiation, (3) AML with maturation, (4) Acute promyelocytic leukemia, (5) acute myelomonocytic leukemia, (6) acute monocytic leukemia, (7) acute erytroleukemia, (8) acute megakaryocytic leukemia. Diverse origin transformation of multipotent (trilineage) myeloid stem cells as evidenced by common cytogenetic abnormalities in granulocytic and erythroid precursors, though myeloblasts dominate the blood and bone marrow. Or common granulocyte monocyte precursor involvement gives rise to myelomonocytic disease (Saunders '94: 648-662).

In patients with AML, a complete remission (CR) is defined as a normal peripheral blood cell count (absolute neutrophil count  $>1,000/\text{mm}^3$  and platelet count  $>100,000/\text{mm}^3$ ) and normocellular marrow with less than 5% blasts in the marrow and no signs or symptoms of the disease (Döhner et al '10). Difficult to treat, 60% achieve remission but only 15 to 30% remain free for five years. 50 to 60% of those who undergo allogeneic bone marrow transplantation at first remission appeared cured (Saunders '94: 648-662). Remission rates in adult AML are inversely related to age, with an expected remission rate of more than 65% for those younger than 60 years. A study of 30 patients who had AML that was in remission for at least 10 years demonstrated a 13% incidence of secondary malignancies (Micalief et al '01). Advances in the treatment of AML have resulted in substantially improved complete remission (CR) rates. Treatment should be sufficiently aggressive to achieve CR because partial remission offers no substantial survival benefit. Approximately 60% to 70% of adults with AML can be expected to attain CR status after appropriate induction therapy. More than 25% of adults with AML (about 45% of those who attain CR) can be expected to survive 3 or more years and may be cured (SEER '20).

Most patients with AML who undergo intensive therapy are treated with an anthracycline. Anthracyclines have been associated with increased risk of congestive heart failure (CHF) (Steinherz et al '91). Anthracycline cardiotoxicity is dose-dependent. In one study, doxorubicin-related CHF was 5% at a lifetime cumulative dose of 400 mg/m<sup>2</sup>, rising to 26% at a cumulative dose of 550 mg/m<sup>2</sup> (Swain et al '03). Of 31 female long-term survivors of AML or acute lymphoblastic leukemia (ALL) (diagnosed before age 40 years), 26 resumed normal menstruation after completion of therapy. Among 36 live offspring of survivors, two congenital problems occurred (Micalief et al '01). Patients who undergo allogeneic hematopoietic stem cell transplantation (HSCT) can experience a large number of long-term or late side effects of treatment, including chronic fatigue, thyroid and gonadal dysfunction, infertility, chronic infection, accelerated coronary heart disease, osteopenia, cataracts, iron overload, adverse psychological outcomes, and second cancers as a result of high-dose chemotherapy and/or radiation, and as an effect of chronic graft-versus-host disease and immunosuppression (Inamoto et al '17). In the Bone Marrow Transplant Survivor Study, hematopoietic cell transplantation (HCT) survivors had accelerated aging and were 8.4 times more likely to be frail than their siblings (95% confidence interval). In a multivariable analysis, frailty was associated with a 2.76-fold increase in the risk of death as compared with a non-frail state (Arora et al '16).

One of the following combination chemotherapy regimens may be used as intensive remission induction therapy: Cytarabine plus daunorubicin (Dilma et al '91). Cytarabine plus idarubicin (Wiernik et al '92). Cytarabine plus mitoxantrone (Löwenberg et al '98). Cytarabine plus anthracycline plus midostaurin (Stone et al '17). Cytarabine plus anthracycline plus gemtuzumab ozogamicin (Hills et al '14). Liposomal daunorubicin-cytarabine (CPX-351) (Lancet et al '18). Intrathecal cytarabine or methotrexate may be used to treat central nervous system (CNS) leukemia, if present. The two-drug regimen of cytarabine given as a continuous infusion for seven days and a three-day course of anthracycline (the so-called 7+3 induction therapy) results in a complete response rate of approximately 65%. In most instances, there is no further clinical benefit when adding potentially non-cross-resistant drugs (such as fludarabine, topoisomerase inhibitors, thioguanine, mitoxantrone, histone deacetylases inhibitors, or clofarabine) to a 7+3 regimen (Holowiecki et al '04). In patients aged 60 years and younger, outcomes for those who received daunorubicin (90 mg/m<sup>2</sup>/dose, total induction dosing at 270 mg/m<sup>2</sup>) were superior to those who received more traditional dosing (45 mg/m<sup>2</sup>/dose; total dose = 135 mg/m<sup>2</sup>). The

complete remission (CR) rate was 71% versus 57%, and the median survival was 24 months versus 16 months (Fernandez et al '09). CPX-351 is a two-drug liposomal encapsulation that delivers cytarabine and daunorubicin at a fixed 5:1 synergistic molar ratio. Compared with 7+3 induction chemotherapy, CPX-351 resulted in a better overall remission rate (47.7% vs. 33.3%, and improved median OS (9.56 vs. 5.95 months) (Lancet et al '18).

Some patients may decline or be too frail for intensive induction chemotherapy. The addition of the FLT3/multikinase inhibitor midostaurin, versus placebo, to cytarabine and daunorubicin induction chemotherapy in patients with *FLT3*-mutated AML led to improved survival (median, 75 vs. 26 months (Stone et al '17). Low-dose cytarabine, decitabine, azacitidine, or best supportive care can be considered equivalently effective treatment approaches for older patients with AML who decline traditional 7+3 induction chemotherapy. Unlike a succinct course of 7+3 induction, these less-intensive therapies are continued indefinitely, as long as the patient is deriving benefit (i.e., until disease progression or significant toxicity occurs). The hypomethylating agent azacitidine is used commonly in this population of older adults, particularly in the United States (Kantarjian et al '06). Azacitidine led to a median OS of 10.4 months, as compared with 6.5 months. Median OS was not significantly improved for patients receiving decitabine (Welch et al '16). Low-dose cytarabine, administered twice daily for 10 days in cycles repeated every 4 to 6 weeks. The CR rate using this regimen was 18% compared with 1% for patients treated with hydroxyurea (Burnett et al '07). Two nonrandomized open-label clinical trial (phase Ib) of venetoclax in combination with azacitidine found 50% CR, the median duration of response for all patients was 8.4 months (Wei et al '19). Glasdegib, an oral inhibitor of the hedgehog pathway, of patients over age 75 with AML who received glasdegib plus low-dose cytarabine, 24% of patients had a CR compared with 5% (2 of 38) of patients who received low-dose cytarabine alone, median OS was 8.2 months (Cortes et al '19). Similar to venetoclax, glasdegib was approved by the U.S. FDA in combination with low-dose cytarabine for the treatment of AML in patients aged 75 years or older or who are unable to receive intensive induction chemotherapy. The FDA has approved ivosidenib for the treatment of AML that has a susceptible *IDH1* mutation (detected by an FDA-approved diagnostic test) in adults aged 75 years or older. For ivosidenib the rate of CR was 42.4% and median overall survival OS was 12.65 months. (Roboz et al '20).

Supportive care during remission induction treatment should routinely include red blood cell and platelet transfusions when appropriate (Murphy et al '86). Empiric broad spectrum antimicrobial therapy is an absolute necessity for febrile patients who are profoundly neutropenic (Hughes et al '90). Antibiotic prophylaxis with a fluoroquinolone and antifungal prophylaxis with an oral triazole or parenteral echinocandin is appropriate for patients with expected prolonged, profound neutropenia (<100/mm<sup>3</sup> for 2 weeks for profound neutropenia lasting >7 days). Nucleoside analog-based antiviral prophylaxis, such as acyclovir, is appropriate for patients who are seropositive for herpes simplex virus undergoing induction chemotherapy (Taplitz et al '18).

**Chronic myeloid leukemia (CML)** is one of the four main types of leukemia, affecting approximately 5,000 people per year in the United States. The disease can occur at any age but is primarily a disease of adults. CML is characterized by a massive over-production of white blood cells. A normal white blood cell count ranges between 4,000 and 10,000; in contrast, patients with CML typically have white blood cell counts ranging from 100,000 to as high as 500,000. Because the white blood cells mature and function normally, infections are not a common feature of CML. Rather, symptoms include fatigue due to anemia or abdominal discomfort due to an enlarged spleen. CML is a clonal disorder that is usually easily diagnosed because the leukemic

cells of more than 95% of patients have a distinctive cytogenetic abnormality, the Philadelphia chromosome (Ph1) (Goldman et al '03). The Ph1 results from a reciprocal translocation between the long arms of chromosomes 9 and 22 and is demonstrable in all hematopoietic precursors.[4] Clinical signs indicative of accelerated phase or blast crisis (fever, enlarged spleen, or >20% blasts in the peripheral blood) suggest the clinical utility for bone marrow testing (Hidalgo-López et al '18). At the time of diagnosis of patients with CML, splenomegaly is the most-common finding on physical examination (Jabbour et al '12).

Historically, patients with CML lived no more than three to five years, during which time the disease would quickly transform from a chronic leukemia to an aggressive and fatal acute leukemia. In 1960, Peter Nowell and David Hungerford, working in Philadelphia, described a shortened chromosome in the blood and bone marrow of patients with CML. This was the first consistent chromosomal abnormality associated with a human cancer. Then, in 1973, Janet Rowley showed that this abnormal chromosome, now called the Philadelphia chromosome, came about because of an exchange of genetic material between two chromosomes. In the 1980s, it was demonstrated that the consequence of this chromosome exchange was the production of an abnormal gene called *BCR-ABL* fueling the excess growth of white blood cells in CML. With the target identified, a drug discovery program was started, aimed at developing a drug to shut down the activity of *BCR-ABL*. The compound that became known as imatinib (Gleevec) was developed in 1992, and studies showed that this compound killed CML cells without harming normal cells. In 1998, the drug was tested in patients with CML who had exhausted standard treatment options and whose life expectancy was limited. Within six months of starting the clinical trials of imatinib, all of the patients had their blood counts return to normal. Remarkably, this once-a-day pill had minimal side effects. These unprecedented results were confirmed in much larger clinical trials, and imatinib was approved by the U.S. Food and Drug Administration (FDA) in 2001, less than three years from the start of the clinical trials. With longer follow-up, this once routinely fatal leukemia now has a five-year survival rate of 95 percent. Newer drugs (dasatinib and nilotinib) have been developed that can shut down most of the mutated forms of *BCR-ABL*, and have significant activity in patients with resistance to imatinib; these drugs are also FDA-approved (Druker '08).

Chronic-phase CML is characterized by bone marrow and cytogenetic findings as described above with less than 10% blasts and promyelocytes in the peripheral blood and bone marrow. Accelerated-phase CML is characterized by 10% to 19% blasts in either the peripheral blood or bone marrow. Blastic-phase CML is characterized by 20% or more blasts in the peripheral blood or bone marrow. When 20% or more blasts are present in the face of fever, malaise, and progressive splenomegaly, the patient has entered blast crisis (Cortes et al '06). Relapsed CML is characterized by any evidence of progression of disease from a stable remission. This may include the following: Increasing myeloid or blast cells in the peripheral blood or bone marrow. Cytogenetic positivity when previously cytogenetic-negative. FISH positivity for BCR/ABL translocation when previously FISH-negative. Detection of the BCR/ABL translocation by RT-PCR during prolonged remissions does not constitute relapse on its own. However, exponential drops in quantitative RT-PCR measurements for 3 to 12 months correlates with the degree of cytogenetic response, just as exponential rises may be associated with quantitative RT-PCR measurements that are closely connected with clinical relapse (Martinelli et al '06).

The optimal front-line treatment for patients with chronic-phase CML is the subject of active clinical evaluation but involves specific inhibitors of the BCR/ABL tyrosine kinase. In a randomized trial that compared imatinib mesylate with interferon plus cytarabine, at 10.9 years'

median follow-up, imatinib mesylate induced complete cytogenetic responses in 83% of newly diagnosed patients; in addition, the annual rate of progression to accelerated phase or blast crisis dropped from 2% to less than 1% in the fourth year on the imatinib arm. Although evidence-based survival advantages are unavailable because of crossover in randomized trials, the overall survival (OS) rate for all patients at 10 years is 83.3%, with fewer than 50% of all deaths (4.5%) caused by CML (Hochhaus et al '17). In a randomized, prospective study of 846 patients that compared nilotinib with imatinib, the rate of major molecular response (MMR) at 24 months was 71% and 67% for two-dose schedules of nilotinib and 44% for imatinib. Progression to accelerated-phase CML or blast crisis occurred in 17 patients who received imatinib (14%), but this progression occurred in only two patients and in five patients, respectively, who received two-dose schedules of nilotinib (Kantarjian et al '11). In a randomized prospective study of 536 patients that compared bosutinib with imatinib, the MMR at 12 months was 47.2% in the bosutinib arm versus 36.9% in the imatinib arm (Cortes et al '18). Allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT) has also been applied with curative intent. Long-term data beyond 10 years of therapy are available, and most long-term survivors show no evidence of the BCR/ABL translocation by any available test (e.g., cytogenetics, RT-PCR, or fluorescent in situ hybridization). Some patients, however, are not eligible for this approach because of age, comorbid conditions, or lack of a suitable donor. In addition, substantial morbidity and mortality result from allogeneic BMT or SCT; a 5% to 10% treatment-related mortality can be expected, depending on whether a donor is related and on the presence of mismatched antigens. In a prospective trial of 427 transplant-eligible, previously untreated patients, 166 patients were allocated to allogeneic SCT, and 261 patients were allocated to drug treatment (mostly imatinib); there was no difference in 10-year OS (Gratwohl et al '16).

For patients resistant to several tyrosine kinase inhibitors, omacetaxine mepesuccinate (a cephalotaxine, formerly known as homoharringtonine, with activity independent of BCR/ABL) has shown a hematologic response rate of 67% and a median PFS of 7 months in a small, phase II study of 46 patients (Cortes et al '13). Approximately 10% to 20% of patients treated with interferon alpha have a complete cytogenetic response with no evidence of BCR/ABL translocation by any available test, and the majority of these patients are disease free beyond 10 years (Lee et al '98). A trial randomly assigning 1,106 previously untreated patients to imatinib mesylate or to interferon plus cytarabine documented an 82.8% complete cytogenetic response rate with imatinib mesylate versus 14% for interferon plus cytarabine at a median follow-up of 10.9 years (Hockhaus et al '17). Hydroxyurea is given daily by mouth (1–3 g per day as a single dose on an empty stomach). Hydroxyurea is superior to busulfan in the chronic phase of CML, with significantly longer median survival and significantly fewer severe adverse effects. A dose of 40 mg/kg per day is often used initially, and frequently results in a rapid reduction of the white blood cell (WBC) count. When the WBC count drops below 20,000 mm<sup>3</sup>, the hydroxyurea is often reduced and titrated to maintain a WBC count between 5,000 and 20,000 (Hehlmann et al '93).

The only consistently successful curative treatment of CML has been high-dose therapy followed by allogeneic BMT or SCT (Gratwohl et al '96). A retrospective review of 2,444 patients who received myeloablative allogeneic SCT showed OS at 15 years of 88% (95% confidence interval [CI], 86%–90%) for sibling-matched transplant and of 87% (95% CI, 83%–90%) for unrelated donor transplant (Goldman et al '10). The cumulative incidences of relapse were 8% (95% CI, 7%–10%) for sibling-matched transplant and 2% (95% CI, 1%–4%) for unrelated donor transplant (Lee et al '97). Although the procedure is associated with considerable acute morbidity and mortality, 50% to 70% of patients transplanted in the chronic phase survive 2 to 3

years, and the results are better in younger patients, especially those younger than 20 years. The results of patients transplanted in the accelerated and blastic phases of the disease are progressively worse. Most transplant series suggest improved survival when the procedure is performed within 1 year of diagnosis (Hansen et al '98). The data supporting early transplant, however, have never been confirmed in controlled trials. In a randomized, clinical trial, disease-free survival and OS were comparable when allogeneic transplantation followed preparative therapy with cyclophosphamide and total-body irradiation (TBI) or busulfan and cyclophosphamide without TBI. The latter regimen was associated with less graft-versus-host disease (GVHD) and fewer fevers, hospitalizations, and hospital days (Clift et al '94). With the advent of imatinib, dasatinib, and nilotinib, the timing and sequence of allogeneic BMT or SCT has been cast in doubt (Saussele et al '10). Allogeneic SCT is the preferred choice for some patients presenting with accelerated-phase disease, for most patients with blast-phase disease, for almost all patients with a *T315I* mutation resistant to ponatinib (an oral tyrosine kinase inhibitor), and those with complete intolerance to the pharmacologic options (O'Brien et al '11).

Induction of remission using a tyrosine kinase inhibitor followed by an allogeneic SCT, when feasible, is a standard approach for patients with accelerated-phase CML (Jiang et al '11). Imatinib mesylate. Among 176 patients with accelerated-phase CML, the complete hematologic response was 82%, and the complete cytogenetic response was 43%; with a median follow-up of 41 months, the estimated 4-year survival was 53% (Kantarjian et al '05). Imatinib mesylate, dasatinib, and nilotinib have demonstrated activity in patients with myeloid blast crisis and lymphoid blast crisis or Philadelphia chromosome–positive acute lymphoblastic leukemia (Saglio et al '10). Two trials of imatinib mesylate and one trial of dasatinib involving a total of 518 patients in blastic-phase chronic myelogenous leukemia (CML) confirm a hematologic response rate of 42% to 55% and a major cytogenetic response rate of 16% to 25%, but the estimated 2-year survival rate is under 28% (Sawyers et al '02). In the setting of relapse or intolerance to imatinib, the use of dasatinib resulted in a 7-year major molecular response rate of 46% and an overall survival (OS) rate of 65% (Shah et al '16). In case of treatment failure or suboptimal response, patients should undergo BCR/ABL kinase domain mutation analysis to help guide therapy with the newer tyrosine kinase inhibitors or with allogeneic transplantation (Parker et al '11). Next-generation sequencing appears to be more sensitive than Sanger sequencing for identifying actionable mutations (Soverini et al '20). Mutations in the tyrosine kinase domain can confer resistance to imatinib mesylate; alternative inhibitors such as dasatinib, nilotinib, or bosutinib, higher doses of imatinib mesylate, and allogeneic stem cell transplantation (SCT) have been studied in this setting (Khoury et al '12). In particular, the *T315I* mutation marks resistance to imatinib, dasatinib, nilotinib, and bosutinib. In a phase II study with 449 patients, 60% of the 129 patients with the *T315I* mutation had a molecular response to ponatinib, an oral tyrosine kinase inhibitor (Cortes et al '13). Ponatinib also has activity in heavily pretreated-resistant CML and in a third of the patients with accelerated-phase or blast-crisis phase CML (Shacham et al '18). For patients resistant to several tyrosine kinase inhibitors, omacetaxine mepesuccinate (a cephalotaxine, formerly known as homoharringtonine, with activity independent of BCR/ABL) has shown a hematologic response rate of 67% and a median progression-free survival of 7 months in a small, phase II study of 46 patients (Cortes et al '13). Infusions of buffy-coat leukocytes or isolated T cells obtained by pheresis from the bone marrow transplant donor have induced long-term remissions in more than 50% of patients who relapse following allogeneic transplant (Kaeda et al '06).

The **myelodysplastic/myeloproliferative neoplasms** (MDS/MPN) are clonal myeloid disorders that possess both dysplastic and proliferative features but are not properly classified as either

myelodysplastic syndromes (MDS) or chronic myeloproliferative disorders (CMPD) (Vardiman et al '09). This category is composed of three major myeloid disorders: chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), and atypical chronic myeloid leukemia (aCML). Myeloid disease that shows features of both MDS and CMPD but does not meet the criteria for any of the three major MDS/MPN entities is designated as myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-UC). The World Health Organization (WHO) created the MDS/MPN category to provide a less restrictive view of myeloid disorders, which in some instances clearly overlap (Arber et al '16). The incidence of MDS/MPN varies widely, ranging from approximately 3 per 100,000 individuals older than 60 years annually for CMML to as few as 0.13 per 100,000 children from birth to 14 years annually for JMML (Vardiman et al '02). The pathophysiology of MDS/MPN involves abnormalities in the regulation of myeloid pathways for cellular proliferation, maturation, and survival. Clinical symptoms are caused by complications resulting from the following: [6] Cytopenia(s). Dysplastic cells that function abnormally. Leukemic infiltration of various organ systems. General constitutional symptoms, such as fever and malaise. Patients with MDS/MPN do not have a Philadelphia chromosome or *BCR/ABL* fusion gene (Savona et al '15).

CMML is a clonal disorder of a bone marrow stem cell. Morphologically, the disease is characterized by a persistent peripheral blood monocytosis (always  $>1 \times 10^9/L$ ) that may exceed  $80 \times 10^9/L$  with monocytes typically accounting for more than 10% of the white blood cells. Fewer than 20% blasts are seen in the blood or bone marrow. Neutrophilia occurs in nearly 50% of patients with neutrophil precursors (e.g., promyelocytes and myelocytes) accounting for more than 10% of the white blood cells (Emanuel '05). Treatment with hydroxyurea is an option for patients with worsening leukocytosis, thrombocytosis, or splenomegaly (Bennett '02). In a randomized clinical trial, 105 patients with advanced CMML were enrolled to compare treatment with hydroxyurea versus treatment with etoposide. Doses were scheduled to escalate to hydroxyurea 4 g/d and etoposide 600 mg/week in the absence of response and finally to adjust to maintain white blood cells between  $5 \times 10^9/L$  and  $10 \times 10^9/L$ . Median actuarial survival was 20 months in the hydroxyurea arm versus 9 months in the etoposide arm (Wattel et al '96). Azacitidine may improve both the dysplastic and proliferative features of CMML. Erythropoietic growth factors may help to reduce transfusion requirements when anemia supervenes. This trial, in which patients were randomized to supportive care versus azacitidine (75 mg/m<sup>2</sup>/day subcutaneously for 7 days every 28 days), included 10 patients with CMML (Kaminskas et al '05). Lenalidomide with or without azacitidine has also been studied in CMML (Padron et al '13). Inhibitors of *JAK2*, such as ruxolitinib, are also being evaluated (Sekeres et al '12). In a review of 118 young MDS patients (median age 24, age range 0.3–53 years) who received allogeneic BMT from matched unrelated donors, the actuarial probability of survival at 2 years for the 12 patients with CMML was 10%. Transplant-related mortality was influenced by the age of the patient (i.e., <18 years, 40%; 18–35 years, 61%; >35 years, 81%) (Arnold et al '98). In a recent review of 50 allogeneic transplantations for CMML (i.e., median age 44, age range 19–61 years) from related or unrelated (donors, the 5-year-estimated overall survival was 21%. The 5-year estimated probability of relapse was 49% (Kröger et al '02). A case report suggests that targeted therapy with imatinib mesylate may be effective in a subset of patients with CMML related to *PDGFβR* fusion oncogenes (Magnusson et al '02). Various chemotherapy regimens for CMML have been used with only modest success (Bennet '02). In a study evaluating single-agent therapy with topotecan, a topoisomerase I inhibitor, 25 patients with CMML were treated with topotecan at doses that induce bone marrow aplasia (2.0 mg/m<sup>2</sup>/day by continuous infusion for 5 days). Complete hematologic remissions were induced in 28% of patients. Toxic effects were significant, and the median duration of remission was 8 months (Beran et al '98). In a

follow-up study, topotecan was used in combination with cytarabine, a pyrimidine-analog antimetabolite. This combination regimen induced complete remission in 44% of patients with CMML; median duration of complete response was 50 weeks, and patients required monthly maintenance therapy (Beran et al '99).

JMML (also known as **juvenile chronic myelomonocytic leukemia**) is a rare hematopoietic malignancy of childhood accounting for 2% of all childhood leukemias (Aricò et al '97). All three major criteria are required. No Philadelphia chromosome or *BCR/ABL* fusion gene. Peripheral blood monocytosis is greater than  $1 \times 10^9/L$ . Fewer than 20% blasts (including promonocytes) in the blood and bone marrow. Laboratory testing can distinguish whether JMML or infectious diseases have affected the clinical and hematologic findings (Niemeyer et al '97). JMML typically presents in young children (median age approximately 1 year) and occurs more commonly in boys (male to female ratio approximately 2.5:1). The cause for JMML is not known (Emanuel et al '08). Children with neurofibromatosis type 1 (NF1) are at increased risk for developing JMML, and up to 14% of cases of JMML occur in children with NF1 (Niemeyer et al '97). The median survival times for JMML vary from approximately 10 months to more than 4 years, depending partly on the type of therapy chosen (Locatelli et al '97). Prognosis is related to age at the time of diagnosis. The prognosis is better in children younger than 1 year at the time of diagnosis. Children older than 2 years at the time of diagnosis have a much worse prognosis (Vardiman et al '01). A low platelet count and a high Hb F level have been associated with a worse prognosis. Approximately 10% to 20% of cases may evolve to acute leukemia (Niemeyer et al '97). No consistently effective therapy is available for JMML. Historically, more than 90% of patients have died despite the use of chemotherapy (Freedman et al '88). A recent retrospective review described 60 children with JMML treated with chemotherapy (nonintensive and intensive) and/or bone marrow transplantation (BMT) using sibling or unrelated human leukocyte antigen (HLA)-matched donor marrow or autologous marrow. The median survival was 4.4 years (Luna-Fineman et al '99). BMT seems to offer the best chance of cure for JMML (Smith et al '02). A summary of the outcome of 91 patients with JMML treated with BMT in 16 different reports is as follows: 38 patients (41%) were still alive at the time of reporting, including 30 of the 60 (50%) patients who received grafts from HLA-matched or 1-antigen mismatched familial donors, 2 of 12 (17%) with mismatched donors, and 6 of 19 (32%) with matched unrelated donors (Aricò et al '97).

**Atypical chronic myelogenous leukemia (aCML)** is a leukemic disorder that exhibits both myelodysplastic and myeloproliferative features at the time of diagnosis. Atypical CML is characterized pathologically by the following: Peripheral blood leukocytosis with increased numbers of mature and immature neutrophils. Prominent dysgranulopoiesis. No Philadelphia chromosome or *BCR/ABL* fusion gene. Neutrophil precursors (e.g., promyelocytes, myelocytes, and metamyelocytes) accounting for more than 10% of white blood cells. Minimal absolute basophilia with basophils accounting for less than 2% of white blood cells. Absolute monocytosis with monocytes typically account for less than 10% of white blood cells. Hypercellular bone marrow with granulocytic proliferation and granulocytic dysplasia. Fewer than 20% blasts in the blood or bone marrow; Thrombocytopenia. No Philadelphia chromosome or *BCR/ABL* fusion gene exists. The exact incidence of aCML is unknown. The median age at the time of diagnosis of this rare leukemic disorder has been reported to be in the seventh or eighth decade of life. The median survival times for aCML are reported to be less than 20 months, and thrombocytopenia and marked anemia are poor prognostic factors. Atypical CML evolves to acute leukemia in approximately 25% to 40% of patients (Orazi et al '08). In the remainder, fatal complications include resistant leukocytosis, anemia, thrombocytopenia,

hepatosplenomegaly, cerebral bleeding associated with thrombocytopenia, and infection. The optimal treatment of aCML is uncertain because of the rare incidence of this chronic leukemic disorder. Treatment with hydroxyurea may lead to short-lived partial remissions of 2- to 4-months' duration. Atypical CML, appears to respond poorly to treatment with interferon-alpha (Kurzrock et al '01).

**Myelodysplastic/ Myeloproliferative Neoplasm, Unclassifiable (MDS/ MPN-UC)** (also known as mixed myeloproliferative/myelodysplastic syndrome, unclassifiable and overlap syndrome, unclassifiable) shows features of both myeloproliferative disease and myelodysplastic disease but does not meet the criteria for any of the other MDS/MPN entities. The combination of four sets of criteria (a–d): (a) Clinical, laboratory, and morphologic features of myelodysplastic syndrome (MDS) (e.g., refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, and refractory anemia with excess of blasts) with fewer than 20% blasts in the blood and bone marrow. (b) Prominent myeloproliferative features, e.g. platelet count greater than  $600 \times 10^9/L$  associated with megakaryocytic proliferation, or white blood cell count greater than  $13.0 \times 10^9/L$  with or without splenomegaly. (c) No history of an underlying chronic myeloproliferative disorder (CMPD), MDS, or recent cytotoxic or growth factor therapy that could cause the myelodysplastic or myeloproliferative features. (d) No Philadelphia chromosome or *BCR/ABL* fusion gene, *del(5q)*, *t(3;3)(q21;q26)*, or *inv(3)(q21q26)*. Mixed myeloproliferative and myelodysplastic features that cannot be assigned to any other category of MDS, CMPD, or MDS/MPN. Hepatomegaly and splenomegaly are present (Orazi et al '08). Adult patients with MDS/MPN associated with platelet-derived growth factor receptor gene rearrangements are candidates for imatinib mesylate at standard dosages (FDA '06).

**Hairy cell leukemia** is an indolent, low-grade, B-cell lymphoma usually characterized by the following: Circulating B-cells with cytoplasmic projections ("hairy" appearance). Splenomegaly. Absent lymphadenopathy. Pancytopenia. Monocytopenia. In addition to the B-cell antigens CD19, CD20, and CD22, the cells coexpress CD11c, CD25, and CD103. The *BRAF-V600E* mutation is a hairy cell leukemia–defining genetic lesion that can be used diagnostically (Tiacci et al '12). The decision to treat is based on symptomatic cytopenias, massive splenomegaly, or the presence of other complications. About 10% of all patients will never require therapy (Naik et al '12). No generally accepted staging system is useful for both prognosis and therapy. Untreated hairy cell leukemia is characterized by splenomegaly, varying degrees of leukopenia (occasionally leukocytosis) and/or pancytopenia, and bone marrow infiltration by an atypical cell with prominent cytoplasmic projections (i.e., hairy cells). The bone marrow is usually fibrotic and is not easily aspirated; therefore, bone marrow biopsies are required for diagnosis and evaluation of the degree of hairy cell infiltration. After the initiation of treatment with cladribine (2-chlorodeoxyadenosine, 2-CdA), pentostatin, or interferon-alpha, the survival rate of patients with advanced hairy cell leukemia appears to be higher than 85% at 5 years' follow-up (Grever et al '17).

The initial therapies of choice for hairy cell leukemia are either cladribine (2-chlorodeoxyadenosine, 2-CdA) or pentostatin (Grever et al '11). Cladribine is administered as a one-time continuous infusion or series of subcutaneous injections and is associated with a high rate of febrile neutropenia (Jehn et al '04). Rarely, more than one course of treatment is required to induce a desirable response. Treatment should be discontinued once complete remission or stable partial remission with normalization of peripheral blood counts is reached. The presence of residual disease may be predictive of relapse but does not seem to affect survival (Goodman et al '03). While most patients remain disease free 10 years after treatment with these purine

analogs, no patient has been monitored long enough to assess cure (Chadha et al '05). Both nucleoside analogs cause profound suppression of CD4 counts, which may last for a year, and a potential increased risk of second malignancies has been reported (Goodman et al '03). A study of 3,104 survivors of hairy cell leukemia from the Surveillance, Epidemiology, and End Results (SEER) database showed an increased risk of second cancers especially for Hodgkin and non-Hodgkin lymphomas (Hisada et al '07). With the use of cladribine, an increased risk of second malignancies is possible among patients with hairy cell leukemia (observed to expected ratio of about 1.8 in several series after 6 years) (Goodman et al '03). Several series using pentostatin did not report an increased risk of second malignancies (Flinn et al '00). For a few patients, such as those with severe thrombocytopenia, splenectomy might be considered (Golomb et al '83). After splenectomy, 50% of patients will require no additional therapy, and long-term survivors are common. Therapy with interferon-alpha is another treatment option, especially for patients with intercurrent infection (Grever et al '95).

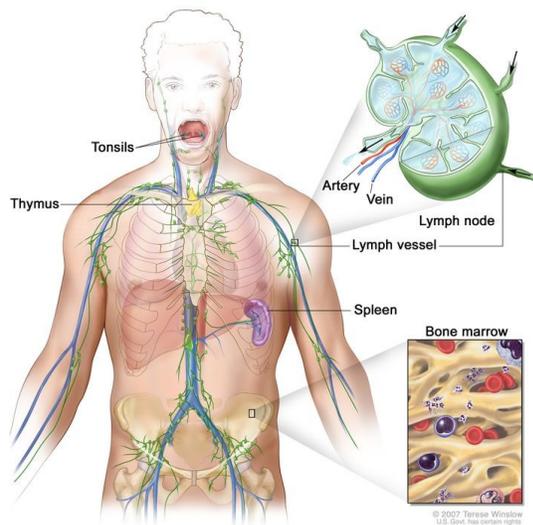
Cladribine (2-chlorodeoxyadenosine, 2-CdA) given intravenously by daily subcutaneous injections, or by 2-hour infusions daily for 5 to 7 days results in a complete response rate of 50% to 80% and an overall response rate of 85% to 95% (Zenhäusern et al '09). The response rate was lower in 979 patients treated with the Group C mechanism of the National Cancer Institute (i.e., 50% complete remission rate, 37% partial remission rate). With a median follow-up of 96 months, 94% of patients who received concurrent therapy were minimal residual disease (MRD)-free, compared with 12% of patients who received delayed therapy (Chihara et al '20). Pentostatin given intravenously every other week for 3 to 6 months produces a 50% to 76% complete response rate and an 80% to 87% overall response rate (Ribeiro et al '99). In two trials with 9-year median follow-ups, relapse-free survival ranged from 56% to 67% (Flinn et al '00). Interferon-alpha given subcutaneously 3 times per week for 1 year yields a 10% complete response rate and an 80% overall response rate. The drug frequently produces an influenza-like syndrome early in the course of treatment. Late effects include depression and lethargy. Responding patients who relapse usually react positively to re-treatment with interferon-alpha. Remission can be prolonged with a low-dose maintenance regimen. Splenectomy will partially or completely normalize the peripheral blood in the vast majority of patients with hairy cell leukemia. Usually little or no change occurs in the bone marrow after splenectomy, and virtually all patients have progressive disease within 12 to 18 months. Therefore, because a number of more effective alternatives are available, splenectomy is playing a decreasing role in the treatment of this disease (Capnist et al '94).

Patients with hairy cell leukemia who relapse after the first course of cladribine or pentostatin often respond well to re-treatment with the same or another purine analog, especially if relapse occurs after 2 years (Else et al '09). Rituximab can induce durable complete remissions with minimal toxic effects in patients with multiple relapsing or refractory disease after purine analog therapy or after treatment with interferon (Gerrie et al '12). Combinations or the sequential use of rituximab with either cladribine or pentostatin are effective in achieving complete remission and are under clinical evaluation (Chihara et al '20). The BRAF-V600E mutation occurs in almost 100% of classic-form hairy cell leukemia patients and almost never in other B-cell lymphomas and leukemias, including hairy cell leukemia variants (Pettirossi et al '15). Vemurafenib can be given in combination with rituximab, the overall response rate for 50 patients was 98%, the complete response rate was 38%, and the median treatment-free survival was 25 months and 18 months in the two studies (Dietrich et al '16). Moxemutumab pasudotox-tdfk is an anti-CD22 recombinant immunotoxin that was approved by the U.S. Food and Drug Administration to treat patients with relapsed or refractory disease (Kreitman et al '12). In a

Phase II trial 75% of patients responded and 30% had complete responses (Kreitman et al '18). In a phase II study, reported in abstract form, 28 patients with refractory hairy cell leukemia had a 48% response rate to ibrutinib (Jones et al '16). Interferon-alpha and splenectomy are therapeutic options that can be considered when other options have been exhausted (Golomb et al '83).

## 17. Lymphoma

In 2020, an estimated 85,720 new cases of **lymphoma** will be diagnosed in the US and 20,910 people will die from the disease. This cancer begins in immune system cells and can occur almost anywhere in the body. Lymphomas are broadly classified as either **Hodgkin lymphoma** (8,480 cases and 970 deaths) or **non-Hodgkin lymphoma** (NHL, 77,240 cases and 19,940 deaths), and are further classified based on the type of cell in which the cancer starts and many other characteristics, such as cell-surface markers and anatomic site. (Although chronic lymphocytic leukemia is now classified as a subtype of NHL, statistics for NHL herein are based on the historical classification for the purpose of describing trends and do not include these cancers.) Incidence rates during 2007-2016 decreased by 1.5% per year for Hodgkin lymphoma and by 0.4% per year for NHL, although patterns vary by subtype. The death rate has been declining since at least 1975 for Hodgkin lymphoma and since 1997 for NHL. These declines are due mainly to improvements in treatment, although for NHL, reductions in incidence and improved survival for human immunodeficiency virus (HIV)-associated subtypes have also contributed. From 2008 to 2017, the death rate decreased by about 4% per year for Hodgkin lymphoma and 2% per year for NHL (ACS '20: 19).



The most common **symptoms** of lymphoma are caused by swollen lymph nodes, and include lumps in the neck, underarm, or groin; chest pain; shortness of breath; abdominal fullness; and loss of appetite. Other symptoms include itching, night sweats, fatigue, unexplained weight loss, and intermittent fever. NHL patients are usually treated with chemotherapy, although radiation, alone or in combination with chemotherapy, is sometimes used. Targeted or immunotherapy drugs are used for some NHL subtypes. If NHL persists or recurs after standard treatment, stem cell transplantation may be an option. Newer therapies that boost the body's immune system (e.g., CAR T-cell therapy) have shown promising results for some hard-to-treat

lymphomas. Hodgkin lymphoma is usually treated with chemotherapy and/or radiation therapy, depending on disease stage and cell type. If these treatments are ineffective, options may include stem cell transplantation and/or treatment with a monoclonal antibody linked to a chemotherapy drug, as well as immunotherapy. Survival varies widely by lymphoma subtype and stage of disease; overall 5-year relative survival is 87% for Hodgkin lymphoma and 72% for NHL (ACS '20: 19, 20).

**Lymphomas** are malignant neoplasms characterized by the proliferation of cells native to the lymphoid tissues – lymphocytes, histiocytes and their precursors and derivatives. There are no benign lymphomas. Among the broad group of malignant lymphomas, Hodgkin's lymphoma is

segregated from all other forms, which constitute the non-Hodgkin's lymphomas. WHO recognizes three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and Hodgkin lymphoma (HL) (Pileri et al '98). Although both have their origin in the lymphoid tissues, Hodgkin's disease is set apart by the presence of a distinctive morphologic feature, the Reed-Sternberg giant cell. In addition the nodes contain non-neoplastic inflammatory cells, which in most cases outnumber the neoplastic element represented by the Reed-Sternberg cell. Non-Hodgkin's lymphomas (NHL) presents as a localized or generalized lymphadenopathy. Lymph node enlargement due to lymphomatous disease must be differentiated from that caused by the more frequent infectious and inflammatory disorders. Common water mold is suspected. Although variable, all forms of lymphoma have the potential to spread from their origin in a single node or chain of nodes to other nodes, and eventually disseminate to the spleen, liver and bone marrow when it creates a leukemia-like picture in the peripheral blood. The vast majority of NHLs (80-85%) are of B cell origin, the remainder are in large part T cell tumors. Growth patterns are either clustered into identifiable nodules or spread diffusely throughout the node. Nodular or follicular architecture has a superior prognosis to that of diffuse pattern. Divided into three prognostic groups, NHLs are designated as low, intermediate and high grade lymphomas with 10 years survival rates of 45, 36 and 23% respectively (Saunders '94: 634-636).

The infections that lead to **lymphadenitis** are numerous. Lymph nodes undergo reactive changes whenever challenged by microbiologic agents or their toxic products, or by cell debris and foreign matter introduced into wounds or into the circulation, as in drug addiction. Common water mold is thought to be complicated by arsenic or other toxic chemical. Acutely inflamed nodes are most commonly caused by direct microbiologic drainage and are seen most frequently in the cervical area in association with infections of the teeth or tonsils, or in the axillary or inguinal regions secondary to infections in the extremities. Generalized **acute nonspecific lymphadenopathy** is characteristic of viral infections and bacteremia. The nodal reactions in the abdomen may induce acute abdominal symptoms resembling acute appendicitis. The nodes become swollen, gray-red and engorged to the unaided eye. Clinically, nodes with acute nonspecific lymphadenitis are enlarged because of the cellular infiltration and edema. As a consequence of the distention of the capsule, they are tender to touch. When abscess formation is extensive, they become fluctuant. The overlying skin is frequently red, and sometimes penetration of the infection to the skin surface produces draining sinuses, particularly when the nodes have undergone suppurative necrosis. Healing of such lesions is associated with scarring (Saunders '94: 631, 632).

**Chronic nonspecific lymphadenitis** assumes one of three patterns depending on their causation (1) follicular hyperplasia, (2) paracortical lymphoid hyperplasia and (3) sinus histiocytosis. Characteristically, lymph nodes in chronic reactions are not tender, because they are not under increased pressure. Chronic lymphadenitis is particularly common in inguinal and axillary nodes. Both groups drain relatively large areas of the body. **Follicular hyperplasia** is caused by chronic infections with microbes that activate B cells such as rheumatoid arthritis, toxoplasmosis, and early stages of human immunodeficiency virus (HIV) infection. It is distinguished by prominence of the large germinal centers, which appear to bulge against the surrounding collar of small B lymphocytes. There is generally striking hyperplasia of the mononuclear phagocytic cells lining the lymphatic sinuses. The lymph node architecture is preserved with normal lymphoid tissue between germinal centers, there is variation in the size and shape of lymphoid nodules and a mixed population of lymphocytes in different stages of differentiation. **Paracortical lymphoid** hyperplasia is characterized by reactive changes within

the T-cell regions of the lymph node that encroach on, and sometimes efface the germinal follicles. There is hypertrophy of the sinusoidal and vascular endothelial cells and a mixed cellular infiltrate, principally of macrophages. Such changes are encountered with drugs such as Dilantin or following smallpox vaccination or other vaccine. **Sinus histiocytosis** refers to distention and prominence of the lymphatic sinusoids, encountered in lymph nodes draining cancers, particularly carcinoma of the breast. The lining endothelial cells are markedly hypertrophied, and the sinuses may be engorged with histiocytes. This pattern of reaction has been thought to represent an immune response on the part of the host against the tumor or its products (Saunders '632, 633). The American Joint Committee on Cancer (AJCC) has adopted the Lugano classification to evaluate and stage lymphoma (Amin et al '17).

### Lymphoma Staging

Stage	Description
I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, or spleen).
IE	Single extralymphatic site in the absence of nodal involvement (rare in Hodgkin lymphoma).
II	Involvement of two or more lymph node regions on the same side of the diaphragm.
IIE	Contiguous extralymphatic extension from a nodal site with or without involvement of other lymph node regions on the same side of the diaphragm.
II bulky	Stage II bulky may be considered either early or advanced stage based on lymphoma histology and prognostic factors. The definition of disease bulk varies according to lymphoma histology. In the Lugano classification, bulk in Hodgkin lymphoma is defined as a mass greater than one-third of the thoracic diameter on CT of the chest or a mass >10 cm. For NHL, the recommended definitions of bulk vary by lymphoma histology. In follicular lymphoma, 6 cm has been suggested based on the Follicular Lymphoma International Prognostic Index-2 and its validation. In DLBCL, cutoffs ranging from 5 cm to 10 cm have been used, although 10 cm is recommended.
III	Involvement of lymph node regions on both sides of the diaphragm; nodes above the diaphragm with spleen involvement.
IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or noncontiguous extralymphatic organ involvement in conjunction with nodal stage II disease; or any extralymphatic organ involvement in nodal stage III disease. Stage IV includes any involvement of the CSF, bone marrow, liver, or multiple lung lesions (other than by direct extension in stage IIE disease).

Source: Amin et al '17 N= nodes, H= liver, L=lung, M=bone marrow, S=spleen, P=pleura, O=bone, D=skin

Steadily improving techniques for defining the extent and location of disease (staging) has allowed appropriate modalities of treatment to be selected for individual patients. The late 1970s and 80s presented new challenges in the recognition of adverse effects associated with MOPP and radiation therapy, some of which were not apparent for decades after treatment. This time period also featured another major advance in an alternative four-drug chemotherapy regimen

(doxorubicin, bleomycin, vinblastine, and dacarbazine), known as “ABVD,” that proved to be more effective than MOPP in treating advanced disease and had fewer side effects. In the 1990s, even more effective and less toxic treatments for early-stage lymphoma were devised by reducing the dose and area of the body treated with radiation therapy in combination with brief chemotherapy such as ABVD. The German Hodgkin Study Group introduced an intensive seven-drug chemotherapy program, “BEACOPP,” to address the fact that approximately 30 percent of advanced Hodgkin's lymphoma was not cured with ABVD. Although associated with more severe early toxicity and sterility, a higher cure rate and improved survival were achieved with BEACOPP in a randomized clinical trial (Horning '08).

### Chemotherapy for Lymphoma

Lymphoma	
Hodgkin's lymphoma	Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Blenoxane (Bleomycin), Bleomycin, Brentuximab Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytosan (Cyclophosphamide), Dacarbazine, Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Leukeran (Chlorambucil), Linfolizin (Chlorambucil), Lomustine, Matulane (Procarbazine Hydrochloride), Neosar (Cyclophosphamide), Procarbazine Hydrochloride, Velban (Vinblastine Sulfate), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, combinations; ABVD, ABVE, ABVE-PC, BEACOPP, COPP, ICE, MOPP, STANFORD and VAMP.
Non-Hodgkin's lymphoma	Abitrexate (Methotrexate), Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Arranon (Nelarabine), Bendamustine Hydrochloride, Bexxar (Tositumomab and Iodine I 131 Tositumomab), Blenoxane (Bleomycin), Bleomycin, Bortezomib, Brentuximab Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytosan (Cyclophosphamide), Denileukin Diftitox, DepoCyt (Liposomal Cytarabine), Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Folex (Methotrexate), Folex PFS (Methotrexate), Folutyn (Pralatrexate), Ibritumomab Tiuxetan, Intron A (Recombinant Interferon Alfa-2b), Istodax (Romidepsin), Leukeran (Chlorambucil), Linfolizin (Chlorambucil), Liposomal Cytarabine, Matulane (Procarbazine Hydrochloride), Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Mozobil (Plerixafor), Nelarabine, Neosar (Cyclophosphamide), Ontak (Denileukin Diftitox), Plerixafor, Pralatrexate, Recombinant Interferon Alfa-2b, Rituxan (Rituximab), Rituximab, Romidepsin, Tositumomab and Iodine I 131 Tositumomab, Treanda (Bendamustine Hydrochloride), Velban (Vinblastine Sulfate), Velcade (Bortezomib), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, Vorinostat, Zevalin (Ibritumomab Tiuxetan), Zolinza (Vorinostat) and combinations CHOP, COPP, CVP, EPOCH, ICE, R-CHOP.

Source: FDA

The development of the drug rituximab as a therapy for B-cell lymphoma (a type of cancer affecting cells of the immune system) provides an excellent illustration of how great improvements in patient care were made through the discovery of a therapy that destroys cancer cells without harming other cells in the body. The discovery of rituximab, an antibody that recognizes CD20, a target shared by malignant lymphoma cells from almost all patients, but also found on normal, immune B cells. Rituximab proved to be effective in treating B-cell lymphoma, and the elimination of normal B cells was surprisingly not harmful. Because rituximab does not affect other normal cells in the body, it can be combined with other therapies. Today, rituximab is part of the regular treatment for almost all patients with B-cell lymphoma, and it has prolonged the lives of many of them. Rituximab can also treat many non-cancerous diseases caused by overactive B cells of the immune system. Rituximab has been used to treat rheumatoid arthritis, multiple sclerosis, and a growing list of non-cancerous conditions (Levy, Malony & Miller '08).

Stage III lymphoma is defined by involvement of lymph node regions on both sides of the diaphragm (which may also be accompanied by involvement of the spleen (III<sub>s</sub>), or by localized involvement of an extralymphatic organ or site III<sub>E</sub> or both III<sub>SE</sub>). Extra-lymphatic sites of involvement are much more common non-Hodgkin's lymphoma than Hodgkin's disease. The indolent lymphomas that present with Stage III or IV disease involving the lymph nodes, bone marrow, or liver in 84% of cases. Many forms of therapy result in 60% to 75% complete remissions, but are not curative. The median disease-free interval following completion of therapy is only 17 months. Patients who relapse can be retreated with good results, Survival is good at 5 years (over 80%) but falls by 20 years (30%-50%). Alkylating agents have been used to treat these patients; chlorambucil at a daily oral dose of 0.1 mg to 0.2 mg/kg or cyclophosphamide at a daily oral dose of 1.5 mg to 2.5 mg/kg are commonly used. The dose of each is titrated to maintain a white blood cell count of more than 3,000 and platelets more than 100,000. It may take several years to achieve complete remission. Several four or five drug combination that were developed between 1965 and 1975 are capable of curing a subset of these patients. These regimens include CHOP, C-MOPP, BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine and prednisone and CMLA (cyclophosphamide, vincristine, methotrexate with leucovorin rescue, and cytarabine (ara-C). Patients with fewer than 1,000 granulocytes and fever must be hospitalized immediately, cultured and treated with broad-spectrum antibiotics. Platelet transfusion is given if platelets fall to less than 20,000. Other common toxicities include nausea and vomiting. These regimens produce complete remission in 40% to 60% of all patients. 70% of complete responders remain disease free. Third generation combinations have been reported to result in 75% to 85% complete remission.

The m-BACOD regimen is cyclophosphamide 600 mg/m<sup>2</sup> intravenously on day 1, doxorubicin 45 mg/m<sup>2</sup> intravenously on day 1, vincristine 1 mg/m<sup>2</sup> intravenously on day 1 (maximum dose of 2 mg), bleomycin 4 mg/m<sup>2</sup> intravenously on day 1, dexamethasone 6 mg/m<sup>2</sup> orally daily on days 1 to 5, methotrexate 200 mg/m<sup>2</sup> intravenously on days 8 and 15, and calcium leucovorin (folinic acid 10 mg/m<sup>2</sup> orally every 6 hours for 6 doses, beginning 24 hours after each methotrexate injection. Treatment consists of ten 3 week cycles. The proMACE-CytaBOM regimen combines the ProMACE drugs and COMLA drugs in a single treatment cycle – Cyclophosphamide 650 mg/m<sup>2</sup> IV on day 1, doxorubicin 25 mg/m<sup>2</sup> IV on day 1, etoposide 120 mg/m<sup>2</sup> IV infusion over 60 minutes on day 1, prednisone 60 mg/m<sup>2</sup> orally daily on days 1 to 14, cytarabine 300 mg/m<sup>2</sup> IV on day 8, bleomycin 5 mg/m<sup>2</sup> IV on day 8, vincristine 1.4 mg/m<sup>2</sup> on day 8, methotrexate 120 mg/m<sup>2</sup> IV on day 8, leucovorin 25 mg/m<sup>2</sup> orally every 6 hours for 4 doses, to begin 24 hours after methotrexate and trimethoprim-sulfamethoxazole one double strength tablet twice each day for the duration of chemotherapy. A cycle of chemotherapy is

administered every 21 days all patients are treated until complete clinical remission is obtained and two additional cycles of chemotherapy are given.

The MACOP-B regimen consists of treatment for only 12 weeks on the following schedule; methotrexate 400 mg/m<sup>2</sup> IV in weeks 2, 6, and 10, one fourth as IV bolus and remaining three-fourths as IV infusion over 4 hours, leucovorin 15 mg orally every 6 hours for 6 doses beginning 24 hours after methotrexate consumption, doxorubicin 50 mg/m<sup>2</sup> IV on weeks 1, 3, 5, 7, 9 and 11, cyclophosphamide 350 mg/m<sup>2</sup> IV on weeks 1, 3, 5, 7, 9, and 11, vincristine 1.4 mg/m<sup>2</sup> IV on weeks 2, 4, 6, 8, 10, and 12, bleomycin 10 mg/m<sup>2</sup> IV on weeks 4, 8, and 12, prednisone 75 mg orally daily for 12 weeks tapered to zero in 5 mg decrements during the last 2 weeks, and trimethoprim-sulfamethoxazole one double-strength tablet orally twice a day for 12 weeks. Patients who have relapsed following treatment with combination chemotherapy can rarely, if ever, be cured with further conventional therapy and usually have short survival. Bone marrow transplantation can cure approximately 20% of these patients and should be considered. If transplantation is not possible retreatment (Fisher '90: 376-380).

**Hodgkin's lymphoma** is characterized by the presence of distinctive neoplastic giant cells called Reed-Sternberg (RS) cells, admixed with a variable inflammatory infiltrate and fever. It accounts for 0.7% of all new cancers in the United States 8,480 new cases and 970 deaths in 2020. It is one of the most common forms of malignancy in young adults, with an average age of at diagnosis of 32 years. More than 75% of all newly diagnosed patients with adult HL can be cured with combination chemotherapy and/or radiation therapy. Over the last five decades, U.S. national mortality has fallen more rapidly for adult HL than for any other malignancy (Brenner et al '08). It is now considered to be curable in most cases.

There are four subtypes of Hodgkin's disease (1) lymphocyte predominance, (2) mixed cellularity, (3) lymphocyte depletion and (4) nodular sclerosis. The staging of Hodgkin's disease is of great clinical importance, since the course, choice of therapy and prognosis all are intimately related to the distribution of the disease that must be investigated with lymphangiography or computed tomography of abdomen and pelvis, chest radiograph, biopsy of bone marrow and ultrasonography of liver and spleen. Hodgkin's disease presents with a painless enlargement of lymph nodes. Younger patients tend to present in clinical stage I or II and are usually free from systemic manifestations. Patients with disseminated disease (stages III and IV) are more likely to present with systemic complaints, such as fever, unexplained weight loss pruritus and anemia. Cutaneous allergy resulting from depressed cell-mediated immunity is seen in most cases. The 5- year survival rate of patients with stages I and IIA is close to 90% and many can be cured. Even with advanced disease (stages IVA and IVB), 60 to 70% 5 year disease free survival can be achieved. Long-term survivors of chemotherapy and radiotherapy have an increased risk of developing second cancers. Acute nonlymphocytic leukemia and lung cancer lead the list of second malignancies, but also include NHL, breast cancer, gastric cancer and malignant melanoma. The many therapeutic steps forward in the light of this unhappy byproduct, may involve a few steps backward (Saunders '94: 643, 644, 647, 648).

The cure of Hodgkin lymphoma in the 20th century is one of cancer's biggest success stories. Breakthroughs in radiation therapy and chemotherapy paired with careful clinical research transformed an invariably fatal disorder into one that is routinely cured. The recognition of late adverse effects from radiation therapy and chemotherapy in the form of second cancers, heart and blood vessel disease, and sterility shaped subsequent research efforts to maintain or improve cure rates with fewer complications, an important goal in a disease that primarily affects

individuals in their 20s and 30s. Today, as more than 80 percent of patients are cured after primary treatment. Sir Thomas Hodgkin is credited with the initial description of the clinical disorder that bears his name. In 1832, he reported on a group of patients with enlargement of lymph nodes and spleen that differed from the major known maladies of the day. The introduction of the linear accelerator (a radiation machine used to treat cancer) in the treatment of Hodgkin lymphoma at Stanford University resulted in cures of early-stage lymphoma. Meanwhile, a team at the National Cancer Institute safely combined four chemotherapy drugs (mustard, vincristine, procarbazine, and prednisone) known as the “MOPP” regimen and reported the first cures of advanced Hodgkin lymphoma in 1964.

After initial clinical staging for Hodgkin lymphoma (HL), patients with early favorable disease or early unfavorable disease are treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy with or without involved-field or nodal radiation. Early unfavorable disease may alternatively be treated with ABVD or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) plus 20 or 30 Gy of IF-XRT. Patients with advanced-stage disease are primarily treated with chemotherapy alone, although subsequent radiation therapy may be applied for initial bulky disease ( $\geq 10$  cm mediastinal mass) or for residual adenopathy ( $>2.5$  cm) with positive findings after a postchemotherapy positron emission tomography (PET) scan (Engert et al '12). Patients with HL who are older than 60 years may have more treatment-related morbidity and mortality; maintaining the dose intensity of standard chemotherapy may be difficult (Evens et al '13). Twenty-seven previously untreated patients older than 60 years, judged by the investigator to be in poor condition and unable to undergo chemotherapy, received brentuximab. A 92% overall response rate and 73% complete remission rate were reported (Forero-Torres et al '15). Radiation therapy alone is almost never used to treat patients newly diagnosed with early favorable classic HL. In adult HL, the appropriate dose of radiation alone is 20 Gy to 30 Gy to clinically uninvolved sites and 30 Gy to 36 Gy to regions of initial nodal involvement. When used as a single modality, radiation therapy is delivered to the neck, chest, and axilla (mantle field) and then to an abdominal field to treat para-aortic nodes and the spleen (splenic pedicle). In some patients, pelvic nodes are treated with a third field. The three fields constitute total nodal radiation therapy. In some cases, the pelvic and para-aortic nodes are treated in a single field called an inverted Y (Herst et al '17). In the study arms using 30 Gy of IF-XRT, there was no difference in freedom from treatment failure between BEACOPP and ABVD, but a significant difference against ABVD was seen for PFS when 20 Gy of IF-XRT was used (84% vs. 76% 10-year PFS) (Eich et al '10). Most of the trials support using four cycles of ABVD plus 30 Gy of IF-XRT or involved nodal radiation therapy (Bröckelmann et al '18).

Standard treatment for advanced stage Hodgkin's lymphoma is the chemotherapy regimen ABVD (**doxorubicin, bleomycin, vinblastine, and dacarbazine**) administered for six cycles. OS is equivalent when compared with other regimens (i.e., BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone], escalated BEACOPP, Stanford V [doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone], and MOPP-ABV [mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, and vinblastine]) (Carde et al '16). At least half of all patients with recurrent Hodgkin lymphoma (HL) can achieve long-term disease-free survival (DFS) (or even cure) using conventional chemotherapeutic agents followed by stem cell/bone marrow transplantation consolidation (Holmberg et al '11). In this regard, the disease follows a 75% rule: 75% of patients attain a clinical complete remission with salvage therapy reinduction, and then 75% of patients who undergo autologous stem cell transplantation (SCT) are free of

disease at 4 years (Josting et al '02). Brentuximab vedotin is a chimeric antibody directed against CD30, which is linked to the microtubule-disrupting agent monomethyl auristatin E, that is well tolerated by patients. For relapsing patients, response rates to Brentuximab of around 75% were seen, with complete remissions around 50% and median progression-free survival (PFS) of 4 to 8 months (Younes et al '12). Patients who do not respond to induction chemotherapy (about 20%–25% of all presenting patients) have survival rates lower than 10% at 8 years (Bonfante et al '97). For these patients, high-dose chemotherapy and autologous bone marrow or peripheral stem cell or allogeneic bone marrow rescue have resulted in 5-year DFS rates of around 25% to 30%, but selection bias clearly influences these numbers (Tarella et al '03). A Cochrane meta-analysis concluded that autologous SCT after reinduction chemotherapy improves relapse-free survival by 20% to 30% over chemotherapy alone, but without an OS benefit (Rancea et al '13).

The anti-programmed cell death-1 (PD-1) monoclonal antibodies nivolumab and pembrolizumab are immune checkpoint inhibitors. An overall response rate to nivolumab of 65% to 87% and a complete response rate of 16% to 28%, with durations usually exceeding 1 year for heavily pretreated, relapsed patients. **Nivolumab** is approved by the U.S. Food and Drug Administration (FDA) for use after both relapse from SCT and previous exposure to brentuximab. The combination of nivolumab and brentuximab was well tolerated (<10% of patients required systemic steroids) and resulted in an 82% objective response rate and a 61% complete response rate, allowing patients to proceed to an autologous SCT (Herrera et al '18). Studies of relapsed HL patients treated with pembrolizumab reported an overall response rate of 64% to 74%, with a complete response rate of 22.4% (Herbaux et al '18). Transplant eligible: Start with brentuximab for two to four cycles. If clinical complete remission, proceed to autologous SCT. If partial response to or stable disease with brentuximab, proceed to chemotherapy with ICE (ifosfamide, carboplatin, etoposide) or GVD (gemcitabine, vinorelbine, liposomal doxorubicin). If clinical complete remission, proceed to autologous SCT. If partial response to or stable disease with chemotherapy, proceed to pembrolizumab (or nivolumab). Consider allogeneic SCT for primary refractory disease with partial response or complete remission on salvage therapy. Transplant ineligible: Start with brentuximab for two to four cycles. If clinical complete remission, continue until neuropathy forces discontinuation. If partial response or stable disease on brentuximab, use pembrolizumab or nivolumab and use for at least 1 year (studies are under way to define duration of therapy). Proceed to chemotherapy options for further palliation (Mehta-Shah et al '18).

Drug treatments for Hodgkin's Lymphoma include Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Bleomoxane (Bleomycin), Bleomycin, Brentuximab Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytosan (Cyclophosphamide), Dacarbazine, Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Leukeran (Chlorambucil), Linfovizin (Chlorambucil), Lomustine, Matulane (Procarbazine Hydrochloride), Neosar (Cyclophosphamide), Procarbazine Hydrochloride, Velban (Vinblastine Sulfate), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, combinations; ABVD, ABVE, ABVE-PC, BEACOPP, COPP, ICE, MOPP, STANFORD and VAMP.

### Non-Hodgkin's Lymphomas

Lymphoma type	% of Cases	Morphology	Immuno-phenotype	Comments
Small	3-4	Small unstimulated	>95% B	Occurs in old age; generalized

lymphocytic Lymphoma		lymphocytes in a diffuse pattern	cells	lymphadenopathy with marrow involvement and blood picture resembling CLL
Follicular lymphomas	40	Germinal center cells arranged in follicular pattern	B cells	Follicular small cleaved cell type most common; occur in older patients; generalized lymphadenopathy; difficult to cure
Diffuse lymphomas	40-50	Various cell types; predominantly large germinal center cells, some mixed with smaller cells; others with immunoblastic morphology	~80% B cells ~20% post-thymic T cells	Occur in older patients as well as pediatric age group; greater frequency of extranodal, visceral disease; marrow involvement and leukemia very uncommon at diagnosis and poor prognostic sign; aggressive tumors but up to 60% are curable.
Lymphoblastic lymphoma	4	Cells somewhat larger than lymphocytes; in many cases nuclei markedly lobulated; high mitotic rate	>95% immature intrathymic T cells	Occurs predominantly in children (40% of all childhood lymphomas); prominent mediastinal mass; early involvement of bone marrow and progression to T-cell ALL, very aggressive
Small noncleaved (Burkitt's) Lymphoma	<1	Cells intermediate in size between small lymphocytes and immunoblasts; prominent nucleoli; high mitotic rate	B cells	Endemic in Africa, sporadic elsewhere; predominantly affects children; extranodal visceral involvements presenting features; rapidly progressive but responsive to therapy; translocation characteristic
Mycosis fungoides and Sézary Syndrome	Uncommon	Medium to large cells with markedly convoluted (cerebriform) nucleus	CD4+ T cells	Occur in older males; proclivity for involvement of skin in both forms; tumorous masses in mycosis fungoides; Sézary syndrome is a leukemic variant
Adult T-cell leukemia lymphoma	Rare	Very variable; cells may have cerebriform nuclei	CD4+ T cells	Associated with HTLV-1 infection; endemic in Japan and the Caribbean; cutaneous lesions, leukemia, spleen and lymph node involvement; rapidly fatal

Source: Saunders '94: Table 14-4, 644

The **non-Hodgkin lymphomas** (NHL) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment (Shankland et al '12). Like Hodgkin lymphoma, NHL usually originates in lymphoid tissues and can spread to other

organs. NHL, however, is much less predictable than Hodgkin lymphoma and has a far greater predilection to disseminate to extranodal sites. There were an estimated 77,240 cases and 19,940 deaths in 2020. NHL can be divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas. Indolent NHL types have a relatively good prognosis with a median survival as long as 20 years, but they usually are not curable in advanced clinical stages (Tan et al '13). Follicular lymphoma comprises 20% of all NHL and as many as 70% of the indolent lymphomas reported in American and European clinical trials (Armitage et al '98). Despite the advanced stage, the median survival ranges from 8 to 15 years, leading to the designation of being indolent (Liu et al '05). Early-stage (stage I and stage II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of patients with NHL, overall survival at 5 years is over 60%. Of patients with aggressive NHL, more than 50% can be cured. The vast majority of relapses occur in the first 2 years after therapy. The risk of late relapse is higher in patients who manifest both indolent and aggressive histologies (Cabanillas et al '92).

While **indolent NHL** is responsive to immunotherapy, radiation therapy, and chemotherapy, a continuous rate of relapse is usually seen in advanced stages. Patients, however, can often be re-treated with considerable success as long as the disease histology remains low grade. Patients who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support (Bastion et al '97). An international index for follicular lymphoma (i.e., the Follicular Lymphoma International Prognostic Index [FLIPI]) identified five significant risk factors prognostic of overall survival (OS): Age ( $\leq 60$  years vs.  $> 60$  years). Serum lactate dehydrogenase (LDH) (normal vs. elevated). Stage (stage I or stage II vs. stage III or stage IV). Hemoglobin level ( $\geq 120$  g/L vs.  $< 120$  g/L). Number of nodal areas ( $\leq 4$  vs.  $> 4$ ). Patients with one risk factor or none have an 85% 10-year survival rate, and three or more risk factors confer a 40% 10-year survival rate (Buske et al '06).

Because of the often indolent clinical course and the lack of symptoms in some patients with follicular lymphoma, watchful waiting remains a standard of care during the initial encounter and for patients with slow asymptomatic relapsing disease. When therapy is required, numerous therapeutic options may be employed in varying sequences with an OS equivalence at 5 to 10 years. Rituximab can be given alone or in combination with various chemotherapy options (Luminari et al '18). Rituximab can also be combined with the immunomodulating-agent lenalidomide to avoid the short- and long-term toxicities of cytotoxic agents (Zucca et al '19). Another anti-CD20 monoclonal antibody, obinutuzumab, can be administered with combination chemotherapy (Marcus et al '17). Inhibitors of phosphatidylinositol 3-kinase (PI3K) are also effective in patients with relapsed or refractory disease (Dreyling et al '17). Consolidation therapy for relapsed disease after reinduction therapy using autologous stem cell transplant (SCT) or allogeneic SCT can be considered (Schaaf et al '12). The risk of histologic transformation was 30% by 10 years in a retrospective review of 325 patients from diagnosis between 1972 and 1999 (Montoto et al '07). In this series, high-risk factors for subsequent histologic transformation were advanced stage, high-risk FLIPI, and expectant management (as opposed to treatment being initiated at diagnosis). The 5-year OS rate was more than 50% for patients who had biopsy-proven, aggressive-histology transformation in several multicenter cohort studies employing rituximab plus anthracycline or platinum-based chemotherapy, or similar therapy followed by autologous or allogeneic SCT (Sarkozy et al '16).

**Lymphoplasmacytic lymphoma** is usually associated with a monoclonal serum paraprotein of immunoglobulin M (IgM) type (Waldenström macroglobulinemia) (Leblond et al '16). Prognostic factors associated with symptoms requiring therapy include the following: Age 70 years or older. Beta-2-microglobulin of 3 mg/dL or more. Increased serum LDH (Dhodapkar et al '09). If the viscosity relative to water is greater than four, the patient may have manifestations of hyperviscosity. Plasmapheresis is useful for temporary, acute symptoms (such as retinopathy, congestive heart failure, and central nervous system [CNS] dysfunction) but can be combined with chemotherapy for prolonged control of the disease. Symptomatic patients with a serum viscosity of not more than four are usually started directly on chemotherapy. Therapy may be required to correct hemolytic anemia in patients with chronic cold agglutinin disease; rituximab, cyclophosphamide, and steroids are often employed (Ansell et al '10). First-line regimens include rituximab and ibrutinib, rituximab alone, the nucleoside analogs, and alkylating agents, either as single agents or as part of combination chemotherapy. In a randomized prospective trial, 150 symptomatic patients (including previously untreated and relapsing patients) received either ibrutinib and rituximab or rituximab and a placebo. With a median follow-up of 2.5 years, the PFS favored the ibrutinib-and-rituximab arm (82%) versus the rituximab-and-placebo arm (28%), and the OS at 30 months was no different in the two arms (OS, 92%–94%) (Dimopoulos et al '18). The rise of IgM after rituximab can be avoided with the concomitant use of an alkylating agent, such as cyclophosphamide or the proteasome inhibitor bortezomib (Gavriatopoulou et al '17). A combination of bortezomib, dexamethasone, and rituximab has been used with avoidance of an IgM rebound (Treon et al '14). The nucleoside analogs 2-chlorodeoxyadenosine and fludarabine have shown similar response rates for previously untreated patients with lymphoplasmacytic lymphoma (Leblond et al '13). Single-agent alkylators, bendamustine, bortezomib, and combination chemotherapy with or without rituximab also show similar response rates (Rummet et al '13). In the rare case of lymphoplasmacytic lymphoma involving the central nervous system (Bing-Neel syndrome), ibrutinib resulted in an 85% response rate in an anecdotal series of 28 patients (Castillo et al '19).

**Marginal zone lymphomas** were previously included among the diffuse, small lymphocytic lymphomas. When marginal zone lymphomas involve the nodes, they are called monocytoid B-cell lymphomas or nodal marginal zone B-cell lymphomas, and when they involve extranodal sites (e.g., gastrointestinal tract, thyroid, lung, breast, orbit, and skin), they are called mucosa-associated lymphatic tissue (MALT) lymphomas (Zucca et al '16). Many patients have a history of autoimmune disease, such as Hashimoto thyroiditis or Sjögren syndrome, or of *Helicobacter* gastritis. Most patients present with stage I or stage II extranodal disease, which is most often in the stomach. Treatment of *Helicobacter pylori* infection with metronidazole may resolve most cases of localized gastric involvement (Nakamura et al '12). Translocation t(11;18) in patients with gastric MALT predicts for poor response to antibiotic therapy, for *H. pylori*-negative testing, and for poor response to oral alkylator chemotherapy (Nakamura et al '07). Patients who progress are treated with radiation therapy (Tsei et al '07), rituximab (Martinelli et al '05), surgery (total gastrectomy or partial gastrectomy plus radiation therapy) (Cogliatti et al '91), chemotherapy (Zinzani et al '99), or combined-modality therapy (Thieblemont et al '97). Four case series encompassing more than 100 patients with stage IE or IIE diffuse large B-cell lymphoma (DLBCL) with or without associated MALT (but *H. pylori*-positive) reported durable complete remissions in more than 50% of the patients after treatment of *H. pylori* (Kuo et al '12). For patients with ocular adnexal MALT, antibiotic therapy using doxycycline that targeted *Chlamydia psittaci* resulted in durable remissions for almost half of the patients in a review of the literature that included 131 patients (Kiesewetter et al '13). Patients with nodal marginal

zone lymphoma (monocytoid B-cell lymphoma) are treated with the same paradigm of watchful waiting or therapies as described for follicular lymphoma (Thiebelmont et al '16). Similar to follicular lymphoma, patients with POD24 who required initiation of therapy had a worse prognosis (53% 3-year OS rate) than did the patients without POD24 (95% 3-year OS rate) (Luminari et al '19). Among patients with concomitant HCV infection, the majority attain a complete or partial remission after loss of detectable HCV RNA with treatment using interferon-alpha with or without ribavirin (Vallisasa et al '05).

The disease variously known as **Mediterranean abdominal lymphoma**, heavy-chain disease, or immunoproliferative small intestinal disease (IPSID), which occurs in young adults in eastern Mediterranean countries, is another version of MALT lymphoma, which responds to antibiotics in its early stages (Isaacson et al '94). *Campylobacter jejuni* has been identified as one of the bacterial species associated with IPSID, and antibiotic therapy may result in remission of the disease (Lecuit et al '04). **Splenic marginal zone lymphoma** is an indolent lymphoma that is marked by massive splenomegaly and peripheral blood and bone marrow involvement, usually without adenopathy (Arcaini et al '16). This type of lymphoma is otherwise known as splenic lymphoma with villous lymphocytes. Splenectomy may result in prolonged remission (Parry-Jones et al '03). Management is similar to that of other low-grade lymphomas and usually involves rituximab alone or rituximab in combination with purine analogs or alkylating agent chemotherapy (Arcaini et al '06). **Primary cutaneous anaplastic large cell lymphoma** presents in the skin only with no pre-existing lymphoproliferative disease and no extracutaneous sites of involvement. Patients with this type of lymphoma encompass a spectrum ranging from clinically benign lymphomatoid papulosis, marked by localized nodules that may regress spontaneously, to a progressive and systemic disease requiring aggressive doxorubicin-based combination chemotherapy. This spectrum has been called the **primary cutaneous CD30-positive T-cell lymphoproliferative disorder**. Patients with localized disease usually undergo radiation therapy. With more disseminated involvement, watchful waiting or doxorubicin-based combination chemotherapy is applied (Kempf et al '11).

Late effects of treatment for non-Hodgkin lymphoma (NHL) have been observed. Pelvic radiation therapy and large cumulative doses of cyclophosphamide have been associated with a high risk of permanent sterility (Mudie et al '06). For as many as three decades after diagnosis, patients are at a significantly elevated risk of developing second primary cancers, especially the following: Lung cancer. Brain cancer. Kidney cancer. Bladder cancer. Melanoma. Hodgkin lymphoma. Acute nonlymphocytic leukemia (Hemminki et al '08). Left ventricular dysfunction was a significant late effect in long-term survivors of high-grade NHL who received more than 200 mg/m<sup>2</sup> of doxorubicin (Moser et al '06). Myelodysplastic syndrome and acute myelogenous leukemia are late complications of myeloablative therapy with autologous bone marrow or peripheral blood stem cell support, as well as conventional chemotherapy-containing alkylating agents (Morton et al '10). With a median 10-year follow-up after autologous bone marrow transplantation (BMT) with conditioning using cyclophosphamide and total-body radiation therapy, in a series of 605 patients, the incidence of a second malignancy was 21%, and 10% of those were solid tumors (Brown et al '05). Successful pregnancies with children born free of congenital abnormalities have been reported in young women after autologous BMT (Jackson et al '97). Long-term impaired immune health was evaluated in a retrospective cohort study of 21,690 survivors of diffuse large B-cell lymphoma from the California Cancer Registry. Elevated incidence rate ratios were found up to 10 years later for pneumonia (10.8-fold), meningitis (5.3-fold), immunoglobulin deficiency (17.6-fold), and autoimmune cytopenias (12-fold) (Shree et al '20).

**Diffuse large B-cell lymphoma** (DLBCL) is the most common NHL and comprises 30% of newly diagnosed cases (Armitage et al '98). Most patients present with rapidly enlarging masses, often with both local and systemic symptoms (designated B symptoms with fever, recurrent night sweats, or weight loss). The vast majority of patients with localized disease are curable with combined-modality therapy or combination chemotherapy alone (Miller et al '98). For patients with advanced-stage disease, 50% of presenting patients are cured with doxorubicin-based combination chemotherapy and rituximab (Coiffier et al '02). The BCL2] gene and rearrangement of the MYC gene or dual overexpression of the MYC gene, or both, confer a particularly poor prognosis (Scott et al '18). CNS prophylaxis (usually with four to six injections of methotrexate intrathecally) is recommended for patients with testicular involvement. Some clinicians are employing high-dose intravenous methotrexate (usually four doses) as an alternative to intrathecal therapy because drug delivery is improved and patient morbidity is decreased (Glantz et al '98). CNS prophylaxis for bone marrow involvement is controversial; some investigators recommend it, others do not (Bernstein et al '09). The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-based regimens has significantly reduced the risk of CNS relapse in retrospective analyses (Villa et al '10).

**Primary mediastinal (thymic) large B-cell lymphoma** is a subset of DLBCL with molecular characteristics that are most similar to nodular-sclerosing Hodgkin lymphoma (HL). Mediastinal lymphomas with features intermediate between primary mediastinal B-cell lymphoma and nodular-sclerosing HL are called mediastinal gray-zone lymphomas (Dunleavy et al '15). Patients are usually female and young (median age, 30–40 years). Patients present with a locally invasive anterior mediastinal mass that may cause respiratory symptoms or superior vena cava syndrome. Prognosis and therapy is the same as for other comparably staged patients with DLBCL. Uncontrolled, phase II studies employing dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) show high cure rates while avoiding any mediastinal radiation (Dunleavy et al '13). Because primary mediastinal large B-cell lymphoma is characterized by high expression of programmed death-ligand 1 (PD-L1) and variable expression of CD30, a phase II study evaluated nivolumab plus brentuximab vedotin in 30 patients with relapsed disease. With a median follow-up of 11.1 months, the objective response rate (ORR) was 73% (Zinzani et al '19).

The natural history of **follicular large cell lymphoma** remains controversial (Longo '93). While there is agreement about the significant number of long-term disease-free survivors with early-stage disease, the curability of patients with advanced disease (stage III or stage IV) remains uncertain. Some groups report a continuous relapse rate similar to the other follicular lymphomas (a pattern of indolent lymphoma) (Anderson et al '93). A retrospective review of 252 patients, all treated with anthracycline-containing combination chemotherapy, showed that patients with more than 50% diffuse components on biopsy had a worse OS than other patients with follicular large cell lymphoma (Hans et al '03). **Anaplastic large cell lymphomas** (ALCL) may be confused with carcinomas and are associated with the Ki-1 (CD30) antigen. These lymphomas are usually of T-cell origin, often present with extranodal disease, and are found especially in the skin.[50] The translocation of chromosomes 2 and 5 creates a unique fusion protein with a nucleophosmin-anaplastic lymphoma kinase (ALK) (Haggod et al 15). In a prospective randomized trial of 452 patients with CD30-positive T-cell lymphoma, 70% of whom had ALCL (22% ALK-positive and 48% ALK-negative patients), the previously used standard regimen, CHOP, was compared with brentuximab vedotin (an anti-CD30 monoclonal antibody conjugated to a cytotoxic agent) combined with cyclophosphamide, doxorubicin, and prednisone. With a

median follow-up of 35 months, the brentuximab combination (3-year OS, 77%) showed an OS advantage over CHOP (3-year OS, 68%)(Horwitz et al '19). For patients with relapsed disease, anecdotal responses have been reported for brentuximab vedotin (anti-tubulin agent attached to a CD30-specific monoclonal antibody)(Pro et al '17), romidepsin (Coiffier et al '12), and pralatrexate (O'Connor et al '09). In a phase II study 66% of 58 patients attained a CR with brentuximab vedotin. At a median follow-up of 58 months, the 5-year PFS was 57% (95% CI, 41%–74%), and the 5-year OS was 79% with 42% of these patients undergoing hematopoietic SCT (Pro et al '17). For patients with relapsed disease, autologous or allogeneic SCT showed a 50% 3-year PFS for 39 patients in a retrospective review (Smith et al '13). ALCL in children is usually characterized by systemic and cutaneous disease and has high response rates and good OS with doxorubicin-based combination chemotherapy (Seidemann et al '01). Patients with breast implant–associated ALCL may do well without chemotherapy after capsulectomy and implant removal if the disease is confined to the fibrous capsule, and no associated mass or lymphadenopathy is present (Jaffe et al '20).

**Extranodal natural killer (NK)-/T-cell lymphoma (nasal type)** is an aggressive lymphoma marked by extensive necrosis and angioinvasion, most often presenting in extranodal sites, in particular the nasal or paranasal sinus region (Tse et al '13). In most cases, Epstein-Barr virus (EBV) genomes are detectable in the tumor cells and immunophenotyping shows CD56 positivity. Cases with blood and marrow involvement are considered NK-cell leukemia. In a retrospective review of 303 previously untreated patients from an international consortium who received nonanthracycline chemotherapy, the OS rates were identical for early-stage patients (72%–74% at 5 years) who received either concurrent chemotherapy and radiation therapy or chemotherapy followed by radiation therapy (Kwong et al '18). Higher doses of radiation therapy administered at more than 50 Gy are associated with improved outcomes according to anecdotal reports (Vargo et al '17). L-asparaginase-containing regimens have shown anecdotal response rates greater than 50% for relapsing, refractory, or newly diagnosed patients (Li et al '18). Lymphomatoid granulomatosis is an EBV-positive large B-cell lymphoma with a predominant T-cell background (Myers et al '95). The histology shows association with angioinvasion and vasculitis, usually manifesting as pulmonary lesions or paranasal sinus involvement. Patients are managed like others with diffuse large cell lymphoma and require doxorubicin-based combination chemotherapy.

**Angioimmunoblastic T-cell lymphoma (AITL or ATCL)** was formerly called angioimmunoblastic lymphadenopathy with dysproteinemia. Characterized by clonal T-cell receptor gene rearrangement, this entity is managed like diffuse large cell lymphoma (Lunning et al '17). Patients present with profound lymphadenopathy, fever, night sweats, weight loss, skin rash, a positive Coombs test, and polyclonal hypergammaglobulinemia (Rizvi et al '06). Doxorubicin-based combination chemotherapy, such as the CHOP regimen, is recommended as it is for other aggressive lymphomas (Lunning et al '17). For CD30-positive cases, brentuximab combined with cyclophosphamide, doxorubicin, and prednisone is the standard of care (Horwitz et al '19). The International Peripheral T-Cell Lymphoma Project involving 22 international centers identified 243 patients with AITL or ATCL; the 5-year OS and failure-free survival rates were 33% and 18%, respectively (Frederico et al '13).

Patients with peripheral **T-cell lymphoma** have diffuse large cell or diffuse mixed lymphoma that expresses a cell surface phenotype of a postthymic (or peripheral) T-cell expressing CD4 or CD8 but not both together (Rüdiger et al '02). Most investigators report worse response and survival rates for patients with peripheral T-cell lymphomas than for patients with comparably

staged B-cell aggressive lymphomas. Most patients present with multiple adverse prognostic factors (i.e., older age, stage IV, multiple extranodal sites, and elevated LDH), and these patients have a low (<20%) failure-free survival and OS at 5 years (Weisenberger et al '11). As with other lymphomas (e.g., DLBCL or follicular lymphoma), event-free survival at 24 months predicts a 5-year OS of 78% (Maurer et al '11). Therapy involves doxorubicin-based combination chemotherapy (such as CHOP or CHOPE [CHOP plus etoposide]), which is also used for DLBCL (Carson et al '17). For CD30-positive cases, brentuximab combined with cyclophosphamide, doxorubicin, and prednisone is the standard of care (Horwitz et al '19). For relapsing patients, pralatrexate has shown a 30% response rate and a median 10-month duration of response for 109 evaluable patients in a prospective trial.[59,115] Similar response rates were seen for romidepsin for 130 evaluable patients in a prospective trial (Coiffier et al '12).

**Enteropathy-type intestinal T-cell lymphoma** involves the small bowel of patients with gluten-sensitive enteropathy (celiac sprue). Because a gluten-free diet prevents the development of lymphoma, patients diagnosed with celiac sprue in childhood rarely develop lymphoma. The diagnosis of celiac disease is usually made by finding villous atrophy in the resected intestine. Surgery is often required for diagnosis and to avoid perforation during therapy. Therapy is with doxorubicin-based combination chemotherapy, but relapse rates appear higher than for comparably staged diffuse large cell lymphoma (Di Sabatino et al '12). Intravascular lymphomatosis is characterized by large cell lymphoma confined to the intravascular lumen. The brain, kidneys, lungs, and skin are the organs most likely affected by intravascular lymphomatosis. With the use of aggressive combination chemotherapy, the prognosis is similar to more conventional presentations (Shimada et al '08).

**Burkitt lymphoma/diffuse small noncleaved-cell lymphoma** typically involves younger patients and represents the most common type of pediatric NHL (Blum et al '04). These types of aggressive extranodal B-cell lymphomas are characterized by translocation and deregulation of the C-Myc gene on chromosome 8 (Onciu et al '06). A subgroup of patients with dual translocation of C-Myc and BCL2 appear to have an extremely poor outcome despite aggressive therapy (5-month OS) (Macpherson et al '99). Endemic cases, usually from Africa, involve the facial bones or jaws of children, mostly containing EBV genomes. Sporadic cases usually involve the gastrointestinal system, ovaries, or kidneys. Patients present with rapidly growing masses and a very high LDH but are potentially curable with intensive doxorubicin-based combination chemotherapy. Treatment of Burkitt lymphoma/diffuse small noncleaved-cell lymphoma involves aggressive multidrug regimens in combination with rituximab, similar to those used for the advanced-stage aggressive lymphomas (diffuse large cell) (Ribrag et al '16). Aggressive combination chemotherapy, which is patterned after that used in childhood Burkitt lymphoma, has been very successful for adult patients with more than 60% of advanced-stage patients free of disease at 5 years (Mead et al '02). Adverse prognostic factors include bulky abdominal disease and high serum LDH. Patients with Burkitt lymphoma have a 20% to 30% lifetime risk of CNS involvement. Prophylaxis with intrathecal chemotherapy is required as part of induction therapy (Rizzier et al '04). Patients with HIV-associated Burkitt lymphoma also benefit from less-toxic modification of the aggressive multidrug regimens in combination with rituximab (Noy et al '15).

Lymphoblastic lymphoma (precursor T-cell) is a very aggressive form of NHL. It often, but not exclusively, occurs in young patients (Morel et al '92). It is commonly associated with large mediastinal masses and has a high predilection for disseminating to bone marrow and the CNS. Treatment is usually patterned after that for acute lymphoblastic leukemia. Intensive combination

chemotherapy with or without bone marrow transplantation is the standard treatment for this aggressive histologic type of NHL (Thomas et al '04). Radiation therapy is sometimes given to areas of bulky tumor masses.

**Adult T-cell leukemia/lymphoma (ATL)** is caused by infection with the retrovirus human T-lymphotrophic virus 1 and is frequently associated with lymphadenopathy, hypercalcemia, circulating leukemic cells, bone and skin involvement, hepatosplenomegaly, a rapidly progressive course, and poor response to combination chemotherapy (Foss et al '03). ATL has been divided into four clinical subtypes: Acute (aggressive course with leukemia, with or without extranodal or nodal involvement). Lymphoma (aggressive course with lymphadenopathy and no leukemia). Chronic (indolent course with leukemia and lymphadenopathy). Smoldering (indolent course with only leukemia) (Takasaki et al '10). The acute and lymphoma types of ATL have done poorly with strategies of combination chemotherapy and allogeneic SCT with a median OS under 1 year. Using combination chemotherapy, less than 10% of 807 patients were alive after 4 years (Katsuya et al '12). Anecdotal durable remissions have been reported after allogeneic SCT and even after subsequent donor lymphocyte infusion for relapses after transplant (Itonaga et al '13). Among 815 patients who underwent allogeneic SCT in two retrospective reviews, the 3-year OS rates were 36% and 26% (Katsuya et al '15). The combination of zidovudine and interferon-alpha has activity against ATL, even for patients who failed previous cytotoxic therapy. Durable remissions are seen in the majority of presenting patients with this combination but are not seen in patients with the lymphoma subtype of ATL (Bazarbachi et al '11). In a multicenter phase II study of 26 relapsed patients, 42% responded to lenalidomide (including four CR) (Ishida et al '16). Symptomatic local progression of all subtypes responds well to palliative radiation therapy (Simone et al '12). In the relapsed setting, an ORR above 50% is seen using mogamulizumab, a humanized monoclonal antibody against the C-C chemokine receptor 4 (CCR4) (Ureshino et al '19). For CD30-positive cases, brentuximab combined with cyclophosphamide, doxorubicin, and prednisone is the standard of care (Horwitz et al '19).

**Mantle cell lymphoma** is found in lymph nodes, the spleen, bone marrow, blood, and sometimes the gastrointestinal system (lymphomatous polyposis). Mantle cell lymphoma is characterized by CD5-positive follicular mantle B cells, a translocation of chromosomes 11 and 14, and an overexpression of the cyclin D1 protein (Cohen et al '17). Mantle cell lymphoma may be divided into two clinical subtypes: a classical version with lymphadenopathy with high SOX-11 expression that manifests with an aggressive clinical course and a worse prognosis versus a leukemic, non-nodal version with low SOX-11 expression and a more indolent course and a better prognosis (Clot et al '18). Like the low-grade lymphomas, mantle cell lymphoma appears incurable with anthracycline-based chemotherapy and occurs in older patients with generally asymptomatic advanced-stage disease. The median survival, however, is significantly shorter (5–7 years) than that of other lymphomas, and this histology is now considered to be an aggressive lymphoma (Herrmann et al '09). Several induction chemotherapy regimens may be employed for symptomatic progressing disease. These regimens range in intensity from rituximab alone to rituximab plus bendamustine, to R-CHOP, to high-dose intensive regimens such as R-hyper-C-VAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine). Some physicians use autologous SCT or allogeneic SCT consolidation next, while others prefer rituximab maintenance, reserving high-dose consolidation for a later time (Gerson et al '19). Ibrutinib, lenalidomide, and bortezomib have shown activity in relapsing patients, and these drugs are being incorporated upfront (Ruan et al '18)(Wang et al '15). With a median follow-up of 7.6 years, the median OS was significantly shorter after R-FC than after R-CHOP (3.9 years versus 6.4 years). In the same

trial, with a median follow-up of 8 years for the 316 responding patients, rituximab maintenance resulted in improved OS over interferon maintenance (median OS, 9.8 years vs. 7.1 years). Patients responsive to R-CHOP benefitted most from rituximab in OS (median 9.8 years vs. 6.4 years) (Kluin-Nelemans et al '20).

A prospective, randomized trial of 487 patients compared VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone) with R-CHOP. With a median follow-up of 82 months, the median OS was longer for VR-CAP (90.7 months) compared with R-CHOP (55.7 months) (Robak et al '18). Lenalidomide with or without rituximab also shows response rates of around 50% in relapsed patients, with even higher response rates for previously untreated patients (Trněný et al '16). The B-cell receptor-inhibitor, ibrutinib, showed a response rate of 86% (21% CR rate) in previously treated patients with a median PFS time of 14 months (Wang et al '13). With a median follow-up of 15 months, the median PFS favored ibrutinib (14.6 months vs. 6.2 months). [206] Ibrutinib has been combined with another active agent, venetoclax, in a phase II study of 23 patients with relapsed or refractory mantle cell lymphoma. An unprecedented 71% of patients had CR and 78% of responding patients maintained response at 15 months (Dreyling et al '16). Acalabrutinib (another B-cell receptor inhibitor via the Bruton tyrosine kinase pathway) was studied in 124 patients with relapsed/refractory mantle cell lymphoma. In a phase II study, there was an 81% objective response rate, 40% CR rate, and the 1-year PFS rate was 67% (Wang et al '18). Rituximab, lenalidomide, ibrutinib, acalabrutinib, and venetoclax represent directed biologic agents that may lead the way to chemotherapy-free strategies for patients with mantle cell lymphoma (Martin et al '17). Patients with relapsed or refractory mantle cell lymphoma whose disease did not respond to ibrutinib or acalabrutinib were enrolled in a phase II trial using KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy. With a median follow-up of 12 months, 60 patients had an overall response rate of 93% and a 67% CR. Grade 3 or higher cytokine release syndrome occurred in 15% of patients, and neurologic events occurred in 31% of patients (Wang et al '20).

Patients who undergo transplantation of the heart, lung, liver, kidney, or pancreas usually require lifelong immunosuppression. This may result in **post-transplantation lymphoproliferative disorder** (PTLD) in 1% to 3% of recipients, which appears as an aggressive lymphoma (Morrison et al '94). In some cases, withdrawal of immunosuppression results in eradication of the lymphoma. When this is unsuccessful or not feasible, a course of rituximab may be considered, because it has shown durable remissions in approximately 60% of patients and a favorable toxicity profile (Evens et al '10). If these measures fail, doxorubicin-based combination chemotherapy (R-CHOP) is recommended, although some patients can avoid cytotoxic therapy (Trappe et al '17). Instances of EBV-negative PTLT occur even later (median, 5 years posttransplant) and have a worse prognosis; R-CHOP chemotherapy can be applied directly in this circumstance (Leblond et al '98). A sustained clinical response after failure from chemotherapy was attained using an immunotoxin (anti-CD22 B-cell surface antigen antibody linked with ricin, a plant toxin) (Senderowicz et al '97).

**True histiocytic lymphomas** are very rare tumors that show histiocytic differentiation and express histiocytic markers in the absence of B-cell or T-cell lineage-specific immunologic markers (Soslow et al '96). Care must be taken with immunophenotypic tests to exclude ALCL or hemophagocytic syndromes caused by viral infections, especially EBV. Therapy is modeled after the treatment of comparably staged diffuse large cell lymphomas, but the optimal approach remains to be defined. Primary effusion lymphoma presents exclusively or mainly in the pleural, pericardial, or abdominal cavities in the absence of an identifiable tumor mass. Patients are

usually HIV seropositive, and the tumor usually contains Kaposi sarcoma-associated herpes virus/human herpes virus 8 (Shimada et al '18). The prognosis of primary effusion lymphoma is extremely poor. Plasmablastic lymphoma is most often seen in patients with HIV infection and is characterized by CD20-negative large B cells with plasmacytic features. This type of lymphoma has a very aggressive clinical course, including poor responses and short remissions with standard chemotherapy. Anecdotal reports suggest using aggressive chemotherapy for Burkitt or lymphoblastic lymphoma, followed by SCT consolidation in responding patients, when feasible (Castillo et al '15).

**Primary central nervous system (CNS) lymphoma** is defined as lymphoma limited to the cranial-spinal axis without systemic disease. An increasing incidence of this disease has been seen among patients with AIDS and among other immunocompromised persons. Computed tomography (CT) scans may show ring enhancement in 50% of AIDS patients while patients without AIDS almost always show only homogeneous enhancement (Fine et al '93). Median overall survival in published trials generally ranges from 2 to 5 years (Fox et al '19). Older age (>65 years) and HIV positivity are the most clinically relevant poor prognostic factors, but the prognosis for HIV-associated primary CNS lymphoma has improved with the use of combination antiretroviral therapy (Gupta et al '17). When tumor progression occurs, it is usually confined to the CNS and/or the eye. Occult systemic disease can be excluded by positron emission tomography-CT scans of the chest, abdomen, and pelvis, and sometimes with bone marrow biopsy (Abrey et al '05). In one prospective case series of 282 patients, 17% were found to have meningeal dissemination by cytomorphology, polymerase chain reaction of rearranged immunoglobulin heavy-chain genes, or meningeal enhancement on magnetic resonance imaging (Fischer et al '08).

Because of the diffuse nature of **central nervous system (CNS) lymphomas**, aggressive surgical decompression with partial or gross total removal of the tumor is of no benefit to the patient. Median survival with surgery alone is in the range of only 1 to 5 months. Until the mid-1990s, radiation therapy had been the standard treatment, with doses of up to 45 Gy using standard fractionation. A prospective trial by the Radiation Therapy Oncology Group (RTOG-8315) used 40 Gy whole-brain radiation therapy (WBRT) and a 20 Gy boost to the tumor and found that the results were no better than had been previously reported, with a median survival of 1 year and 28% of the patients surviving 2 years (Nelson et al '92). Disease recurs in the brain in 92% of patients despite high doses of radiation. Two multicenter, prospective trials (including RTOG-8806) used preirradiation cyclophosphamide, doxorubicin, vincristine, and dexamethasone followed by WBRT (Schultz et al '96). Median survival times were no better than for radiation therapy alone. The International Extranodal Lymphoma Study Group investigated three different induction combinations in 227 patients with newly-diagnosed HIV-negative primary CNS lymphoma who were randomly assigned to one of three groups: High-dose methotrexate + high-dose cytarabine. High-dose methotrexate + high-dose cytarabine + rituximab. High-dose methotrexate + high-dose cytarabine + rituximab + thiotepa (the MATRix regimen). With a median follow-up of 30 months, the four-drug combination had a complete remission rate of 49% compared with 23% for the two-drug combination and with 30% for the three-drug combination (Ferreri et al '16). The so-called DA-TEDDI-R regimen incorporates temozolomide, etoposide, liposomal doxorubicin, dexamethasone, ibrutinib, and rituximab. Among 18 patients (five previously untreated), the complete remission rate was 86%, but high rates (39%) of invasive aspergillosis were reported (Lionakis et al '17). Aspergillosis can be treated with corticosteroids or sporanox (itraconazole), that is indicated for prophylaxis in leukemia to prevent osteonecrosis from Cushing's disease.

## 14. Sarcomas

Approximately 7,000 new **sarcomas** are diagnosed in the United States each year (an incidence of 2 in 100,000), constituting 1% and 15% of adult and pediatric malignancies, respectively. While the incidence is roughly the same as Hodgkin's disease, twice as many people die of sarcomas. Risk factors include radiation, chemical exposure and genetic abnormalities. Prior radiation exposure can be documented for less than 5% of sarcomas, predominantly osteosarcoma, fibrosarcoma, and mixed Mullerian sarcomas. The dose of radiation may be only several Gray (Gy) in radium watch-dial painters. The latent period is 4 to 24 years. Herbicides, wood preservatives, vinyl chloride, arsenic and thorium dioxide have been associated with sarcomas. Asbestos clearly causes mesothelioma. Patients with hereditary retinoblastomas incur a 7% risk of osteosarcoma not only in radiation ports but also in distant long bones. Cytomegalovirus (CMV) and human immunodeficiency virus (HIV) have been associated with Kaposi's sarcoma in African patients and in patients with acquired immunodeficiency syndrome (AIDS). Sarcomas are classified into those arising in bone and those in soft-tissue. Soft-tissue sarcomas are further subdivided into somatic (extremities and retroperitoneum) and visceral sarcomas (gastrointestinal and gynecologic). A miscellaneous group includes Kaposi's sarcoma and mesothelioma (Elias & Antman '90: 292).

**Osteosarcoma** (OS) is a spindle cell tumor that produces malignant osteoid. About 900 new cases occur per year in the United States with a male to female ratio of 1.5-2:1. The age distribution peaks in the second and third decades and also in the sixth decade. The tumor classically arises in the growth plates of long bones (distal femur, proximal tibia, and humerus) during the adolescent growth spurt (between ages 10 and 25) or in sites of prior radiotherapy, preexisting bone lesions, or Paget's disease in older adults. Axial lesions occur in less than 10% of pediatric patients but in 30% to 50% of adults. Although parosteal sarcoma, a low-grade variant, grows slowly, the tumor growth rate of classical OS is rapid. Relapses occur early, usually in the first 2 years after primary therapy. Metastases most frequently appear in the lung and in bone. Surgical treatment of OS may include either amputation or limb-sparing surgery. Limb-sparing surgery currently achieves local control rates (90% to 97%) and survival similar to amputation in selected patients. Functional results are excellent in 60% to 75% of limb-sparing procedures. Complications may necessitate later amputation. Of 62 patients with no tumor recurrent, 14 required subsequent amputation for infection, dislocation or fractures. Patients with significant soft-tissue or neurovascular involvement generally require amputation. 5 year survival rates of OS patients treated with surgery alone improved from 13% between 1963 and 1968 to 42% for 1972 and 1974. Centers using preoperative intra-arterial or intravenous chemotherapy have reported a 50% to 80% disease free survival at 2 to 5 years. A poorer survival was observed when preoperative intra-arterial chemotherapy only was given compared with preoperative intra-arterial chemotherapy and systemic postoperative chemotherapy. Tumor necrosis of more than 90% in tumors resected after preoperative chemotherapy is associated with better survival and local control. For patients with less than 90% tumor necrosis, the use of other effective agents postoperatively may increase the disease free survival to 40%. Between 20% and 40% of patients with OS who undergo resection of pulmonary metastases are cured. If there has been an interval of 6 months or longer since the last adjuvant treatment re-administration of the same drugs might achieve palliation. The most active single agent in OS include doxorubicin, 60 mg to 90 mg/m<sup>2</sup> (21% response rate); methotrexate 8g to 12 g/m<sup>2</sup> with leukovorin rescue (30% to 40%); cisplatin, 100 mg/m<sup>2</sup> (25%) and ifosfamide, 5 g to 10 g/m<sup>2</sup>.

Cyclophosphamide, melphalan, mitomycin C and dacarbazine (DTIC) all have response rates of about 15% (Elias & Antman '90: 292, 293).

**Ewing's sarcoma** (ES) predominantly affects adolescents (5 to 30 years) and is easily distinguished from OS with patients complaining of fever, weight loss, malaise and poorly localized bone pain in the area of the primary lesion. While a 60% disease free survival may be observed in patients with no apparent metastases, less than 30% of those with metastases survive, but mortality is more than 90% after surgical resection alone. Initial treatment consists of vincristine, actinomycin D, cyclophosphamide and doxorubicin (VACA). Doxorubicin is the most effective single agent. Although higher and lower dose schedules exist, doses used in the Intergroup Ewing Sarcoma Study were vincristine, 1.5 mg/m<sup>2</sup>/week, weeks 1 to 6 and 8 to 13; actinomycin D, 0.15 mg/kg daily, days 1 to 5 every 12 weeks; cyclophosphamide, 500 mg/m<sup>2</sup>/week; and doxorubicin, 30 mg/m<sup>2</sup> daily, says 1 to 3 every 3 weeks. Radiotherapy of about 6000 cGy to the primary (begun during the fourth or fifth cycle of chemotherapy controls local disease in most patients. Chondrosarcoma, fibrosarcoma, malignant giant cell tumors of bone, and malignant fibrous histiocytoma (MFH) are less responsive to chemotherapy and are generally treated as soft-tissue sarcomas (Elias & Antman '90: 295).

### Staging System for Soft-Tissue Sarcomas

T	Primary Tumor
TX	Minimum requirements to assess the primary tumor cannot be met.
T0	No demonstrable tumor.
T1	Tumor less than 5 cm in diameter.
T2	Tumor 5 cm or more in diameter.
T3	Clear radiographic evidence of destruction of cortical bone, with invasion; histopathologic confirmation of invasion of major artery or nerve.
G	Tumor Grade
G1	Well differentiated.
G2	Moderately well differentiated.
G3	Poorly differentiated.
N	Nodal Involvement
NX	Minimum requirements to assess the regional nodes cannot be met.
N0	No histologically verified metastases to lymph nodes.
N1	Histologically verified regional lymph node metastasis.
M	Distant Metastasis
MX	Minimum requirements to assess the presence of distant metastasis cannot be met.
M0	No (known) distant metastasis.
M1	Distant metastasis present.
<b>Stage</b>	<b>Grouping</b>
Stage I	
IA	G1, T1, N0, M0
IB	G1, T2, N0, M0
Stage II	
IIA	G2, T1, N0, M0
IIB	G2, T2, N0, M0
Stage III	
IIIA	G3, T1, N0, M0
	G3, T2, N0, M0

IIIB	G1-3, T1-2, N2, M0
IIIC	
Stage IV	
IVA	G1-3, T3, N0-1, M0 G1-3, T1-3, N0-1, M1
IVB	

Source: Elias & Antman '90: Table 34-2, Pg. 296

**Soft-tissue sarcomas** cause a mass, swelling, or pain in the trunk or extremities. Retroperitoneal tumors generally present late with weight-loss or deep-seated pain. Gynecologic and gastrointestinal sarcomas most frequently present with bleeding. Definitive surgical resection requires a wide surgical excision with 2 cm to 4 cm pathologically documented margins of normal tissue or pre or postoperative radiotherapy and a conservative resection with pathologically documented tumor-free margins. Wide re-excision after local failure should be followed by 6600 cGy radiotherapy. Local control rate (90+%) and overall disease-free survival (60%) in limb-sparing surgery are similar to that after amputation or radical resection. The local failure rate where radiotherapy was not used was 30%. An initial dose of 5000 cGy in 200 cGy fractions should be delivered to the entire compartment and surgical field with at least a 5 cm margin. A boost to a shrinking field to the tumor bed with an additional 1000 cGy and 600 cGy more to the scar is also indicated, with sparing of one third of the circumference of the extremity, at least 2 cm to 4 cm on the forearm, or thigh, to prevent lymphedema. Despite advances in surgery and radiation therapy 40% to 60% of patients with high-grade tumors die of metastatic disease despite primary control. Studies have not proven improved survival advantage with either single agent doxorubicin or combination therapy adjuvant to surgery and chemotherapy. Major toxicities included a 14% incidence of doxorubicin-induced congestive heart failure, as well as an 18% withdrawal rate due to gastrointestinal and hematologic toxicity. A number of studies have reported a 10% to 40% disease free survival after resection of limited numbers (<10-15) pulmonary nodules provided the patient is a good surgical candidate, the primary site is controlled and no extrapulmonary metastases are present. Single-agent doxorubicin has a response rate of 15% to 35%. A dose-response relationship has been observed with higher response rates at doses greater than 50 mg/m<sup>2</sup> every 3 weeks. Doxorubicin may be less cardiotoxic when administered by continuous infusion over 4 days. DTIC has a single agent response rate of 17%. An improved response rate of the combination of DTIC and doxorubicin has been noted. However nausea and vomiting is increased. Phase II trials of ifosfamide in previously treated patients yield response rates of 20% to 40%. A phase I and II study of combination of doxorubicin, ifosfamide and DTIC with mesna uroprotection in 56 patients yielded a response rate of 48% with 13% complete response (Elias & Antman '90: 295-299).

**Rhabdomyosarcoma (RMS)** is a malignancy of striated muscle that has three histologic variants; embryonal in children 2 to 6 years of age, alveolar in extremity lesions in adolescents and pleomorphic in adults over 40 years of age, although these may be classified as malignant fibrous histiocytoma (MFH). Lymph node metastases occur in about 20% of RMS patients, but rarely with orbital lesions. While most patients have apparently localized disease at diagnosis, without intensive chemotherapy, 80% relapse in distant sites, usually, lung, lymph nodes, and bone marrow. Clinical evaluation should include an x-ray film of the primary, chest CT, bone scan and bilateral bone marrow aspirates and biopsies, and for head and neck primaries, head CT

and spinal fluid examinations. The most important prognostic factor is the presence of metastases, which reduce the 5 year survival rate 25% to 30% despite intensive multimodality therapy. Variations of the vincristine, actinomycin D, cyclophosphamide, and doxorubicin (VACA) chemotherapy regimen are used. **Gastrointestinal sarcomas** are generally leiomyosarcomas that present with pain and bleeding. Obstruction, insusception, perforation or fistula formation 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 years 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.

**Gyneocolic sarcomas** represent 1% of gynecologic malignancies and 1% to 6% of uterine tumors. Uterine smooth muscle tumors constitute a continuum of lesions from benign (fibroids) to malignant high-grade leiomyosarcomas. Leiomyosarcomas have more than 10 mitoses (m) per 10 hpf, (or 5-10 m/ 10 hpf with anaplasia, pleomorphism or epithelial histology. Well differentiated lesions with 2 m to 4 m/10 hpf are "of uncertain malignant potential". "Metastasizing leiomyoma" and "intravenous leiomyomatosis", benign lesions often associated with pregnancy, may spontaneously regress or may respond to hormonal therapy. The differential diagnosis of **endometrial stromal tumor** includes lymphoma or small cell carcinoma of the cervix. Single or small clumps of cells surrounded by reticulum fibers on reticulum stain indicate a stromal sarcoma. Presenting symptoms of uterine sarcomas include heavy, irregular vaginal bleeding and an abdominal mass or pain. An enlarged uterus or gross tumor protruding from the cervix may be noted. While dilatation and curettage will be diagnostic in endometrial stromal sarcomas, it may be negative in leiomyosarcoma and may be misleading in mixed Müllerian tumors in that only one type of tissue may be obtained. Perioperative staging should include CT scans of the chest, abdomen and pelvis. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the treatment of choice for localized disease. Pre- or post operative radiotherapy decreases the local recurrence rate but does not affect survival and frequently precludes delivery of adequate doses of chemotherapy (Elias & Antman '90: 301, 302).

Long considered an obscure tumor **Kaposi's sarcoma** frequently occurs in patients with acquired immunodeficiency syndrome (AIDS). Four forms of the disease are recognized. (1) the classic, or European form, first described by Kaposi in 1862, was endemic to older men of Eastern European (especially Ashkenazic Jews). This form consists of red to purple skin plaques or nodules primarily in the lower extremities, slowly increasing in size and number and spreading to more proximal sites. Rarely do they involve visceral organs or cause the death of the patients. Classic KS most commonly runs a relatively benign, indolent course for 10 to 15 years or more, with slow enlargement of the original tumors and the gradual development of additional lesions. As many as 33% of the patients with classic KS develop a second primary malignancy, which is most often non-Hodgkin lymphoma (Safai et al '80). **African Kaposi's** is clinically similar to the European form, but occurs in children and younger men in equatorial Africa. It has a very high prevalence in these regions, representing up to 10% of all tumors. In young children, the disease is often associated with generalized involvement of lymph nodes, resembling lymphoma. (3) transplant associated Kaposi's sarcoma occurs in organ transplant recipients who receive high doses of immunosuppressive therapy. Lesions are either localized to the skin or widely metastatic but often regress when immunosuppressive therapy is discontinued. (4) AIDS-associated Kaposi's sarcoma is found in approximately one-third of AIDS patients, and it is more common in male homosexuals than in other risk groups. The tumors respond to cytotoxic chemotherapy and to therapy with alpha-interferon. Most patients eventually succumb

to the infectious complications of AIDS rather than directly from the consequences of Kaposi's sarcoma. About one-third of these patients with Kaposi's sarcoma, however, subsequently develop a second malignancy, usually lymphoma, leukemia or myeloma (Schoen '94: 511). Human herpes virus type 8, also known as Kaposi sarcoma herpes virus, was identified in KS tissue biopsies from virtually all patients with classic, transplant-related, and AIDS-associated KS but was absent from noninvolved tissue (Uldrick et al '11).

The AIDS Clinical Trials Group (ACTG) Oncology Committee has published criteria for the evaluation of epidemic KS. The staging system incorporates measures of extent of disease, severity of immunodeficiency, and presence of systemic symptoms. The ACTG criteria categorizes the extent of the tumor as localized or disseminated, the CD4 cell number as high or low, and a systemic illness as absent or present (Krown et al '89). Multivariate analysis showed that immune system impairment was the most important single predictor of survival. In patients with relatively high CD4 counts, tumor stage was predictive. A CD4 count of 150 cells/mm<sup>3</sup> may be a better discriminator than the published cutoff of 200 cells/mm<sup>3</sup> (Krown et al '97). For solitary lesions or lesions of limited extent, modest doses of radiation applied to the lesions with a limited margin provide excellent control of disease in the treated area. Low-voltage (100 kv) photon radiation: 8 Gy to 10 Gy given as a single dose or 15 Gy to 20 Gy given over 1 week because solitary lesions control nearly 100% of local disease, but recurrence in adjacent areas is common (Tsao et al '16). Widespread skin disease is treated with 4 Gy given once weekly for 6 to 8 consecutive weeks, and subtotal- or total-skin radiation therapy given for extensive disease (Nisce et al '81).

Interferon-alfa was the first drug specifically approved for the treatment of Kaposi's. It is of particular interest because of its antiproliferative, antiviral (anti-HIV), antiangiogenic, and immune-modulating properties. The interferon alphas show a 40% objective response rate in patients with epidemic KS (Real et al '86). Two liposomal agents are currently approved for the treatment of KS: liposome-encapsulated daunorubicin (DaunoXome) and liposome-encapsulated doxorubicin (Doxil). Both agents are highly active against KS and have less toxicity than the nonliposomal anthracyclines. Myelosuppression, however, remains the dose-limiting toxicity. In a multicenter trial of 55 patients who were treated over a decade, a 71% overall response rate was seen using pegylated liposomal doxorubicin (Di Lorenzo et al '08). Doxorubicin (also known by its trade name Adriamycin) is a component of the most widely used combination regimen for HIV-associated KS. In one trial, however, weekly treatment with doxorubicin (25 mg/m<sup>2</sup>) in patients with AIDS-related KS achieved a partial response rate of only 10%. The primary toxicity of weekly doxorubicin is myelosuppression, even with the relatively low doses prescribed for KS treatment. The introduction of highly active antiretroviral therapy (HAART) has delayed or prevented the emergence of drug-resistant HIV strains, profoundly decreased viral load, led to increased survival, and lessened the risk of opportunistic infections (Lodi et al '10). The use of HAART has been associated with a sustained and substantial decline in KS incidence in multiple large cohorts (Grabar et al '06). KS can still appear during HAART with complete suppression of HIV; most cases in the United States occur in patients with high CD4 counts and ongoing HAART (Yanik et al '16). Most good-risk patients, defined by the AIDS Clinical Trials Group as T0, show tumor regression with HAART alone. Poor-risk patients, defined as T1, usually require a combination of HAART and chemotherapy with discontinuation of the chemotherapy after disappearance of the skin lesion. The combination of HAART and liposomal doxorubicin resulted in a 5-year overall survival (OS) rate of 85% in 140 patients with T1 disease (Bower et al '14). Bevacizumab, the humanized, antivascular, endothelial growth-factor monoclonal antibody, had a response rate in 5 of 16 patients who did not improve after the

institution of HAART and chemotherapy (Uldrick et al '12). Interleukin-12 had a response rate of 71% (95% confidence interval, 48%–89%) among 24 evaluable patients in a phase I and phase II trial (Little et al '06).

Response rates showing a greater than 50% decrease in lesions have also been reported in small, uncontrolled series for etoposide, taxanes, gemcitabine, and interferon alfa (Régnier-Rosencher et al '13). **Etoposide** (VP-16) has been evaluated as both an oral and an intravenous treatment for KS. As an oral agent, VP-16 has been evaluated primarily in patients who have undergone prior treatment with multiple cytotoxic agents. When VP-16 is given intravenously (150 mg/m<sup>2</sup> on days 1 to 3 every 4 weeks), high response rates (78%) have been reported in patients without prior treatment and with good prognosis (no history of opportunistic infection and no constitutional symptoms). The primary toxicity of this agent is myelosuppression, which may necessitate the use of colony-stimulating factors, particularly in patients with advanced disease receiving other myelosuppressive agents. Additionally, alopecia frequently occurs in association with etoposide therapy, and is a consideration for patients who are receiving treatment of their KS for primarily cosmetic purposes. In patients with KS of poor prognosis, **bleomycin** given intramuscularly (5 mg/day for 3 days) or as a 4-day continuous infusion (6 mg/m<sup>2</sup>/day) produced a 48% partial response rate. Results of a small, single-institution study in which bleomycin was given as a 72-hour infusion (20 mg/m<sup>2</sup>/day) to 17 patients indicated a partial response rate of 65%. Bleomycin toxicity appears to be acceptable, with neutropenia an infrequent complication. Alternating vincristine and vinblastine weekly achieves a response rate of 33%. Toxicity includes vincristine-induced neurotoxicity (which limits its usefulness as a single agent) and vinblastine-induced myelosuppression. Vinca alkaloids are particularly helpful in gastrointestinal and lymphatic KS. Paclitaxel had a partial response in 13 of 20 patients (65%), with 5 of 6 patients with known pulmonary KS responding, as well as 6 previously treated patients with nonpulmonary KS achieving a partial response. In a second trial, of the 30 evaluable patients, 16 (53%) achieved a partial response. The time to response was short (median of three cycles of treatment). Dramatic improvement in symptomatic lymphedema was noted in 25 of 26 patients. Therapy was well tolerated. **Vinorelbine**, a semisynthetic vinca alkaloid with a favorable therapeutic index compared to other vinca alkaloids, was evaluated in previously treated patients with progressive AIDS-related KS. Thirty-five evaluable patients were treated with vinorelbine 30 mg/m<sup>2</sup> every 2 weeks. Clinical complete and partial remissions were achieved in 43% of patients, with a median progression-free survival of 151 days. The agent was well tolerated, with neutropenia the most frequent dose-limiting toxicity.

## 15. Endocrine cancer

In 2020, there will be an estimated 52,890 new cases of **thyroid cancer** diagnosed in the US and 2,180 people will die from the disease. The incidence rate is 3 times higher in women than in men. In 1990 there were only 10,000 cases and 1,000 deaths of thyroid cancer. Until recently, thyroid cancer was the most rapidly increasing cancer in the US, largely due to increased detection (probably including some over-diagnosis) because of increased use of imaging and more sensitive diagnostic procedures. However, the increase of about 7% per year during the 2000s has slowed to 2% per year in men and rates have stabilized in women during 2012 to 2016, likely due in part to the adoption of more conservative diagnostic criteria by clinicians. The death rate for thyroid cancer increased slightly during 2008 to 2017 (0.6% per year) but appears to have stabilized in recent years. Thyroid cancer affects women more often than men and usually occurs in people aged 25 to 65 years. The incidence of this malignancy has been increasing over the last decade. Thyroid cancer commonly presents as a so-called *cold nodule*. It

is detected as a palpable thyroid gland during a physical exam and evaluated with iodine I 131 scans; scintigraphy shows that the isotope is not taken up in an area of the gland. The overall incidence of cancer in a cold nodule is 12% to 15%, but it is higher in people younger than 40 years and in people with calcifications present on preoperative ultrasonography (Khoo et al '02).

**Risk factors** for thyroid cancer include being female, having a history of **goiter** (enlarged thyroid) or thyroid nodules, a family history of thyroid cancer, radiation exposure early in life (e.g., during cancer treatment), excess body weight, and certain rare genetic syndromes, such as familial adenomatous polyposis (FAP). Patients with a history of radiation therapy administered in infancy or childhood for benign conditions of the head and neck (such as enlarged thymus, tonsils, or adenoids; or acne) have an increased risk of cancer and other abnormalities of the thyroid gland. Radiation exposure as a consequence of nuclear fallout has also been associated with a high risk of thyroid cancer, especially in children (Tronko et al '06). People who test positive for a mutation in a gene called RET, which causes a hereditary form of thyroid cancer (familial medullary thyroid carcinoma), can lower their risk of developing the disease by having the thyroid gland surgically removed before cancer develops. Goiter is the most common **symptom** of thyroid cancer is a lump in the neck that is noticed by a patient or felt by a clinician during an exam. Other symptoms include a tight or full feeling in the neck, difficulty breathing or swallowing, hoarseness, swollen lymph nodes, and pain in the throat or neck that does not go away. Many thyroid cancers are diagnosed incidentally in people without symptoms because an abnormality is seen on an imaging test done for another reason (ACS '20: 25).

Despite the rarity of invasive thyroid cancer around 4% of adults exhibit **thyroid nodules**. The most important predisposing factor for the development of thyroid cancer is irradiation in infancy or childhood for various benign conditions including thymic or tonsillar enlargement and skin diseases. Women appear to be at greater risk than men. The carcinogenic effect of radiation persists three to four decades after exposure. Most histologic classifications of the thyroid cancers recognize the subtypes; papillary (80%), follicular (15%), Hürthle cell (6%), medullary (50% familial), anaplastic (7%) and other such as soft-tissue sarcomas, lymphomas, epidermoid carcinoma occur rarely as primary tumors of the thyroid, but the thyroid can serve as a site of metastasis from other sites. Studies of asymptomatic patients with a history of childhood irradiation revealed that about 25% had abnormalities on physical examination or scan, and of those who were surgically explored, 33% or more proved to have thyroid cancer. About 20% of patients coming to surgery with solitary nodules have cancer. Men with solitary nodules are about three times more likely than women to have malignancy. Nodules in children are more likely to be malignant (about 50% are cancer) than in adults. The various laboratory tests of thyroid function, as well as determination of serum thyroglobulin levels and antithyroid antibodies, are nonspecific; elevated serum calcitonin levels, however, strongly suggest C-cell hyperplasia or medullary carcinoma. Ultimately the diagnosis of cancer must rest on histologic or cytologic evaluation. Thyroidologists recommend fine-needle aspiration, false-negative results are in the 5% to 10% range. Patients with negative fine-needle aspiration are placed on T4 suppression and followed carefully. Lesions that do not resolve in around 6 months are biopsied. There is no commonly used staging system (Wittes '90: 304-307).

The American Joint Committee on Cancer has designated staging by the TNM (tumor, node, metastasis) classification to define thyroid cancer (Amin et al '17). Thyroid cancer is generally divided into differentiated thyroid cancer, which includes well-differentiated tumors, poorly differentiated tumors, and undifferentiated tumors (papillary, follicular, or anaplastic) and medullary thyroid cancer. Well-differentiated tumors (papillary and follicular thyroid cancer)

are highly treatable and usually curable. Poorly differentiated and undifferentiated thyroid tumors (anaplastic thyroid cancer) are less common, aggressive, metastasize early, and have a poorer prognosis. Medullary thyroid cancer is a neuroendocrine cancer that has an intermediate prognosis. The thyroid gland may occasionally be the site of other primary tumors, including sarcomas, lymphomas, epidermoid carcinomas, and teratomas. The thyroid may also be the site of metastasis from other cancers, particularly of the lung, breast, and kidney. The prognosis for differentiated carcinoma (papillary or follicular) without extracapsular extension or vascular invasion is better for patients younger than 40 years. A retrospective study of 1,019 patients showed that the 20-year survival rate was 98% for low-risk patients and 50% for high-risk patients (Sanders et al '98).

Most thyroid cancers are **highly curable**, but about 5% (medullary and anaplastic thyroid cancers) are more aggressive and more likely to spread to other organs. Treatment depends on patient age, tumor size and cell type, and extent of disease. The first choice of treatment is usually surgery to partially or totally remove the thyroid gland (thyroidectomy) and sometimes nearby lymph nodes. Treatment with **radioactive iodine** (I-131)(RAI) after complete thyroidectomy (to destroy any remaining thyroid tissue) may be recommended for large tumors or when cancer has spread outside the thyroid. However, although OS is the same with, or without, second malignancies, sialadenitis, sacral and salivary gland dysfunction have been noted with radioactive iodine. RAI may be given with one of two methods of thyroid-stimulating hormone (TSH/thyrotropin) stimulation: withdrawal of thyroid hormone or administration of recombinant human thyrotropin (rhTSH)(Hänscheid et al '06). Administered rhTSH maintains quality of life and reduces the radiation dose delivered to the body compared with thyroid hormone withdrawal. EBRT is typically reserved for palliative treatment of unresectable or metastatic papillary or follicular thyroid cancer (Giuliani et al '14).

The primary treatment of **thyroid cancer** is surgery. More extensive surgery is associated with better survival rates. After surgery radioactive iodine is used to treat residual or metastatic disease. Administration should be schedule no sooner than 4 weeks postoperatively, or when the patient has been off T3 for at least 4 weeks and off T4 for at least 6 weeks. Iodinated contrast agents should not be used. The patient must avoid foods and medicines with iodine content. 50 mCi to 75 mCi usually suffices for ablation, which is deemed successful if, at the time of rescanning 6 weeks later, less than 0.3% of the administered tracer dose remains in the thyroid at 48 hours. Possible medical complications of radioiodine dose of this magnitude include sialadenitis, with permanent cessation of salivary flow in some patients and small risk of later development of acute leukemia. Once ablation is successful patients are placed on T4 suppression in order to keep TSH levels as low as possible. The preferred initial therapy for metastatic thyroid cancer is RAI in full therapeutic doses. In preparation for therapy, thyroid replacement with T4 or T3 is discontinued, and after 4 to 6 weeks elapse and a hypothyroid state has been induced, tracer is administered to establish that the metastatic tumor does indeed concentrate RAI significantly. A 40% cure rate of patients with metastatic disease has been observed with RAI. Side effects are the same as radiation nausea and vomiting, transient bone marrow suppression, pulmonary fibrosis, rare late leukemia and sialadenitis. External radiation may be used for locally persistent or recurrent disease that does not take up radioactive iodine. Excellent control rates in the neck have been found using 200 cGy/fraction, five times a week, for 5 weeks, and doxorubicin 10mg/m<sup>2</sup> IV, 90 minutes before the first RT treatment and weekly thereafter. The optimal regimen is probably the combination of cisplatin (40 mg/m<sup>2</sup>) and doxorubicin (60 mg/m<sup>2</sup>) given every 3 weeks; in a randomized trial involving 84 evaluable patients, this combination yielded a somewhat higher response rate (26%) than doxorubicin

alone (17%) and, perhaps more significantly, produced a number of patients with complete responses (12%) several of whom survived for more than 2 years (Wittes '90: 307-309).

**Sorafenib** is an orally active, multityrosine kinase inhibitor. It has been approved by the U.S. Food and Drug Administration as a treatment option when recurrent disease does not concentrate <sup>131</sup>I or disease recurs after <sup>131</sup>I ablation. The median PFS in the sorafenib group was 10.8 months versus 5.8 months in the placebo group. OS was not significantly improved (Brose et al '14). The median PFS in the **lenvatinib** group was 18.3 months versus 3.6 months in the placebo group. There was no significant difference in OS between the two groups. 6 of 20 deaths occurring during the treatment period were considered to be drug-related (Schlumberger et al '15). The objective response rate of **Selpercatinib** in adolescent and adult patients with any solid tumor type harboring an activating *RET* alteration was 79%. Ninety-five percent of patients with *RET* fusion-positive thyroid cancer received the phase II dose of 160 mg twice daily. At 1 year, 71% of responses were ongoing (95% CI, 39–88) and 64% of patients were progression-free. Thirty percent of patients had dose reductions because of treatment-related adverse events, and 2% of patients discontinued the drug because of adverse events (Wirth et al '20). **Larotrectinib** is a potent and highly selective small-molecule inhibitor of the TRKA, TRKB, and TRKC proteins treated with larotrectinib. For the 24 patients with thyroid cancer, the overall response rate was 79%, regardless of *TRK* fusion status. The objective response rate to **Entrectinib** was 57% but only 20% for thyroid cancer (Doebele et al '20).

**Medullary Thyroid Cancer** (MTC) comprises 3% to 4% of all thyroid cancers. Approximately 25% of reported cases of MTC are hereditary, such as MEN2A syndrome. The overall survival rates of patients with MTC is 86% at 5 years and 65% at 10 years. The clinical staging system of the American Joint Committee on Cancer correlates survival to size of the primary tumor (T), presence or absence of lymph node involvement (N), and presence or absence of distant metastasis (M). Patients with the best prognosis are those who are diagnosed with the hereditary form of MTC after a positive screening for a *RET* mutation (Colson et al '93). Standard treatment options for localized MTC include the following: Total thyroidectomy. External-beam radiation therapy (EBRT). Radioactive iodine is not used in the treatment of patients with MTC. **Vandetanib** is an oral inhibitor of rearranged during transfection (RET) receptor kinase, vascular endothelial growth-factor receptor (VEGFR), and epidermal growth-factor receptor. median PFS estimated at 30.5 months for vandetanib versus 19.3 months for placebo. Overall survival (OS) was not different at 24 months (Wells et al '12). The objective response rate of **Cabozantinib** is an oral tyrosine kinase inhibitor of RET receptor kinase, hepatocyte growth factor receptor MET, and VEGFR-2, was 28%. Estimated median PFS was 11.2 months in the cabozantinib group and 4.0 months in the placebo group, with no difference in OS (Elisei et al '13). **Selpercatinib** is an orally active, highly selective, small-molecule RET kinase inhibitor. For patients with *RET*-mutant MTC who were previously treated with vandetanib or cabozantinib: The objective response rate was 69%. At 1 year, 86% of responses were ongoing and 100% were progression-free. For patients with *RET*-mutant MTC who were not previously treated with vandetanib or cabozantinib, the objective response rate to was 73%. At 1 year, 91% of responses were ongoing, and 92% were progression-free. Thirty percent of patients had dose reductions because of treatment-related adverse events, and 2% of patients discontinued the drug because of adverse events (Wirth et al '20).

Undifferentiated (anaplastic) carcinoma is a highly malignant cancer of the thyroid. It grows rapidly and extends to structures beyond the thyroid. It typically presents as a hard, ill-defined mass, often with extension into the structures surrounding the thyroid. **Anaplastic thyroid**

**cancer** must be carefully distinguished from lymphoma, which can have a similar presentation. This tumor usually occurs in an older age group and is characterized by extensive local invasion and rapid progression (Neff et al '08). Five-year survival with this tumor is poor. Death is usually from uncontrolled local cancer in the neck, usually within months of diagnosis. EBRT may be used in patients who are not surgical candidates or whose tumor cannot be surgically excised. Anaplastic thyroid cancer is not responsive to iodine I 131 therapy. Treatment with individual anticancer drugs has been reported to produce partial remissions in some patients. Approximately 30% of patients achieve a partial remission with doxorubicin (Carling et al '11). The combination of doxorubicin plus cisplatin appears to be more active than doxorubicin alone and has been reported to produce more complete responses (Shimaoka et al '85). The combination of chemotherapy plus radiation therapy in patients after complete resection may provide prolonged survival but has not been compared with any one modality alone (Haigh et al '01). An estimated 25% of anaplastic thyroid cancers harbor an activating *BRAF* (V600E) mutation (Forbes et al '17). A phase II trial of *BRAF* and *MEK* inhibitors, **dabrafenib** and **trametinib**, included 16 patients with *BRAF* (V600E)-mutated anaplastic thyroid cancer. There was a 69% confirmed overall response rate, with median duration of response, progression-free survival (PFS), and overall survival (OS) not reached. Twelve-month estimates were 90% for duration of response, 79% for PFS, and 80% for OS (Subbiah et al '18).

**Parathyroid adenomas** represent a common endocrine problem, whereas **parathyroid carcinomas** are very rare tumors. With an estimated incidence of 0.015 per 100,000 population and an estimated prevalence of .005% in the United States, parathyroid cancer is one of the rarest of all human cancers. In Europe, the United States, and Japan, parathyroid carcinoma has been estimated to cause hyperparathyroidism (HPT) in .017% to 5.2% of the cases; however, many series report this entity to account for less than 1% of patients with primary HPT. The median age in most series is between 45 and 51 years (Rahbari et al '11). The ratio of affected women to men is 1:1 in contrast to primary HPT in which there is a significant female predominance (ratio of 3–4:1). Operatively, parathyroid cancers may be distinguished from adenomas by their firm, stony-hard consistency and lobulation; adenomas tend to be soft, round, or oval in shape, and of a reddish-brown color. In most series, the median maximal diameter of parathyroid carcinoma is between 3.0 cm and 3.5 cm compared with approximately 1.5 cm for benign adenomas. In approximately 50% of the patients, the malignant tumor is surrounded by a dense, fibrous, grayish-white capsule that infiltrates adjacent tissues. Histopathologically, as with other endocrine neoplasms, the distinction between benign and malignant parathyroid tumors is difficult to make (Shane '05). The extent to which capsular and vascular invasion appears to be unequivocally correlated with tumor recurrences and metastases makes a strong case for these findings to be considered the sole pathognomonic markers of malignancy (Iacobone et al '04). There is an increased risk of parathyroid cancer has been associated with multiple endocrine neoplasia 1 and with autosomal dominant familial isolated hyperparathyroidism (Dionisi et al '02). Parathyroid cancer has also been associated with external radiation exposure; however, most reports describe an association between radiation and the more common parathyroid adenoma. At initial presentation, very few patients with parathyroid carcinoma have metastases either to regional lymph nodes (<5%) or distant sites (<2%) (Rahbari et al '11).

Parathyroid cancers are hyperfunctional unlike other endocrine tumors that become less hormonally active when malignant. The clinical features of parathyroid carcinoma are caused primarily by the effects of **excessive secretion of parathormone** (PTH) by the tumor rather than by the infiltration of vital organs by tumor cells. Serum PTH levels may be three to ten times above the upper limit of normal for the assay employed; this marked elevation is uncommon in

primary HPT where serum PTH concentrations are typically less than twice that of normal (Shane '01). Accordingly, signs and symptoms of hypercalcemia typically dominate the clinical picture and may include typical hyperparathyroid bone disease and features of renal involvement, such as nephrolithiasis or nephrocalcinosis (Rahbari et al '11). Renal colic is a frequent presenting complaint of patients with parathyroid carcinoma (Shane '01). In a study involving 43 cases, the prevalence of nephrolithiasis was reported to be 56%, and the prevalence of renal insufficiency was reported to be 84% (Wynne et al '92). The prevalence of bone disease is much greater in patients with parathyroid carcinoma than it is in patients with parathyroid adenoma with 70% or fewer patients manifesting symptoms related to calcium absorption with osteoporosis and bone pain (Nikkilä et al '89). Parathyroid carcinoma should be suspected clinically if the patient presents with the following **diagnostic features**: Hypercalcemia is greater than 14 milligrams per deciliter. Serum PTH levels are greater than twice that of normal. A cervical mass is palpated in a hypercalcemic patient. Hypercalcemia is associated with unilateral vocal cord paralysis. Concomitant renal and skeletal disease are observed in a patient with a markedly elevated serum PTH (Rahbari et al '11). **Conventional treatment** with intravenous fluids, diuretics, and antiresorptive agents such as biphosphonates, gallium, or mithramycin may help control the hypercalcemia (Clayman et al '04). **Calcimimetic agents** that directly block secretion of the parathyroid hormone from the glands may offer an important new approach to medical therapy of primary HPT associated with parathyroid cancer (Strewler et al '00). Nonsurgical forms of therapy for parathyroid carcinoma generally have poor results (Rahbari et al '11).

Although cell type is not known to be of prognostic significance, **histologic cell types** include chief cell, transitional clear cell, and mixed cell types. Features such as dense fibrous trabeculae, trabecular growth patterns, mitoses, and capsular invasions, which have been classically associated with carcinomas, have also been found in parathyroid adenomas (Bondeson et al '93). Capsular and vascular invasion appears to correlate best with tumor recurrence (Iacobone et al '04). Because of the low incidence of parathyroid carcinoma, an American Joint Committee on Cancer staging system has not yet been formulated and thus is not applicable to this malignancy. In addition, neither tumor size nor lymph node status appear to be important prognostic markers for this malignancy (Hundahl et al '99). Patients are considered to have either localized or metastatic disease (Busaidi et al '04). Parathyroid carcinoma most frequently metastasizes to regional lymph nodes and lungs, and it may involve other distant sites, such as liver, bone, pleura, pericardium, and pancreas (Shane '01). The rarity of this tumor does not provide large published series of treatment experience or permit the systematic evaluation of combination therapies. The relatively slow cell-doubling time for this tumor makes radical surgery a therapeutic option even for patients with metastatic disease. Treatment and control of **secondary hypercalcemia** must be the initial treatment goal in all patients with hyperparathyroidism (Rahbari et al '11).

**Surgery** is the only effective therapy for parathyroid carcinoma (Rahbari et al '11). One analysis of the literature indicated an overall 8% evidence of local recurrence after an en bloc resection compared with a 51% incidence after a standard parathyroidectomy (Koea et al '99). The increased potential for long-term local control achieved by en bloc excision outweighs the complication of postoperative vocal cord paralysis, which can be improved with techniques such as Teflon injection into the paralyzed cord. Cervical lymph node dissection should be performed only for enlarged or firm nodes, particularly those found in the level VI paratracheal nodes and levels III and IV internal jugular nodes (Rahbari et al '11). The management of recurrent or metastatic disease is primarily surgical; significant palliation may result from the resection of

even very small tumor deposits in the neck, lymph nodes, lungs, or liver (Sandelin '97). Accessible distant metastases should be resected when possible (Shane '01). Localization studies performed before the first operation or reoperation may include technetium Tc 99m-sestamibi scan, single photon emission computed tomography, CT-MIBI image fusion, ultrasound, computed tomography (CT), selective angiogram, and selective venous sampling for PTH (Fraker '01); CT and magnetic resonance imaging are useful imaging adjuncts for the localization of distant metastases (Shane '01). Approximately 40% to 60% of patients experience a postsurgical recurrence, typically in the range of 2 to 5 years after the initial resection. In most cases, hypercalcemia precedes physical evidence of recurrent disease (Sandelin et al '92). In older studies, distant metastases were reported to occur in 25% of patients, primarily in the lungs but also in the bone and liver (Sandelin et al '94). Approximately 40% to 60% of patients experience a postsurgical recurrence, typically between 2 to 5 years after the initial resection (Sandelin '97). The 10-year survival rate was reported to be approximately 49% (Hundahl et al '99). A smaller series has reported a 10-year survival rate of 77%, which might be related to improvements in supportive medical care and in the prevention of fatal hypercalcemia (Buaidi et al '04).

**Thymoma and thymic carcinoma** (collectively termed *thymic epithelial tumors* [TETs]) are relatively rare tumors arising from the thymus. Surgery is the main treatment, especially for early-stage disease. Multimodality therapy, including chemotherapy and radiation therapy, is used to treat locally advanced disease, and systemic therapy alone is indicated for metastatic TETs (Kelly et al '11). TETs are relatively rare tumors representing about 0.2% to 1.5% of all malignancies. The overall incidence of thymoma is 0.13 cases per 100,000 person years, based on data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program (Engels et al '10). Thymic carcinomas account for approximately 20% of all TETs.[4] In a retrospective study of 40 patients with thymic carcinoma, the OS rates were 38% for 5 years and 28% for 10 years (Rena et al '05). Five-year survival for inoperable, locally advanced carcinoma is 36%; for metastatic thymoma and thymic carcinoma, the 5-year survival is 24% (Kondo et al '03). Autoimmune paraneoplastic diseases are associated with thymoma and are rarely associated with thymic carcinomas (Padda et al '18). Myasthenia gravis is the most common autoimmune paraneoplastic disease associated with thymoma. Approximately 30% to 65% of patients with thymoma have been diagnosed with myasthenia gravis in reported series. A variety of other autoimmune paraneoplastic diseases can be associated with TETs and include virtually any organ system (Marx et al '10). Thymoma patients with myasthenia gravis or other autoimmune paraneoplastic diseases are typically diagnosed with early-stage disease and are more likely to undergo complete surgical resection than are those who do not have myasthenia gravis or other autoimmune paraneoplastic diseases (Kondo et al '05). Thymectomy may not significantly improve the course of thymoma-associated autoimmune paraneoplastic disease in all cases (Evoli et al '02). The presence of autoimmune paraneoplastic disease does not appear to be an independent prognostic factor in patients with TETs (Padda et al '18). Approximately 50% of thymomas are diagnosed by x-ray when they are localized within the thymic capsule and do not infiltrate surrounding tissues (Schmidt-Wolf et al '03).

**Computed tomography (CT) scan** with intravenous contrast is useful in the diagnosis and clinical staging of thymoma. CT is usually accurate in predicting tumor size, location, and invasion into vessels, the pericardium, and the lungs (Sperling et al '03). The histological classification of thymic epithelial tumors (TETs) has evolved and is largely based on the third edition of the World Health Organization (WHO) classification of tumors of the lung, pleura, thymus, and heart that was published in 2004. The fourth edition of the WHO classification,

published in 2015, contains refined histological and immunohistochemical diagnostic criteria and is the most widely accepted cellular classification of TETs. Thymomas arise from the thymic epithelium and consist of epithelial cells mixed with varying proportions of immature T cells. Thymic carcinomas are epithelial tumors with overt cytological atypia and without *organotypic* (i.e., thymus-like) features (Marx et al '15). The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) adopted a new TNM (tumor, node, metastasis) classification system developed by the International Association for the Study of Lung Cancer (IASLC) and ITMIG (Carter et al '17). Stage I Macroscopically, completely encapsulated; microscopically, no capsular invasion. Stage II Macroscopic invasion into surrounding fatty tissue or mediastinal pleura; microscopic invasion into capsule. Stage III Macroscopic invasion into neighboring organs (pericardium, lung, and great vessels). Stage IVa Pleural or pericardial dissemination. Stage IVb Lymphogenous or hematogenous metastases (Amin et al '17). When the Masaoka staging system was applied to a series of 85 surgically treated thymoma patients, its value in determining prognosis was confirmed, with 5-year survival rates of 96% for stage I disease, 86% for stage II disease, 69% for stage III disease, and 50% for stage IV disease (Masaoka et al '81). In a large, retrospective study involving 273 patients with thymoma, 20-year survival rates (as defined by freedom from tumor death) according to the Masaoka staging system were reported to be 89% for stage I disease, 91% for stage II disease, 49% for stage III disease, and 0% for stage IV disease (Okumura et al '02).

Standard primary treatment for patients with thymoma or thymic carcinoma is **surgical resection** with en bloc resection for invasive tumors, if possible (Cameron et al '19). Depending on tumor stage, multimodality treatment options—which include the use of radiation therapy and chemotherapy with or without surgery—may be used (Rimner et al '16). For patients presenting with a mediastinal mass that is highly suspicious for an early-stage thymic epithelial tumor (TET) and is potentially completely resectable, surgical resection is the preferred initial treatment (Maggi et al '91). **Postoperative radiation therapy** (PORT) is associated with survival benefit and is generally recommended for patients with stage II or stage III disease (Rimner et al '16). Patients with stage IVA disease are usually offered multimodality therapy consisting of induction chemotherapy followed by surgery (if the disease is considered resectable) and PORT (Yokoi et al '07). Patients with stage IVB disease are treated with definitive chemotherapy (Lemma et al '11). Commonly used induction chemotherapy regimens include combinations of cisplatin, doxorubicin, and cyclophosphamide, or cisplatin and etoposide. Rates of response to induction chemotherapy ranged from 79% to 100%, with subsequent resectability rates of 36% to 69% (Loehrer et al '97). For patients with stage III or stage IV thymoma, the 5-year survival rates were 93% for patients treated with total resection, 64% for patients treated with subtotal resection, and 36% for patients whose disease was inoperable. (Kondo et al '03). Patients who received PORT had a median OS of 127 months compared with 105 months (Weksler et al '12). Long-term survival rates following induction chemotherapy and surgery with or without radiation therapy and consolidation chemotherapy have ranged from 50% at 4 years, to 77% at 7 years, to 86% for stage III patients and 76% for stage IV patients at 10 years, in different published series (Lucchi et al '06). Similar survival rates have been reported with preoperative radiation therapy without chemotherapy, particularly if great vessels are involved; results showed a 5-year OS rate of 77% and a 10-year OS rate of 59% (Akaogi et al '96).

Evidence (treatment of stage III and IV **inoperable thymoma**): An intergroup trial conducted in the United States reported a predicted 5-year OS rate of 52% in 26 patients who received the **PAC chemotherapy regimen** (cisplatin, doxorubicin, cyclophosphamide) followed by radiation

therapy without surgery (Loehrer et al '97). In a series of 30 patients with stage IV or locally progressive recurrent tumor after radiation therapy, the PAC regimen was administered (Loehrer et al '94). A 50% response rate was achieved, including three complete responses. The median duration of response was 12 months. The 5-year survival rate was 32%. The **ADOC regimen** (doxorubicin, cisplatin, vincristine, cyclophosphamide) was administered to 37 patients (Fornasiero et al '91). 92% response rate (34 of 37 patients) was achieved, including complete responses in 43% of patients. A study of combined chemotherapy with **cisplatin and etoposide** reported the following: A 56% response rate (9 of 16 patients) was achieved. There was a median response duration of 3.4 years and a median survival of 4.3 years (Giaccone et al '96). Patients with invasive thymoma or thymic carcinoma were treated with four cycles of etoposide, ifosfamide, and cisplatin (**VIP**) at 3-week intervals (Loehrer et al '01). 32%, nine of 28 evaluable patients had partial responses. The median follow-up was 43 months (range, 12.8–52.3). The median duration of response was 11.9 months (range, <1–26). The median OS was 31.6 months. The 1-year survival rate was 89% and the 2-year survival rate was 70%, based on Kaplan-Meier estimates. These results appear to be inferior to other combinations. A phase II study evaluated the activity of a combination of **carboplatin and paclitaxel** in 46 patients with unresectable TETs, including 21 patients with unresectable thymoma. 42.9%, nine of 21 patients with thymoma had objective responses. The median duration of response in patients with thymoma was 16.9 months. The median progression-free survival for the thymoma cohort was 16.7 months; median OS was not reached after median follow-up of 59.4 months (Lemma et al '11).

The optimal treatment of **thymic carcinoma** remains undefined because of its rarity. For patients with clearly resectable well-defined disease, surgical resection is often the initial therapeutic intervention. For patients with clinically borderline or frankly unresectable lesions, neoadjuvant (preoperative) chemotherapy, thoracic radiation therapy, or both, have been given (Koizumi et al '02). Standard treatment options for patients with operable thymic carcinoma include the following: Surgery (en bloc surgical resection) followed by postoperative radiation therapy (PORT) with or without postoperative chemotherapy. Standard treatment options for patients with inoperable thymic carcinoma (stage III and stage IV with vena caval obstruction, pleural involvement, pericardial implants, etc.) include the following: Chemotherapy. Chemoradiation therapy. Chemotherapy followed by surgery (if operable) and radiation therapy. In most published studies, surgery has been followed by adjuvant radiation therapy (Hsu et al '02). A prescriptive dose range has yet to be identified. Most studies use 40 Gy to 70 Gy with a standard fractionation scheme (1.8–2.0 Gy per fraction) (Ahmad et al '15). The 5-year survival rates were 67% for patients treated with total resection, 30% for patients treated with subtotal resection, and 24% for patients whose disease was inoperable. The 5-year survival rates for patients with totally resected thymic carcinoma were 81.5% for patients treated with chemotherapy, 46.6% for patients treated with radiation therapy and chemotherapy, 73.6% for patients treated with radiation therapy alone, and 72.2% for patients who received no adjuvant therapy (Kondo et al '03). Surgical resection may be repeated, particularly for local recurrences and, in some cases, pleural and pericardial implants. Patients with recurrent thymomas who undergo repeat resection of recurrent disease may have prolonged survival when complete resection is attained (Urgesi et al '92). In one study, the 10-year survival rate was 70%. In another study the 5-year survival rate was 48% and the 10-year survival rate was 24% (Ruffini et al '97).

A number of studies have demonstrated that certain chemotherapy drugs can induce tumor responses as single-agent or combination therapy. A combination of **carboplatin and paclitaxel** had an objective response rate of 21.7% (Girard et al '15). 25% of thymic carcinoma had an

objective response to etoposide, ifosfamide, and cisplatin (**VIP**) (Loehrer et al '01).

**Pemetrexed** had an objective response rate of 19.2% in patients with thymoma and 9.1% in patients with thymic carcinoma. The median progression-free survival (PFS) was 10.6 months (12.1 months for those with thymoma vs. 2.9 months for those with thymic carcinoma). The median overall survival (OS) was 28.7 months (46.4 months for patients with thymoma vs. 9.8 months for patients with thymic carcinoma). The median duration of response was 4 months in patients with thymoma (range, 3.26–6.28 months) and 3.8 months in the one patient with thymic carcinoma who had a partial response (Gbolahan et al '18). **Capecitabine and gemcitabine** were tried with objective responses were observed in 9 of 22 patients (41%) with thymoma and 3 of 8 patients (38%) with thymic carcinoma. After a median follow-up of 18 months (range, 15–22), the median PFS was 11 months (range, 6.5–16.5). The median PFS was 11 months for patients with thymoma and 6 months for patients with thymic carcinoma. The overall median PFS was also 11 months. One-year and 2-year survival rates for the study population were 90% and 66%, respectively (Palmieri et al '14).

**Octreotide**, a biologic therapy, with or without prednisone may induce responses in patients with octreotide scan-positive thymoma. Six of 16 patients, 37.5%, achieved objective responses to octreotide (1.5 mg every day subcutaneously) associated with prednisone (0.6 mg/kg every day orally for 3 months, 0.2 mg/kg every day orally during follow-up). In one study, six of 16 patients achieved objective responses to octreotide (1.5 mg every day subcutaneously) associated with prednisone (0.6 mg/kg every day orally for 3 months, 0.2 mg/kg every day orally during follow-up) (Palmieri et al '02). In a study of octreotide with or without prednisone, two complete responses (5.3%) and ten partial responses (25%) were observed among 42 patients (Loehrer et al '04). **Sunitinib** at a dose of 50 mg per day administered in 6-week cycles (4 weeks on treatment followed by a 2-week break) (Thomas et al '15). After a median follow-up of 17 months, 6 of 23 assessable patients with thymic carcinoma 26% had an objective response, and 15 patients 65% achieved disease stabilization. Of 16 patients with thymoma, 1 patient 6% had a partial response, and 12 patients 75% had stable disease. The median PFS was 7.2 months for patients with thymic carcinoma and 8.5 months (2.8–11.3) for patients with thymoma. The median OS was not reached for patients with thymic carcinoma and was 15.5 months in patients with thymoma. The estimated OS at 1 year was 78% for patients with thymic carcinoma and 86% (60.9%–96.1%) for patients with thymoma (Thomas et al '15). Objective responses were observed in 3 of 32 patients (9.4%) with thymoma and in 3 of 19 patients (15.8%) with thymic carcinoma treated with oral everolimus. The disease-control rate was 88% (thymoma: 93.8%; thymic carcinoma: 77.8%). After a median follow-up of 25.7 months, the median PFS was 10.1 months (thymoma: 16.6 months; thymic carcinoma: 5.6 months). The median OS was 25.7 months (thymoma: not reached; thymic carcinoma: 14.7 months) (Zucali et al '18). **Lenvatinib** is an orally administered multikinase inhibitor that targets vascular endothelial growth factor receptors, platelet-derived growth factor receptor- $\alpha$ , fibroblast growth factor receptors, c-KIT, and the *RET* proto-oncogene. Objective responses were observed in 16 of 42 patients 38%. The disease-control rate was 95%. After a median follow-up of 15.5 months, the median time to response was 2.0 months, median duration of response was 11.6 months, median PFS was 9.3 months, and the median OS was not reached (NR) (Sato et al '20). **Pembrolizumab** (anti-programmed death ligand 1 antibody) has been evaluated in patients with recurrent TETs with an objective response rate of 28.6%. The median PFS was same for both groups (Cho et al '19).

**Tumors of the adrenal gland** are rare; about 150 to 300 adrenocortical tumors and about 400 pheochromocytomas (of which about 10% are malignant) occur in the United States each year. Clinically inapparent adrenal adenomas are found in 10.4% to 8.7% of autopsies. The

differential diagnosis of an adrenal mass includes cortical adenoma and carcinoma, pheochromocytoma, neuroblastoma, ganglioneuroma, cysts, melolipoma, adenolipoma, and metastases from other primary malignancies. Cortical adenomas are generally small (<6 cm diameter) and characteristically secrete a single steroid activity, usually glucocorticoid; androgenic effects are generally absent. Carcinomas tend to present with large tumors and to secrete multiple classes of steroids, usually glucocorticoids and androgens, and less commonly mineralocorticoids or estrogens. Carcinomas often produce marked elevations of urinary 17-hydroxysteroids (17-OH) and 17-ketosteroids (17KS) and characteristically have a rapid onset and progression of symptoms. Adrenal tumors are very uncommon causes of hypertension in adults. Pheochromocytoma might be suspected in patients with sustained or paroxysmal hypertension and history of sweating, tachycardia or palpitations, anxiety, or headaches. When arising from adrenal tumors, disorders of sex-hormone secretion are usually associated with large tumors that are either palpable or easily imaged with conventional techniques. TNM Staging is by the size of the primary tumor, Stage 1 <5 cm, Stage 2 >5 cm, Stage 3 any sized tumor plus nodes or local invasion, Stage IV any sized tumor plus metastases with or without nodes and local invasion (Wittes '90: 311-313).

The initial treatment of choice for **adrenocortical tumors** is surgical excision. Patients with Cushing's syndrome from an adrenal tumor should be assumed to have a suppressed pituitary-adrenal axis and patients will need long-term glucocorticoid replacement. Perioperative coverage is provided by hydrocortisone, 100 mg IV every 8 hours, on the day of operation. The daily dose is tapered gradually over the next 5 days to maintenance levels of cortisone acetate, 25 mg orally every morning and 12.5 mg orally every night. Patients with residual functional disease after surgery or who have recurrent or metastatic disease not amenable to surgical resection should be treated with mitotane (o,p'-DDD). The usual starting dose is 8 g to 10 g daily, although many patients discontinue due to side-effects. About 70% respond with decreased steroid secretion and in about 30% to 40% tumor size is reduced significantly. Nonresponders can be treated with metyrapone (750 mg orally every 4 hours) or aminoglutethamide (250 mg orally every 6 hours initially, with stepwise dose increase to a total of 2g/day or until dose-limiting side-effects occur). Because metyrapone inhibits 11-beta hydroxylation, patients receiving long-term treatment should be monitored for the development of hypertension. Patients receiving any of these inhibitors of adrenal steroid synthesis may require administration of replacement doses of glucocorticoid and mineralocorticoid and should be assumed to have adrenal insufficiency at times of stress.

**Pheochromocytomas** and extra-adrenal paragangliomas are rare tumors arising from neural crest tissue that develops into sympathetic and parasympathetic paraganglia throughout the body. The most recent World Health Organization classification utilizes the term *pheochromocytoma* exclusively for tumors arising from the adrenal medulla, and the term *extra-adrenal paraganglioma* for similar tumors that arise from other locations. The incidence of pheochromocytoma is 2 to 8 per million persons per year. Pheochromocytoma is present in 0.1% to 1% of patients with hypertension, and it is present in approximately 5% of patients with incidentally discovered adrenal masses. The peak incidence occurs in the third to fifth decades of life; the average age at diagnosis is 24.9 years in hereditary cases and 43.9 years in sporadic cases.[8] The incidence is equal between males and females. Pheochromocytomas and extra-adrenal paragangliomas arise from neural crest tissue. Neural crest tissue develops into sympathetic and parasympathetic paraganglia. Sympathetic paraganglia include the following: The adrenal medulla. The organ of Zuckerkandl near the aortic bifurcation. Other paraganglia along the distribution of the sympathetic nervous system. Parasympathetic paraganglia include

the following: The carotid body. Other paraganglia along the cervical and thoracic branches of the vagus and glossopharyngeal nerves.

No known environmental, dietary, or lifestyle risk factors have been linked to the development of pheochromocytoma. Of all pheochromocytomas and extra-adrenal paragangliomas, 25% occur in the setting of a hereditary syndrome. Major genetic syndromes that have been identified as carrying an increased risk of pheochromocytoma - Multiple endocrine neoplasia type 2A and 2B. von Hippel-Lindau disease. Neurofibromatosis type 1. Hereditary Paraganglioma Syndrome. It has been proposed that all patients diagnosed with a pheochromocytoma or paraganglioma should consider genetic testing because the incidence of a hereditary syndrome in apparently sporadic cases is as high as 25% (Jiménez et al '06). Pheochromocytomas and extra-adrenal paragangliomas can also occur in the following two other very rare syndromes: The Carney triad of extra-adrenal paraganglioma, gastrointestinal stromal tumor (GIST) (Carney '99) and pulmonary chondroma. The Carney-Stratakis dyad of paraganglioma and GIST (Carney et al '02). Other genetic causes of pheochromocytoma and paraganglioma are being studied. For example, truncating germline mutations in the *TMEM127* gene on chromosome 2q11 have been shown to be present in approximately 30% of affected patients with familial disease and in about 3% of patients with apparently sporadic pheochromocytomas without a known genetic cause (Quin et al '10). *TMEM127* is a negative regulator of mammalian target of rapamycin (mTOR) effector proteins.

Patients with pheochromocytomas and sympathetic extra-adrenal paragangliomas may present with symptoms of excess **catecholamine** production, including the following: Hypertension. Headache. Perspiration. Forceful palpitations. Tremor. Facial pallor. These symptoms are often paroxysmal, although sustained hypertension between paroxysmal episodes occurs in 50% to 60% of patients with pheochromocytoma (Lenders et al '05). Patients are often very symptomatic from excess catecholamine secretion. Symptoms of catecholamine excess can be spontaneous or induced by a variety of events, including the following: Strenuous physical exertion. Trauma. Labor and delivery. Anesthesia induction. Surgery or other invasive procedures, including direct instrumentation of the tumor (e.g., fine-needle aspiration). Foods high in tyramine (e.g., red wine, chocolate, and cheese). Urination (e.g., bladder wall tumor, which is rare). Phenoxybenzamine (blocks alpha receptors) is an effective treatment for catecholamine excess and metyrosine (blocks catecholamine synthesis) can be added if needed. Parasympathetic extra-adrenal paragangliomas do not secrete catecholamines and usually present as a neck mass (Else et al '19). A 24-hour urine collection for catecholamines (e.g., epinephrine, norepinephrine, and dopamine) and fractionated metanephrines (e.g., metanephrine and normetanephrine) has a relatively low sensitivity (77%–90%) but a high specificity (98%). Pretest probability is also important. The specificity of plasma-free fractionated metanephrines is 82% in patients tested for sporadic pheochromocytoma versus 96% in patients tested for hereditary pheochromocytoma (Sawka et al '03). In general, it is reasonable to use measurement of plasma-free fractionated metanephrines for initial case detection, which is followed by 24-hour measurement of urine-fractionated metanephrines and catecholamines for confirmation. Test results can be difficult to interpret because of the possibility of false-positive results (Lenders et al '02). A mildly elevated catecholamine or metanephrine level is usually the result of assay interference caused by drugs or other factors. Patients with symptomatic pheochromocytoma almost always have increases in catecholamines or metanephrines two to three times higher than the upper limits of reference ranges (Lenders et al '05).

Once the biochemical diagnosis of a catecholamine-secreting tumor is confirmed, **localization studies** should be performed. Computed tomography (CT) imaging or magnetic resonance imaging (MRI) of the abdomen and pelvis (at least through the level of the aortic bifurcation) are the most commonly used methods for localization. Both have similar sensitivities (90%–100%) and specificities (70%–80%) (Ilias et al '04). CT imaging provides superior anatomic detail compared with MRI. Although patients with localized (apparently benign) disease should experience an overall survival approaching that of age-matched disease-free individuals, 6.5% to 16.5% of these patients will develop a recurrence, usually 5 to 15 years after initial surgery. Approximately 50% of patients with recurrent disease experience distant metastasis (Amar et al '05). The 5-year survival in the setting of metastatic disease (whether identified at the time of initial diagnosis or identified postoperatively as recurrent disease) is 40% to 45% (Averbuch et al '88). Long-term follow-up is essential for all patients with pheochromocytoma or extra-adrenal paraganglioma, even when initial pathology demonstrates no findings that are concerning for malignancy (Omura et al '04). Pheochromocytoma and paraganglioma characteristically form small nests of uniform polygonal chromaffin cells (“zellballen”). A diagnosis of malignancy can only be made by identifying tumor deposits in tissues that do not normally contain chromaffin cells (e.g., lymph nodes, liver, bone, lung, and other distant metastatic sites). Regional or distant metastatic disease is documented on initial pathology in only 3% to 8% of patients (Wu et al '09).

**Definitive treatment** for localized and regional pheochromocytoma, including localized disease recurrence, consists of alpha- and beta-adrenergic blockade followed by surgery. For patients with unresectable or metastatic disease, treatment may include a combination of the following: Catecholamine blockade. Surgery. Chemotherapy. Radiofrequency ablation. Cryoablation. Radiation therapy. The cornerstone of treatment of pheochromocytoma is surgical resection, i.e., **adrenalectomy** is the definitive treatment for patients with localized pheochromocytoma. Surgical resection is the definitive treatment for pheochromocytoma or extra-adrenal paraganglioma that is regionally advanced (e.g., from direct tumor extension into adjacent organs or because of regional lymph node involvement) (Zarnegar et al '06). The standard treatment option for patients with inherited pheochromocytoma is surgery. The surgical management of pheochromocytoma in patients with the hereditary syndromes multiple endocrine neoplasia type 2 (MEN2) and von Hippel-Lindau (VHL) disease has been controversial. In both of these syndromes, pheochromocytoma is bilateral in at least 50% of patients; however, malignancy is very uncommon. Bilateral total adrenalectomy commits all patients to lifelong steroid dependence, and up to 25% of patients will experience Addisonian crisis (acute adrenal insufficiency). Current recommendations generally favor preservation of adrenal cortical tissue in patients with MEN2 and VHL syndromes when possible. Patients who initially present with unilateral pheochromocytoma should undergo unilateral adrenalectomy, and patients who present with bilateral pheochromocytomas or who develop pheochromocytoma in their remaining adrenal gland should undergo cortical-sparing adrenalectomy, when technically feasible (Lee et al '96). In a single-institution study involving 56 patients with pheochromocytoma, 57% of patients (i.e., 17 of 30 patients) who underwent one or more cortical-sparing adrenalectomies avoided the need for routine steroid replacement; the clinical recurrence rate was low (i.e., 3 of 30 patients) and none of the patients developed metastatic disease (Yip et al '04).

**Alpha-adrenergic blockade** should be initiated at the time of diagnosis and maximized preoperatively to prevent potentially life-threatening cardiovascular complications, (Hypertensive crisis. Arrhythmia. Myocardial infarction. Pulmonary edema) which can occur as a result of excess catecholamine secretion during surgery. Seven to ten days before operation

phenoxybenzamine, 10 mg to 20 mg three or four times a day, or prazosin, 2 mg to 5 mg orally twice a day, is instituted to induce alpha-adrenergic blockade. Prazosin, terazosin, and doxazosin (selective alpha-1-antagonists) are alternative choices. Prazosin, terazosin, and doxazosin are shorter acting than phenoxybenzamine, and therefore, the duration of postoperative hypotension is theoretically less than with phenoxybenzamine; however, there is less overall experience with selective alpha-1-antagonists than with phenoxybenzamine. A preoperative treatment period of 1 to 3 weeks is usually sufficient; resolution of spells and a target low normal blood pressure for age indicate that alpha-adrenergic blockade is adequate. During alpha-adrenergic blockade, liberal salt and fluid intake should be encouraged because volume loading reduces excessive orthostatic hypotension both preoperatively and postoperatively. If tachycardia develops or if blood pressure control is not optimal with alpha-adrenergic blockade, a beta-adrenergic blocker (e.g., metoprolol or propranolol) can be added only after alpha-blockade (Prys-Roberts et al '02).

**Beta blockade** may also be required if arrhythmias are present during surgery. Beta-adrenergic blockade must never be initiated before alpha-adrenergic blockade; doing so blocks beta-adrenergic receptor-mediated vasodilation and results in unopposed alpha-adrenergic receptor-mediated vasoconstriction, which can lead to a life-threatening crisis (Prys-Roberts et al '02).

**Metyrosin**, 0.25 g to 1 g orally four times a day, can block catecholamine biosynthesis and is a useful adjunct. Chemotherapy has not been shown to improve survival in patients with metastatic pheochromocytoma; however, chemotherapy can be attempted for the palliation of symptoms. The best-established **chemotherapy regimen** is a combination of cyclophosphamide, vincristine, and dacarbazine (the Averbuch protocol)(Averbuch et al '88). Results of this regimen in 18 patients after 22 years of follow-up demonstrated a complete response rate of 11%, a partial response rate of 44%, a biochemical response rate of 72%, and a median survival of 3.3 years (Huang et al '08). The combination of cyclophosphamide, 750 mg/m<sup>2</sup> IV on day 1; vincristine, 1.4 mg/m<sup>2</sup> IV on day 1; and dacarbazine, 600 mg/m<sup>2</sup> IV on days 1 and 2, given in 3 to 4 week treatment cycles has produced impressive antitumor effects in both tumor shrinkage and blood pressure control. Patients treated with cytotoxic chemotherapy should probably have adequate alpha-receptor blockade prior to treatment, since release of catecholamines with tumor lysis has been described (Wittes '90: 313, 314). Disappointing initial results were reported with the mammalian target of rapamycin (mTOR) inhibitor everolimus (Druce et al '09), but results from a very small number of patients treated with the tyrosine kinase inhibitor sunitinib have been more promising (Joshua et al '09). <sup>131</sup>I-MIBG radiation therapy has been used for the treatment of MIBG-avid metastases (Buscombe et al '05). In a phase II study of high-dose <sup>131</sup>I-MIBG radiation therapy involving 49 patients, 8% had a complete response, 14% had a partial response, and the estimated 5-year survival was 64% (Gonias et al '09).

Pheochromocytoma diagnosed during pregnancy is extremely rare (0.007% of all pregnancies) (Harrington et al '08). Prenatal diagnosis clearly results in decreased mortality for both mother and neonate (Freier et al '93). The prenatal diagnosis rate rose to greater than 80% through the 1980s and 1990s, and decreased maternal and neonatal mortality rates were 6% and 15%, respectively (Mannelli et al '02). The diagnosis of pheochromocytoma should be suspected in any pregnant woman who develops hypertension in the first trimester, paroxysmal hypertension, or hypertension that is unusually difficult to treat (Sarathi et al '10). Normal pregnancy does not affect catecholamine levels. Phenoxybenzamine use is safe in pregnancy, but beta-adrenergic blockers should be initiated only if needed because their use has been associated with intrauterine growth retardation (Montan et al '92). Resection of the tumor can often be

performed safely during the second trimester, or tumor resection can be combined with cesarean section when the fetus is ready to be delivered. Case reports have documented successful outcomes in the rare circumstance when surgical resection was delayed until a short time after vaginal delivery (Junglee et al '07).

**Pancreatic neuroendocrine tumors** (NETs) are uncommon cancers with about 1,000 new cases per year in the United States. They account for less than 2% of pancreatic malignancies and overall have a better prognosis than the more common pancreatic exocrine tumors. Islet tumors may either be functional (produce one or more active hormones) or nonfunctional. The functional tumors, which usually present with symptoms of hormone hypersecretion, include: Gastrinoma. Insulinoma. Glucagonoma. Somatostatinoma. VIPoma (Davies et al '09). Most islet cell cancers are functional, but about 15% are nonfunctional, with presentations similar to the far more common exocrine adenocarcinomas of the pancreas (O'Grady et al '08). Because of the presence of several cell types in the pancreatic islets (alpha, beta, delta, A, B, C, D, E, F), the term islet cell tumors refers to at least five distinct cancers that, when functional, produce unique metabolic and clinical characteristics. Functional tumors may even be too small to be detected by conventional imaging techniques. Nonfunctional tumors tend to present at later clinical stages with symptoms attributable to mass effect or metastases. Although nonfunctional tumors do not produce specific clinical syndromes, they may secrete inactive amine and peptide products such as the following: Neurotensin. Alpha-subunit of human chorionic gonadotropin (alpha-hCG). Neuron-specific enolase. Pancreatic polypeptide. Chromogranin A (Davies et al '09).

Surgery is the only curative modality. The AJCC has designated staging by TNM (tumor, node, metastasis) classification to define pancreatic neuroendocrine tumors (islet cell tumors) (Amin et al '17). Effective palliation may be achieved because of the slow-growing nature of the majority of these tumors and the potential use of antihormonal pharmacologic therapy (e.g., cimetidine in the ulcer-producing Zollinger-Ellison syndrome). In patients with indolent, slow-growing metastatic islet cell tumors, the best therapy may be careful observation, and no treatment until palliation is required. In patients with MEN1 in which 85% have pancreatic islet cell tumors, 90% have hyperparathyroidism, and 65% have pituitary tumors, and they are less likely to be cured by pancreatic resection than are patients with sporadic islet cell tumors. With the exception of pain relief from bone metastases, radiation therapy has a limited role in this disease. Tumor localization and staging studies include imaging with computed tomography (CT) with or without magnetic resonance imaging (MRI), and endoscopic ultrasound. In addition, somatostatin-receptor scintigraphy and single-photon emission CT may be useful adjuncts. However, somatostatin-receptor scintigraphy has diminished utility in localizing insulinomas versus other pancreatic NETs, since insulinomas often have a low density of somatostatin receptors (Davies et al '09). If the noninvasive tests do not reveal a tumor, but clinical suspicion remains high, more invasive and technically demanding tests, such as selective arteriography or selective arterial stimulation (with a secretagogue specific for the suspected tumor type), may be useful (King et al '94). Some of the tumor types have unique characteristics that require specific approaches in their diagnosis and initial evaluation.

**Gastrinomas** are responsible for the Zollinger-Ellison syndrome, which consists of fulminant peptic ulcer disease caused by excessive production of gastrin. Diarrhea or steatorrhea are other common presenting symptoms. Zollinger-Ellison syndrome is a condition of unrelenting peptic ulcer disease, diarrhea, and gastric hyperacidity, associated with a gastrin-producing tumor. It accounts for less than 1% of all peptic ulcer disease. About 15% to 35% of gastrinomas are associated with the MEN1 syndrome and up to 50% are malignant. Up to 33% of gastrinomas

have liver metastases (Davies et al '09). Once the diagnosis of gastrinoma is suspected, a serum gastrin, basal acid output (BAO) and other tests should be obtained. BAO:MAO >0.6 BAO : maximal acid output. Overnight AO > 100 mmol. BAO > 10 mmol/hr. Serum gastrin 10x normal or >500 pg/mL, secretin test 1 unit/kg intravenous rapid injection: positive = 100% increase in gastrin within 10 minutes; 2 units/kg: positive = 100% increase over baseline, elevated hCG levels. An elevated serum gastrin and BAO more than 15mEq/hour for a patient not having undergone prior gastric resection (>5 mEq/hour for those having had gastric surgery) are highly suspicious of the diagnosis of Zollinger-Ellison syndrome; a secretin stimulation test is usually confirmatory but is not necessary if the BAO is more than 15 and the serum gastrin higher than 1000 pg/ml. Once the diagnosis has been confirmed, locating the tumor may be difficult. Angiography locates the primary site in only 10% to 30% of patients. Gray-scale ultrasound locates 50% (Kelsen '90: 317-319).

Parietal cell vagotomy and cimetidine, resection of the pancreas and pancreateoduodenectomy are standard treatment with resection, chemoembolization or radioablation of liver metastases. Metastatic disease or disease refractory to surgery and cimetidine: is treated with chemotherapy or Somatostatin analog therapy (Bushnell et al '10). Treatment with proton pump inhibitors or H2 blocking agents may aid in control of peptic symptoms. In the era of proton pump inhibitors and H2 blocking agents, the potentially lethal hyperacidity and hypersecretory states induced by excessive gastrin production can usually be controlled. In a series of 212 patients with Zollinger-Ellison syndrome (ZES), no patients died of causes related to acid hypersecretion. Of those patients, only 2.3% had been subjected to total gastrectomy, and the cohort upon which the report was based had a long median follow-up period of 13.8 years. Although 32% of the patients died during the course of the study, only 50% of the 67 deaths were attributable to ZES-related causes. Those causes were mainly liver metastases with progressive anorexia and cachexia (67%) or secondary endocrine tumors consequent to multiple endocrine neoplasia type 1 syndrome. The development of bone or liver metastases (especially diffuse liver disease) or of ectopic Cushing syndrome during the study period predicted for decreased survival times (Kvols et al '87).

**Long term therapy** options for patients with Zollinger-Ellison syndrome include continued management with cimetidine or ranitidine and anticholinergics; elective total gastrectomy, and resection of the primary tumor. In acute severe Zollinger-Ellison syndrome, continuous nasogastric suction should be started, fluid and electrolyte status should be monitored and replaced, as needed. IV H-2 blockers (e.g. cimetidine or ranitidine) should be started promptly, supplemented with anticholinergics. If acid secretion can be kept at less than 20 mEq/hour, ulcer disease can usually be controlled. Ranitidine, 50 mg three to four times daily, will control most patients with Zollinger-Ellison syndrome. Some patients may require 50 mg IV four times daily. Once the patient is stabilized surgery can be performed. Resection of all functional tumor, defined as return of gastrin levels to normal with negative stimulatory tests, is possible in approximately 20% of patients (Kelsen '90: 319-321).

Among the more common pancreatic endocrine tumors are **insulinomas** (insulin-producing islet cell tumors). They are usually seen in adults in the fourth to sixth decade of life. The diagnosis of insulinoma is confirmed by the finding of an elevated insulin concentration relative to hypoglycemia, usually after a 24 hour fast. While there is a sex difference in the absolute level of hypoglycemia seen during fasting, with women having a lower level than men, the 24 hour value for normal subjects of either sex is rarely, if ever, below 60 mg/dl. If an insulinoma is suspected or proven, measurement of serum alpha-human chorionic gonadotropin (HCG) levels

are seen in malignant islet cell tumors. A normal HCG level does not rule out carcinoma. With careful attention to catheter placement 80% of tumors can be identified. Eighty percent of insulinomas are benign and are cured by surgical resection (Kelsen '90: 317-319). Only 10% are multiple, and only 10% are malignant. About 5% to 8% are associated with MEN1 syndrome. The clinical manifestations are those of hypoglycemia, which results from inappropriate secretion of insulin by the tumor. Fasting hypoglycemia (<40 mg/dL) associated with an elevated insulin level (in the absence of exogenous administration of insulin) is pathognomonic (Davies et al '09).

The combination of preoperative dual-phase thin-section multi-detector CT and endoscopic sonography correctly identified and localized all of the tumors (Gouya et al '03). These tests, with or without MRI, have replaced older, more invasive, and technically challenging tests, such as percutaneous transhepatic portal venous sampling and arterial stimulation with venous sampling except for unusual circumstances in which the imaging tests are unsuccessful (Nikfarjam et al '08). Curative surgical excision, by open laparotomy or laparoscopy, is the treatment of choice when possible. The open surgical approach is used if the tumor is suspected to be malignant because en bloc lymphadenectomy is performed for malignant tumors without distant metastases. Intraoperative ultrasound aids the localization of tumor extent and the relationship to other anatomic structures (Davies et al '09). Standard treatment includes enucleation, if feasible, pancreaticoduodenectomy, distal pancreatectomy, distal pancreatectomy with enucleation of tumors in the head of the pancreas. Metastatic lesions, lymph nodes and distant sites are resected, when possible, radiofrequency and cryosurgical ablation are considered. Unresectable tumors are treated with combination chemotherapy. Pharmacologic palliation: diazoxide 300 to 500 mg/day and Somatostatin analogue therapy. Patients with hepatic-dominant disease and substantial symptoms caused by tumor bulk or hormone-release syndromes may benefit from procedures that reduce hepatic arterial blood flow to metastases (hepatic arterial occlusion with embolization or with chemoembolization) (Gurusamy et al '09).

**Glucagonoma** is the third most common endocrine-secreting islet cell tumor. About 75% of glucagonomas are malignant. Necrolytic migratory erythema, hyperglycemia, and venous thrombosis comprise a virtually diagnostic triad. A serum glucagon level greater than 1,000 pg/mL confirms the diagnosis. These tumors tend to be large and easily visible on CT scan. Somatostatin receptor scintigraphy scanning may be a useful adjunct in detecting metastases (Davies et al '09). Glucagonomas are found in patients with glucagon-producing tumors the clinical syndrome includes diabetes, skin rash (necrolytic migratory erythema), painful glossitis, and hypaminoaciduria. Thromboembolic phenomena are common. Glucagonomas are usually large at presentation, an elevated glucagon level averaging 2100 pg/ml is diagnostic (Kelsen '90: 317-319). As with the other pancreatic neuroendocrine tumors, the mainstay of therapy is surgical resection, and extended survival is possible even when the disease is metastatic. Resection of metastases is also a consideration when feasible (Davies et al '09). Standard treatment is enucleation, if feasible, pancreaticoduodenectomy, distal pancreatectomy, resection of the tail or body of pancreas, resection of metastatic disease, lymph nodes and distant sites. Unresectable disease is treated with combination chemotherapy or Somatostatin analog therapy. Necrotizing erythema of glucagonoma may be relieved in 24 hours with somatostatin analog, with nearly complete disappearance within 1 week. Patients with hepatic-dominant disease and substantial symptoms caused by tumor bulk or hormone-release syndromes may benefit from procedures that reduce hepatic arterial blood flow to metastases (hepatic arterial occlusion with embolization or with chemoembolization) (Gurusamy et al '09). The majority of glucagon-producing tumors are malignant and most patients will have metastases at the time of diagnosis.

Single agent chemotherapy activity, major tumor shrinkage, has been seen in 15% of those treated with doxorubicin, streptozocin, 5-fluorouracil (5-FU), etoposide (VP-16), and cyclophosphamide. In addition alpha-interferon has been shown to cause reduction in hormone production and in fewer patients, tumor masses. In general combination chemotherapy regimens have been based on streptozocin (Kelsen '90: 319-321).

Miscellaneous islet cell tumors are VIPoma (Verner-Morrison syndrome) and Somatostatinoma. **Vipomas** are islet cell tumors producing vasoactive intestinal polypeptide (VIP) that causes a Verner-Morrison syndrome of profuse diarrhea, hypokalemia and achlorhydria. The volume of diarrhea may be 6 to 8 liters per day. Diarrhea that persists more after 48 hours of fasting is highly suspicious. An elevated VIP level is diagnostic. A serum vasoactive intestinal peptide (VIP) greater than 200 pg/mL is diagnostic. These tumors can generally be easily localized by CT scan. Somatostatin receptor scintigraphy scanning may be a useful adjunct in detecting metastases. Immediate fluid resuscitation is often necessary to correct the electrolyte and fluid problems that occur as a result of the watery diarrhea, hypokalemia, and achlorhydria that patients experience. Somatostatin analogs are also used to ameliorate the large fluid and electrolyte losses. Once patients are stabilized, excision of the primary tumor and regional nodes is the first line of therapy for clinically localized disease. In the case of locally advanced or metastatic disease, where curative resection is not possible, debulking and removal of gross disease, including metastases, should be considered to alleviate the characteristic manifestations of vasoactive intestinal peptide overproduction. **Somatostatin-producing islet cell tumors** are very rare. Clinically, patients with somatostatinoma have hypochlorhydria, diabetes, weight loss and malabsorption. They often present with diarrhea, steatorrhea, diabetes, and/or gallstones. Decreased pancreatic secretion of enzymes and bicarbonate accounts for the diarrhea and steatorrhea. Somatostatin-mediated inhibition of cholecystokinin leads to gallstone formation. Somatostatin also inhibits insulin, producing hyperglycemia. The diagnosis is made by a fasting serum somatostatin level greater than 100 pg/mL. CT scan, MRI, and endoscopic ultrasound can usually help localize and stage the tumor. Most of these tumors are malignant and have metastases at diagnosis. Surgical resection is curative (Davies et al '09).

**Carcinoids** are small cell neoplasms that may produce the amine serotonin (among other substances). The majority of these tumors arise in the small bowel. Carcinoids of the appendix are the most common site for this disease and almost always act in a benign fashion. Histologically, they look very much like islet cell tumors: fragile, small, round cells growing in ribbon-like structures. The diagnosis of carcinoid tumor is based on histologic findings; an elevated 5-hydroxyindoleacetic acid (5-HIAA) is of prognostic value. The carcinoid syndrome involves flushing, wheezing, diarrhea and hypotension. Carcinoid heart disease involves the mural and valvular endocardium, primarily the right side. There is no relationship between the syndrome and development of carcinoid heart disease (Kelsen '90: 317-319). For **appendiceal carcinoid**, if the tumor is less than 2 cm in diameter, appendectomy alone is adequate. If the tumor large (>2 cm) more aggressive cancer operations are indicated (hemicolectomy). Medical management of the carcinoid syndrome includes use of alpha-or beta adrenergic blockers (propranolol, phenoxybenzamine), antiserotonin agents (cyproheptadine), phenothiazines (chlorpromazine) and corticosteroids. Propranolol, a beta-blocking agent, has been reported to decrease the frequency and intensity of carcinoid-related flushing. The doses usually used are 10 mg, three times a day, given orally. Phenoxybenzamine, 20 mg/daily, has also been reported to decrease the frequency and severity of flushing and diarrhea. Cyproheptadine (Perictin), 4 mg to 8 mg four times daily, is useful in select patients. In patients bronchial carcinoid, prednisone, 10 mg to 20 mg per day, has been of benefit. Diphenoxylate hydrochloride (lomotil) one to two

tablets two to four times per day, is useful in controlling diarrhea. If the tumor is malignant and has metastasized beyond the possibility of a surgical cure, medical management includes dietary changes such as smaller more frequent meals or increased carbohydrates, IV if needed, if 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 benzothiadiazine diuretic should be given with diazoxide. Propranolol and glucocorticoids have also been used. In carcinoid tumors no advantage was seen in combination therapy (Kelsen '90: 319-321). In islet cell tumors response improved from 36% from streptozocin alone to 63% for 5-FU and streptozocin. If is reasonable to treat symptomatic patients and/or those with clearly progressing tumor with streptozocin, 500 mg/m<sup>2</sup> IV and 5-FU, 400 mg/m<sup>2</sup> IV, daily for 5 days, each cycle repeated in 5 weeks (Kelsen '90: 319-321).

If technically and medically feasible, primary management of endocrine tumors of the pancreas involves **surgical resection** with curative intent. Given the rare nature of these tumors, surgical approaches are based on case series and expert opinion rather than randomized controlled trials. Adjuvant therapy has no proven benefit (Davies et al '09). The symptoms of metastatic functional pancreatic neuroendocrine tumors (NETs) may be ameliorated by the reduction of overall tumor burden through surgical debulking. The liver is a common site of metastasis from pancreatic NETs. Because of the slow growth rate of many NETs, liver metastases are often resected when technically feasible. Resection of all grossly visible liver metastases can be associated with long-term survival and, in the case of symptomatic hormonally functional tumors, symptom relief (Sarmiento et al '03). A variety of alternative approaches to the management of liver metastases have been reported, including gel-foam embolization or transarterial chemoembolization (Gupta et al '05), radioembolization with radioactive microspheres, radiofrequency ablation, cryoablation, and percutaneous alcohol ablation (King et al '08).

Chemotherapy using drugs such as the following, either alone or in combination, has been shown to have antitumor effects, but evidence is weak or conflicting regarding the impact of chemotherapy on overall survival (Kulke et al '09): Streptozocin. Doxorubicin. Fluorouracil. Chlorozotocin. Dacarbazine. Temozolomide. More recently, a variety of systemic agents have shown biologic or palliative activity, including (Yao et al '10): Tyrosine kinase inhibitors (e.g., sunitinib). Temozolomide. Vascular endothelial growth factor pathway inhibitors. Mammalian target of rapamycin inhibitors (e.g., everolimus). Nearly all of the evidence of activity derives from case series. However, there are ongoing placebo-controlled randomized trials of everolimus (Yao et al '10) and sunitinib (Raymond et al '10) that have been reported in abstract form showing an increase in progression-free survival in each case. Favorable responses have been reported in patients with advanced progressive pancreatic NETs after treatment with several radiolabeled somatostatin analogs in which the analogs octreotide, octreotate, lanreotide, or edotreotide are stably attached to the radionuclides indium In 111, yttrium Y 90, or lutetium Lu 177 (Bushnell et al '10).

**Pituitary tumors** represent from 10% to 25% of all intracranial neoplasms. They can be classified as benign adenoma, invasive adenoma or carcinoma. Adenomas comprise the largest portion of pituitary neoplasms with an overall estimated prevalence of approximately 17%. Only a minority of adenomas are symptomatic (Ezzat et al '04). In addition, pituitary adenomas may be distinguished anatomically as intrapituitary, intrasellar, diffuse, and invasive (Kovaks et al '01). Invasive adenomas, which account for approximately 35% of all pituitary neoplasms, may invade the dura mater, cranial bone, or sphenoid sinus (Scheithauer et al '86). Carcinomas

account for 0.1% to 0.2% of all pituitary tumors (Ragel et al '04). The most characteristic presenting features of pituitary adenomas include inappropriate pituitary hormone secretion and visual field deficits (Levy et al '04). Rare signs and symptoms can also include cranial nerve palsies, temporal lobe epilepsy, hydrocephalus and cerebrospinal fluid rhinorrhea. Specific pituitary tumor cell types are prolactinomas, corticotroph adenomas, somatotroph adenomas, thyrotroph adenomas, and nonfunctioning adenomas. Although rare, lymphocytic (i.e., autoimmune) hypophysitis should be considered in the differential diagnosis of any nonsecreting pituitary mass, especially when occurring during pregnancy or postpartum (Caturegli et al '05). In addition, the clinician should consider craniopharyngioma and Rathke cleft cyst in the differential diagnosis of pituitary tumors. Sellar masses may also result from tumors that are metastatic to the pituitary. This typically occurs as a part of a generalized metastatic spread and is usually associated with five or more additional metastatic sites, especially osseous; breast and lung cancer are the most common primary neoplasms metastasizing to the pituitary (Komninos et al '04).

Signs and symptoms of prolactin-producing pituitary tumors, also known as **prolactinomas** and lactotroph adenomas, may include the following: Headache. Visual field deficits. Oligomenorrhea or amenorrhea. Reduced fertility. Loss of libido. Erectile dysfunction. Galactorrhea in the estrogen-primed female breast (Levy et al '04). PRL-producing pituitary tumors, also known as prolactinomas and lactotroph adenomas, secrete PRL and are typically an intrasellar tumor. In women, these adenomas are often small (<10 mm). In either sex, however, they can become large enough to enlarge the sella turcica. These adenomas represent the most common hormone-producing pituitary tumors and account for 25% to 41% of tumor specimens (Ezzat et al '04). Most microprolactinomas and macroprolactinomas respond well to medical therapy with ergot-derived dopamine agonists, including bromocriptine and cabergoline. For many patients, cabergoline has a more satisfactory side effect profile than bromocriptine. Cabergoline therapy may be successful in treating patients whose prolactinomas are resistant to bromocriptine or who cannot tolerate bromocriptine, and this treatment has a success rate of more than 90% in patients with newly diagnosed prolactinomas (Colao et al '00). In a prospective study, cabergoline was safely withdrawn in patients with normalized prolactin levels and no evidence of tumor, which may effect a cure rate of approximately 70% (Calao et al '03). On the basis of its safety record in pregnancy, however, bromocriptine is the treatment of choice when restoration of fertility is the patient's goal (Schlechte et al '03).

Signs and symptoms of adrenocorticotrophic hormone-producing pituitary tumors, also known as **corticotroph adenomas**, may include the following: Headache. Visual field deficits. Proximal myopathy. Centripetal fat distribution. Neuropsychiatric symptoms. Striae. Easy bruising. Skin thinning. Hirsutism. Osteopenia (Levy et al '04). The major manifestation of ACTH-producing pituitary tumors, also known as corticotroph adenomas, is secretion of ACTH, which results in Cushing syndrome. These tumors are initially confined to the sella turcica, but they may enlarge and become invasive after bilateral adrenalectomy (i.e., Nelson syndrome). These adenomas represent the second or third most common hormone-producing pituitary tumors, depending on the series; in one series, these tumors accounted for 10% of all tumor specimens (Ezzat et al '04). For patients with corticotroph adenomas, transsphenoidal microsurgery is the treatment of choice. Remission rates reported in most series are approximately 70% to 90% (Yeh et al '97). In a series of 216 patients, who underwent surgery using a transsphenoidal approach, 75% experienced long-term remission, 21% experienced persistence of Cushing disease, and 9% had recurrence after the initial correction of the hypercortisolism (Mampalam et al '88). The average time interval for reoperation was 3.8 years. Seventy-nine percent of the tumors were

microadenomas, and 18% were macroadenomas; 86% of the cases with microadenoma had long-term remission, whereas, only 46% of those with macroadenoma had remission. In cases in which hypercortisolemia persists, early repeat exploration and/or radiation therapy or laparoscopic bilateral adrenalectomy may be required (Levy '04). Radiation therapy has been used in patients who are deemed to be poor surgical candidates and has also been used as adjunctive therapy in patients with residual or recurrent active tumor (Mahmoud-Ahmed et al '02). Drug therapy is considered to be an adjunct to transsphenoidal microsurgery in cases in which there is a residual tumor and in cases in which one is awaiting the effects of the radiation therapy (Yeh et al '97). Steroidogenesis inhibitors, including mitotane, metyrapone, ketoconazole, and aminoglutethimide are used. Ketoconazole is the best tolerated of these agents and is effective as monotherapy in about 70% of patients (Nieman '02). If untreated, patients frequently succumb to cardiovascular disease or infection.

Signs and symptoms of growth hormone-producing pituitary tumors, also known as **somatotroph adenomas**, may include the following: Headache. Visual field deficits. Growth of hands and feet. Coarsening of facial features. Carpal tunnel syndrome. Snoring and obstructive sleep apnea. Jaw growth and prognathism. Osteoarthritis and arthralgia. Excessive sweating. Dismorphophobia (Levy et al '04). GH-producing pituitary tumors, also known as somatotroph adenomas, produce GH, resulting in gigantism in younger patients and acromegaly in others. Suprasellar extension is not uncommon. These adenomas represent the second or third most common hormone-producing pituitary tumors, depending on the series; in one series these adenomas accounted for 13% of tumor specimens (Ezzat et al '04). Treatment for patients with acromegaly includes surgical, radiation, and medical therapies (Levy '04). Treatment will depend on the size and extent of the tumor and the need for rapid cessation of hormone function that results in serious clinical sequelae (i.e., hypertension and cardiomyopathy). Microadenomectomy or macroadenoma decompression is approached transsphenoidally in most patients. Increasingly, endoscopic surgery is used to allow the entire surgical field to be viewed and to allow tumor tissue that would otherwise be inaccessible with rigid instruments to be safely resected. Complete return of GH concentrations to normal, however, is not often achieved. Increasingly, adjunctive radiation therapy is reserved for tumors that extend beyond the safe operative area and appear to pose an ongoing threat. Drug treatment, whether used as an adjuvant or primary therapy in appropriately selected patients, which is advocated by some (Kleinberg '05), includes the use of somatostatin analogs, such as octreotide; dopamine analogs, such as bromocriptine; and, the GH-receptor antagonist, pegvisomant. As the first of a new class of GH-receptor antagonists, pegvisomant works by inhibiting functional dimerization of GH receptors and thereby inhibits GH action. Preliminary results indicate that it may be the most effective medical treatment for acromegaly reported to date (Stewart '03). In acromegalic patients, impaired glucose tolerance, hypertension, and hyperlipidemia should be vigorously treated concurrently with definitive therapy. A multidisciplinary clinical approach may be required for the treatment of arthritis, carpal tunnel syndrome, obstructive sleep apnea, and prognathism. Mortality is related primarily to cardiovascular and respiratory diseases (Colao et al '04).

Signs and symptoms of thyrotropin (thyroid-stimulating hormone)-producing tumors, also known as **thyrotroph adenomas**, may include the following: Palpitations. Tremor. Weight loss. Insomnia. Hyperdefecation. Sweating (Vance et al '04). Thyrotroph-producing pituitary tumors, also known as thyrotroph adenomas, secrete TSH, also known as thyrotropin, which results in hyperthyroidism without TSH suppression. Many are large and invasive, may be plurihormonal, and secrete both GH and/or PRL. These tumors are rare and account for no more than 2% of tumor specimens (Teramoto et al '04). Transsphenoidal surgery is the treatment of choice for

patients with thyrotropic adenomas (Brucker-Davis et al '99). Adjuvant radiation therapy may be employed when surgery is known to be noncurative even if the patient is still euthyroid because relapse is inevitable, and the full effect of radiation therapy requires months or years. Medical therapy may be required for patients who still have hyperthyroid symptoms despite surgery and external radiation. Somatostatin analogs are the drugs of choice for treatment; however, the efficacy of treatment may wane with time (Teramoto et al '04).

**Gonadotroph adenomas** may secrete FSH and/or LH, or the alpha or beta subunits that comprise these heterodimers, which, depending on gender, may result in ovarian overstimulation, increased testosterone levels, testicular enlargement, and pituitary insufficiency caused by compression of the pituitary stalk or destruction of normal pituitary tissue by the tumor. Many gonadotroph tumors, however, are unassociated with clinical or biochemical evidence of hormone excess and may be considered to be nonfunctioning or endocrine-inactive tumors (Snyder '95). Functional, clinically detectable gonadotroph adenomas are rare (Asa et al '98). Plurihormonal tumors produce more than one hormone. Morphologically, they can be either monomorphous or plurimorphous. Monomorphous plurihormonal adenomas consist of one cell population that produces two or more hormones. The adenoma cells often differ from nontumorous adeno-hypophysial cells, and their cellular derivation may remain obscure despite extensive morphological studies. Plurimorphous plurihormonal adenomas consist of two or more distinct cell types, and each produces one hormone (Kovaks et al '01). Thyrotroph adenomas are often plurihormonal (Teramoto et al '04).

Non-functioning (**endocrine inactive**) tumors arise from the adeno-hypophysis and cause symptoms when they extend beyond the sella, which results in pressure on the surrounding structures rather than secretion of a hormonally active substance. Endocrine-inactive adenomas show positive immunostaining for one or more pituitary hormones (Kovaks et al '01); however, they are not associated with clinical and biochemical evidence of hormone excess.

Gonadotrophic hormones, as detected by antisera to beta-FSH and beta-LH, are present in many clinically nonfunctioning adenomas. Some of these adenomas are recognized by electron microscopy to have gonadotrophic differentiation, but some have characteristics of less well-differentiated cells and resemble the null cells that were initially thought to be undifferentiated precursors of adeno-hypophysial cells (Asa et al '98). Endocrine-inactive pituitary adenomas comprise approximately 30% to 35% of the pituitary tumors in most series and are the most common type of macroadenoma (Yeh et al '97). Surgical management is typically considered the first choice of treatment for patients with endocrine inactive pituitary adenomas because of its effectiveness in ameliorating symptoms of chiasmal compression and headache (Losa et al '01). Radical removal of the tumor, however, is difficult to obtain because of the frequent invasiveness into the cavernous sinus. Seventy percent to 80% of patients experience normalization or improvement of visual field defects, and almost 100% of patients with headache as a presenting symptom experience relief. Regrowth of the tumor after radiologically confirmed gross total removal appears to be uncommon. In a series of 32 patients, only 2 (6.2%) with gross total tumor removal and no postoperative radiation therapy showed radiological recurrence of the tumor at a mean follow-up of 5.5 years (Lillehei '98). Radiation therapy has been administered routinely in the postoperative period and after clear radiological evidence of residual or recurrent tumor has been demonstrated. Drug therapy appears to be of limited value (Losa et al '01).

Oncocytic tumors of the pituitary, also known as pituitary **oncocytomas**, are characterized by an abundance of mitochondria, which may fill up to 50% of the cytoplasmic area, which is normally around 8%, and obscure other organelles. These tumors are usually unassociated with clinical

and biochemical evidence of hormone excess; in some cases, they may be accompanied by various degrees of hypopituitarism and/or mild hyperprolactinemia. Oncocytic change may occur in several other pituitary tumor types (Kovaks et al '01). **Pituitary carcinomas** are usually endocrinologically functional, and ACTH-producing and PRL-producing tumors are the most frequent (Ironsides '03). The histological and cytological characteristics of pituitary carcinomas vary from bland and monotonous to frankly malignant (Pemicone et al '01). Carcinomas show a variable degree of nuclear atypia and cellular pleomorphism, but they also show significantly higher mitotic rates and cell proliferation indices than adenomas (Ironsides '03). Carcinomas account for 0.1% to 0.2% of all pituitary tumors (Ragel et al '04). Breast and lung cancer are the most common primary neoplasms metastasizing to the pituitary. Although tumors that are metastatic to the pituitary have been reported to be as high as 28% in autopsy series, the majority of metastatic tumors are clinically silent (Komninos et al '04). Other tumors that arise in the pituitary include craniopharyngiomas, meningiomas, and germ cell tumors; the rare granular cell tumors, pituicytomas, and gangliogliomas; and the even rarer gangliocytomas, lymphomas, astrocytomas, and ependymomas (Ironsides '03). Standard treatment options for patients with pituitary carcinomas include resection and dopamine agonists for PRL-producing tumors; somatostatin analogs for GH-producing and TSH-producing tumors; radiation therapy, and chemotherapy (Ragel et al '04). These treatments are palliative with the mean survival time ranging from 2 years to 2.4 years, though several case reports of long-term survivors have been published (Vaquero et al '03).

In addition to cell-type specific presentations, pituitary apoplexy (i.e., pituitary adenoma apoplexy) represents another important clinical presentation of pituitary adenomas. **Pituitary apoplexy** can result from an acute hemorrhagic or ischemic infarction of the pituitary in patients harboring often unrecognized secreting or nonfunctioning pituitary adenomas. In a series analyzing 40 cases of pituitary apoplexy, the presenting signs and symptoms included headache (63%), vomiting (50%), visual field defects (61%), ocular paresis (40%), mental deterioration (13%), hyponatremia (13%), and syncope (5%); in only four cases pituitary tumor was diagnosed before presentation. The development of pituitary adenomas may also occur as a component of three familial cancer syndromes: Multiple endocrine neoplasia. Carney complex (e.g., cardiac myxomas, spotty skin pigmentation, and tumors of the adrenal gland and anterior pituitary). Isolated familial acromegaly (Levy et al '04).

As with other tumors of the central nervous system (CNS), no tumor, nodes, metastases-based American Joint Committee on Cancer classification and staging system for pituitary tumors exists (Amin et al '17). Pituitary tumors are classified according to size and divided into microadenomas (i.e., the greatest diameter is <10 mm) and macroadenomas (i.e., the greatest diameter is  $\geq 10$  mm) (Ezzat et al '04). Most pituitary adenomas are microadenomas. The most widely used radioanatomical classification was based primarily on a neuroradiological examination including skull x-rays, pneumoencephalography, polytomography, and carotid angiography. Subsequently validated by the application of more accurate magnetic resonance imaging (MRI) and computed tomography, this radioanatomical classification places adenomas into one of four grades (I–IV) and has been augmented by additional studies including immunohistochemistry and electron microscopy (Asa et al '98). Currently, MRI is considered the imaging modality of choice for the diagnosis of pituitary disorders because of its multiplanar capability and good soft tissue contrast enhancement (Ezzat et al '04). Because no unequivocal histopathologic features of pituitary carcinoma exist, the diagnosis of malignancy is reserved for pituitary neoplasms that have metastasized to remote areas of the CNS or to outside of the CNS (Kemink et al '99). The radiographical classification for pituitary adenomas is as follows :[3,8] 0:

Normal pituitary appearance. I: Enclosed within the sella turcica, microadenoma, smaller than 10 mm. II: Enclosed within the sella turcica, macroadenoma, 10 mm or larger. III: Invasive, locally, into the sella. IV: Invasive, diffusely, into the sella. The grading schema for suprasellar extensions is as follows: A: 0 to 10 mm suprasellar extension occupying the suprasellar cistern. B: 10 mm to 20 mm extension and elevation of the third ventricle. C: 20 mm to 30 mm extension occupying the anterior of the third ventricle. D: An extension larger than 30 mm, beyond the foramen of Monro, or Grade C with lateral extensions (Yeh et al '97).

The goals of treatment of pituitary adenomas include normalization of hormonal secretion (i.e., normalization of hyper-secretion and improvement in hypo-function) and resolution or cessation of the progression of neurological defects. **Standard treatments** for patients with pituitary tumors include the following: Surgery. Radiation therapy. Medical therapy. A combination of surgery, radiation therapy, and medical therapy. The treatment of choice must be individualized and is dictated by the type of tumor, the nature of the excessive hormonal expression, and whether or not the tumor extends into the brain around the pituitary (Asa et al '98). The **transsphenoidal microsurgical approach** to a pituitary lesion is the most widely employed surgical approach to pituitary lesions and represents a major development in the safe surgical treatment of both hormonally active and nonfunctioning tumors (Yeh et al '97). A contraindication to this approach includes tumors with a significant suprasellar extension with an hourglass-shaped narrowing between the intrasellar and suprasellar component because blind attempts to reach the suprasellar tumor may lead to cerebral damage. An infection in the sphenoid sinus is potentially a contraindication to the transsphenoidal approach. Rapid deterioration of vision is an immediate indication for surgery to relieve pressure produced by an expanding tumor mass, except in the case of macroprolactinomas (where intensive observation with a patient on dopaminergic agonists may be an acceptable alternative). Progressive deterioration of visual fields is often the primary neurological criterion on which surgical management decisions are based (Levy et al '04).

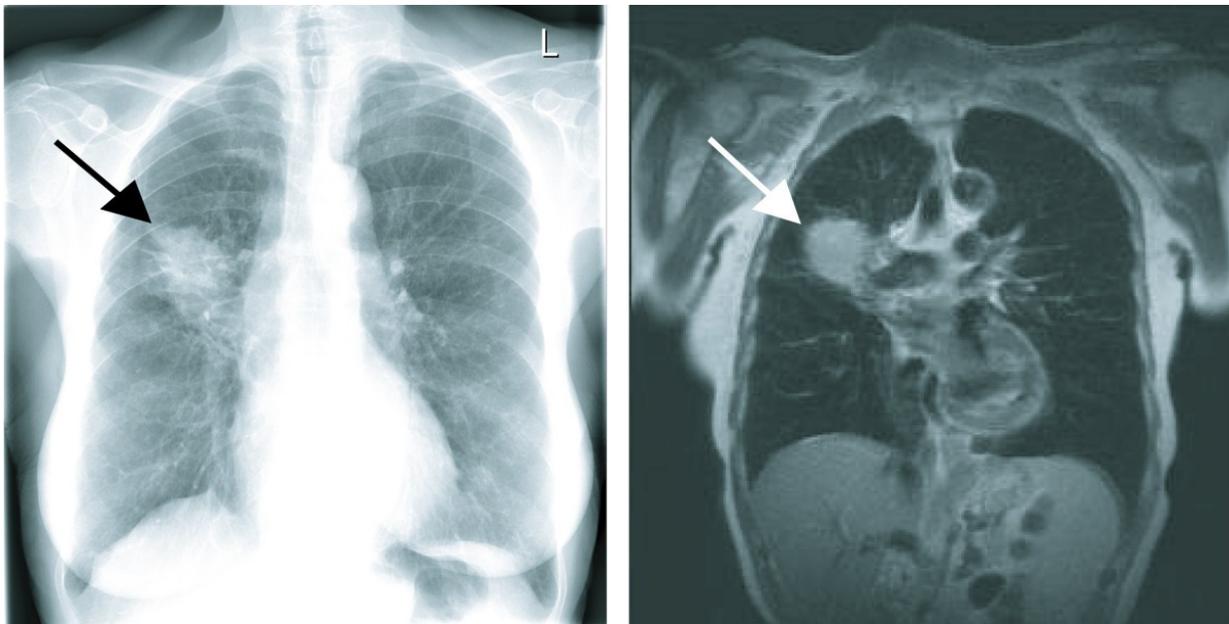
Hormone-secreting tumors may be treated with surgery or radiation therapy. Surgical therapy is the treatment of choice for growth hormone-(GH) producing, adrenocorticotrophic hormone-(ACTH) producing, and endocrine-inactive adenomas. GH-secreting tumors can be treated with somatostatin analogs, dopamine analogs, and the newer GH-receptor antagonists, such as pegvisomant (Levy et al '04). Ketoconazole, an inhibitor of steroidogenesis, is considered the first drug of choice as adjunctive medical therapy for ACTH-producing tumors (Yeh et al '97). Somatostatin analogs are the drugs of choice for treatment of thyroid-stimulating, hormone-producing adenomas; however, the efficacy of treatment may wane with time (Levy et al '04). Standard treatment options for recurrent pituitary tumors include the following: Radiation therapy for postsurgical recurrence, which offers a high likelihood of local control (Tsang et al '94). Reirradiation, which provides long-term local control and control of visual symptoms (Schoenthaler et al '92). Conventional **radiation** therapy is an effective adjunct to the treatment of pituitary tumors (Yeh et al '97). Radiation may require from 2 years to 10 years for complete and sustained remission. In addition, radiation therapy carries a substantial risk of hypopituitarism (i.e., approximately 30% at 10 years). Stereotactic radiation surgery is under clinical evaluation (Laws et al '04).

## IV. Treatment

### 1. Diagnosis

There is no single test that can accurately diagnose cancer. The complete evaluation of a patient usually requires a thorough history and physical examination along with diagnostic testing. Many tests are needed to determine whether a person has cancer, or if another condition (such as an infection) is mimicking the symptoms of cancer. Effective diagnostic testing is used to confirm or eliminate the presence of disease, monitor the disease process, and to plan for and evaluate the effectiveness of treatment. In some cases, it is necessary to repeat testing when a person's condition has changed, if a sample collected was not of good quality, or an abnormal test result needs to be confirmed. Diagnostic procedures for cancer may include tumor biopsy, imaging, laboratory tests (including tests for tumor markers), endoscopic examination, surgery, or genetic testing. Tissue or cell **biopsies** can be taken from almost any part of the body. How samples are taken depends on where the tumor is and what type of cancer is suspected. Some types of biopsies remove an entire organ. These types are done only by surgeons. Other types of biopsies may remove tumor samples through a thin needle or through an endoscope (a flexible lighted tube). These biopsies are often done by surgeons, but can also be done by other doctors. The most common biopsy types used in cancer diagnosis are needle biopsy, fine needle aspiration, core biopsy, excisional or incisional biopsy, endoscopic biopsy, laparoscopic, thoracoscopic, and mediastinoscopic biopsy, laparotomy and thoracotomy, skin biopsies, and sentinel lymph node mapping and biopsy.

### X-ray of Thoracic Tumor



Credit: translational-medicine.com

**X-rays** are the most common imaging techniques and they may be made more specific by using a Barium enema. This is used for detection of stomach and small intestinal growths and cancers. **Mammogram** is an X-ray of the breasts used to screen for and/or detect breast lumps and growths. **Computed tomography (CT)** is an imaging procedure that uses special x-ray equipment to create a series of detailed pictures, or scans, of areas inside the body. It is also called computerized tomography and computerized axial tomography (CAT) scanning. In cancer, CT may be used to help detect abnormal growths; to help diagnose tumors; to provide information about the extent, or stage, of disease; to help in guiding biopsy procedures or in

planning treatment; to determine whether a cancer is responding to treatment; and to monitor for recurrence. Although CT is an important tool in medicine, it has the potential—like other sources of ionizing radiation—to cause cancer. People should discuss the risks and benefits of CT with their doctors. **Magnetic Resonance Imaging (MRI)** uses a powerful magnetic field to create detailed computer images of the body's soft tissue, large blood vessels and major organs. Both CT scan and MRI can also be used with contrast radio-labelled dyes to obtain a more clear and specific picture of the cancer. **Ultrasound** uses high-frequency sound waves to determine if a suspicious lump is solid or fluid. These sound waves are transmitted into the body and converted into a computerized image. **Bone scan** is specifically used to identify and locate new areas of cancer spread to the bone. Normally a **Positron imaging test (PET scan)** is used. A **Gallium scan** is another nuclear medicine test in which a special camera takes pictures of tissues of the body after a special radioactive tracer is injected into a vein. The cancerous areas light up under the scanner.

Clinical chemistry uses chemical processes to measure levels of chemical components in body fluids and tissues, most commonly blood and urine. Many different tests exist to detect and measure almost any type of chemical component in blood or urine. Components may include blood glucose, electrolytes, enzymes, hormones, lipids (fats), other metabolic substances, and proteins. A variety of **blood tests** are used to check the levels of substances in the blood that indicate how healthy the body is and whether infection is present. For example, blood tests revealing elevated levels of waste products, such as creatinine or blood urea nitrogen (BUN), indicate that the kidneys are not working efficiently to filter those substances out. Other tests check the presence of electrolytes - chemical compounds such as sodium and potassium that are critical to the body's healthy functioning. Coagulation studies determine how quickly the blood clots. A **complete blood count (CBC)** measures the size, number, and maturity of the different blood cells in a specific volume of blood. This is one of the most common tests performed. Red blood cells are important for carrying oxygen and fighting anemia and fatigue; the hemoglobin portion of the CBC measures the oxygen carrying capacity of the red blood cells while the hematocrit measures the percentage of red blood cells in the blood. White blood cells fight infection. Increased numbers of white blood cells, therefore, may indicate the presence of an infection. Platelets prevent the body from bleeding and bruising easily. **Urinalysis** breaks down the components of urine to check for the presence of drugs, blood, protein, and other substances. Blood in the urine (hematuria) may be the result of a benign (noncancerous) condition, but it can also indicate an infection or other problem. High levels of protein in the urine (proteinuria) may indicate a kidney or cardiovascular problem. **Cytogenetic analysis** involves analysis of blood or bone marrow cells for organizations of chromosomes to detect any genetic mutations.

**Tumor markers** are substances either released by cancer cells into the blood or urine or substances created by the body in response to cancer cells. Tumor markers are used to evaluate how well a patient has responded to treatment and to check for tumor recurrence. Research is currently being conducted on the role of tumor markers in detection, diagnosis, and treatment of cancers. According to the National Cancer Institute (NCI), tumor markers are useful in identifying potential problems, but they must be used with other tests for the following reasons: People with benign conditions may also have elevated levels of these substances in their blood. Not every person with a tumor has tumor markers. Some tumor markers are not specific to any one type of tumor. **Prostate-specific antigen (PSA)** is always present in low concentrations in the blood of adult males. An elevated PSA level in the blood may indicate prostate cancer, but other conditions such as benign prostatic hyperplasia (BPH) and prostatitis can also raise PSA levels. PSA levels are used to evaluate how a patient has responded to treatment and to check for

tumor recurrence. **Prostatic acid phosphatase (PAP)** originates in the prostate and is normally present in small amounts in the blood. In addition to prostate cancer, elevated levels of PAP may indicate testicular cancer, leukemia, and non-Hodgkin's lymphoma, as well as some noncancerous conditions. Ovarian cancer is the most common cause of elevated **CA 125**, but cancers of the uterus, cervix, pancreas, liver, colon, breast, lung, and digestive tract can also raise CA 125 levels. Several noncancerous conditions can also elevate CA 125. CA 125 is mainly used to monitor the treatment of ovarian cancer. **Carcinoembryonic antigen (CEA)** is normally found in small amounts in the blood, colorectal cancer is the most common cancer that raises this tumor marker. Several other cancers can also raise levels of carcinoembryonic antigen.

**Alpha-fetoprotein (AFP)** is normally elevated in pregnant women since it is produced by the fetus. However, AFP is not usually found in the blood of adults. In men, and in women who are not pregnant, an elevated level of AFP may indicate liver cancer or cancer of the ovary or testicle. Noncancerous conditions may also cause elevated AFP levels. **Human chorionic gonadotropin (HCG)** is another substance that appears normally in pregnancy and is produced by the placenta. If pregnancy is ruled out, HCG may indicate cancer in the testis, ovary, liver, stomach, pancreas, and lung. Marijuana use can also raise HCG levels. The **CA 19-9 marker** is associated with cancers in the colon, stomach, and bile duct. Elevated levels of CA 19-9 may indicate advanced cancer in the pancreas, but it is also associated with noncancerous conditions, including gallstones, pancreatitis, cirrhosis of the liver, and cholecystitis. The **CA 15-3 marker** is most useful in evaluating the effect of treatment for women with advanced breast cancer. Elevated levels of CA 15-3 are also associated with cancers of the ovary, lung, and prostate, as well as noncancerous conditions such as benign breast or ovarian disease, endometriosis, pelvic inflammatory disease, and hepatitis. Pregnancy and lactation also can raise CA 15-3 levels. The **CA 27-29 marker**, like CA 15-3, is used to follow the course of treatment in women with advanced breast cancer. Cancers of the colon, stomach, kidney, lung, ovary, pancreas, uterus, and liver may also raise CA 27-29 levels. Noncancerous conditions associated with this substance are first trimester pregnancy, endometriosis, ovarian cysts, benign breast disease, kidney disease, and liver disease. **Lactate dehydrogenase (LDH)** is a protein that normally appears throughout the body in small amounts. Many cancers can raise LDH levels, so it is not useful in identifying a specific kind of cancer. Measuring LDH levels can be helpful in monitoring treatment for cancer. Noncancerous conditions that can raise LDH levels include heart failure, hypothyroidism, anemia, and lung or liver disease. **Neuron-specific enolase (NSE)** is associated with several cancers, but it is used most often to monitor treatment in patients with neuroblastoma or small cell lung cancer.

Acne is most common in teens but can strike at any age. Almost 100 percent of people between 12 and 17 years old have at least an occasional blemish. More than 40 percent of cases are severe enough to require treatment by a doctor. About 15 million people in the United States have some form of eczema, including 10 to 20 percent of babies. In about half of these babies, the condition will largely clear up between the ages of 5 and 15. This condition usually appears during infancy. About 5 percent of the U.S. population has foot infections, including athlete's foot, other fungal infections and warts every year. Psoriasis affects more than 7 million Americans, about 2.6 percent of the population. More than 150,000 new cases are reported every year, 20,000 of them in children under 10. It is most commonly diagnosed between ages 15 and 35. About 1 to 2 percent of the world's population, 40 to 50 million people, suffer from vitiligo, 2 to 5 million in the U.S. It generally develops before age 40 and affects all races and genders equally. Most skin cancer is non-melanoma cancer, such as basal or squamous cell

carcinoma. More than 1 million of these cases are diagnosed every year. About 54,000 melanomas are diagnosed every year, causing 7,500 deaths. About 2,000 die from non-melanoma skin cancer. Skin cancer is the most common cancer. About 1.5 million Americans have a form of lupus. Lupus is much more prevalent among people of color, and 90 percent of cases occur in women. Systemic lupus usually develops between ages 15 and 45 (Davenport '03: 102, 103).

The basic primary lesions described in dermatology are: **Macules** are up to 1 cm in size, circumscribed, flat discolorations of the skin: Examples: freckles, flat nevi. **Patches** are larger than 1 cm, circumscribed, flat discolorations of the skin. Examples: vitiligo, senile freckles, measles rash. **Papules** are up to 1 cm in size, circumscribed, elevated, superficial, solid lesions. Examples: elevated nevi, warts, lichen planus. A wheal is a type of papule that is edematous and transitory. Examples: hives, insect bites. **Plaques** are larger than 1 cm, circumscribed, elevated, superficial, solid lesions. Examples: mycosis fungoides, localized neurodermatitis. **Nodules** range to 1 cm in size and are solid lesions with depth; they may be above, level with, or beneath the skin surface. Examples: nodular secondary or tertiary syphilis, epitheliomas, xanthomas. **Tumors** are larger than 1 cm, solid lesions with depth; they may be above, level with, or beneath the skin surface. Examples: tumor stage of mycosis fungoides, larger epitheliomas. **Vesicles** range to 1 cm in size and are circumscribed elevations of the skin containing serous fluid. Examples: early chickenpox, zoster, contact dermatitis. **Bullae** are larger than 1 cm, circumscribed elevations containing serous fluid - blisters. Examples: pemphigus, second-degree burns. **Pustules** vary in size and are circumscribed elevations of the skin containing purulent fluid. Examples: acne, impetigo. **Petechiae** are up to 1 cm in size and are circumscribed deposits of blood or blood pigments. Examples: certain insect bites and drug eruptions. **Purpura** is a larger than 1 cm circumscribed deposit of blood or blood pigment in the skin. **Scales** (squamae) are shedding, dead epidermal cells that may be dry or greasy. Examples: dandruff, psoriasis. **Crusts** are variously colored masses of skin exudates. Examples: impetigo, infected dermatitis. **Excoriations** are abrasions of the skin, usually superficial and traumatic. Examples: scratched insect bites, scabies. **Fissures** are linear breaks in the skin, sharply defined with abrupt walls. Examples: congenital syphilis, athlete's foot. **Ulcers** are irregularly sized and shaped excavations in the skin extending into the corium. Examples: stasis ulcers of legs, tertiary syphilis. **Scars** are formations of connective tissue replacing tissue lost through injury or disease. Keloids are hypertrophic scars. **Lichenification** is a diffuse area of thickening and scaling with resultant increase in the skin lines and markings. Several combinations of primary and secondary lesions commonly exist on the same patient (Sauer '85: 17, 18).

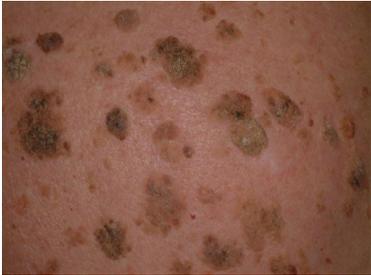
**Diagnosis** of a skin trouble localized to one part of the body generalization is the rule. In diagnosing a rather generalized skin eruption, the following three mimicking conditions must be considered (1) drug eruption, (2) contact dermatitis, and (3) secondary syphilis. By region: **Scalp**: Seborrheic dermatitis, contact dermatitis, psoriasis, folliculitis, pediculosis, and hair loss due to the following: male or female pattern, alopecia areata, tinea, chronic discoid lupus erythematosus, post pregnancy, or trichotillomania. **Ears**: Seborrheic dermatitis, psoriasis, infectious eczematoid dermatitis, senile keratosis, and rarely, fungal infection. **Face**: Acne, rosacea, impetigo, contact dermatitis, seborrheic dermatitis, folliculitis, herpes simplex, and less commonly, lupus erythematosus and actinic dermatitis. **Eyelids**: Contact dermatitis due to fingernail polish or hair sprays, seborrheic dermatitis or atopic eczema. **Posterior Neck**: Neurodermatitis, seborrheic dermatitis, psoriasis, or contact dermatitis. **Mouth**: Aphthae, herpes simplex, geographic tongue, contact dermatitis, and less frequently syphilis, lichen planus and pemphigus. **Axillae**: Contact dermatitis, seborrheic dermatitis, hidradenitis suppurativa, and less

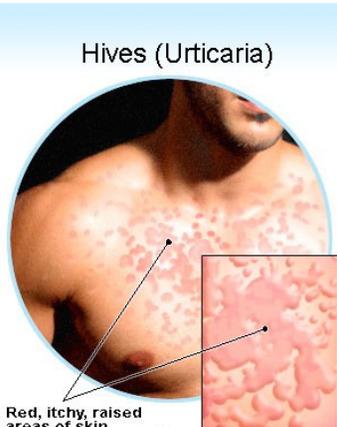
commonly, erythrasma, acanthosis nigricans, and Fox-Fordyce disease. **Chest and Back:** Tinea versicolor, pityriasis rosea, acne, seborrheic dermatitis, psoriasis, and secondary syphilis. **Groin and Crural areas:** Tinea infection, candida infection, bacterial intertrigo, scabies, pediculosis, and granuloma inguinale. **Penis:** Contact dermatitis, fusospirochetal and candida balanitis, chancroid, herpes simplex, primary and secondary syphilis, and, less frequently, scabies and balanitis xerotica obliterans. **Hands:** Contact dermatitis, dyshidrosis, id reaction to fungal infection of the feet, atopic eczema, erythema multiforme, secondary syphilis, and fungal infection. **Cubital Fossae and Popliteal Fossae:** Atopic eczema, contact dermatitis and prickly heat. **Elbows and Knees:** Psoriasis, xanthomas, and, occasionally, atopic eczema. **Feet:** Fungal infection, primary or secondary bacterial infection, contact dermatitis from footwear or foot care, and less frequently, psoriasis, atopic eczema, erythema multiforme and secondary syphilis (Sauer '85: 15-23).

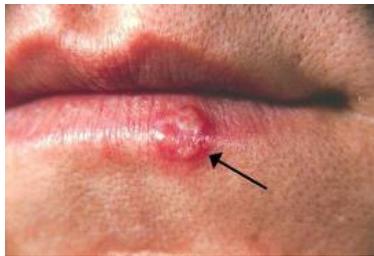
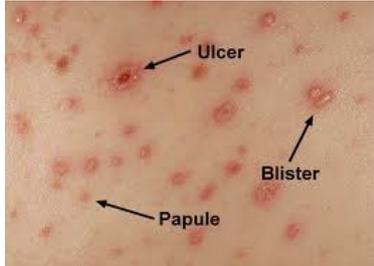
Certain dermatoses have an increased incidence in various seasons of the year, winter being the busiest season for dermatologists. **Winter:** Atopic eczema, contact dermatitis of hands, psoriasis, seborrheic dermatitis, nummular eczema, winter itch and dry skin (xerosis), and rarely ichthyosis. **Spring:** Pityriasis rosea, dyshidrosis, erythema multiforme (Hebra), and Acne (flares). **Summer:** Contact dermatitis due to poison ivy and oak, tinea of the feet and the groin, candida intertrigo, miliaria or prickly heat, impetigo and other pyodermas, actinic dermatitis, insect bites, tinea versicolor (noticed after suntan), and uncommonly Darier's disease and epidermolysis bullosa. **Fall:** Winter itch, senile pruritis, atopic eczema, pityriasis rosea, contact dermatitis due to ragweed, tinea of the scalp (schoolchildren) and acne (flares). In least developed and **war ravaged areas** of the world there is an increased incidence of: Scabies, pediculosis, syphilis and other sexually transmitted diseases, bacterial dermatoses, jungle rot in tropical climates: tinea of the feet and the groin, pyoderma, dyshidroses, and miliaria. Some skin diseases are seen with **greater frequency in blacks** than whites: Keloids, dermatosis papulosa nigra, pyodermas of legs in children, pigmentary disturbances from many causes, both hypopigmented and hyperpigmented, traumatic marginal alopecia (from braids and from heated irons used in hair straightening), seborrheic dermatitis of scalp, aggravated by grease on hair, ingrown hairs of beard, acne keloidalis, annular form of secondary syphilis, granuloma inguinale and Mongolian spots. Certain skin conditions **rarely seen in blacks:** Squamous cell or basal cell epitheliomas, actinic keratosis and psoriasis (Sauer '85: 23-28).

### Common Skin Diseases

Image	Diagnosis	Treatment
	<p>Eczema is an inflammation of the skin that causes the sensation of itch and makes the sufferer want to scratch. An alternative name for eczema is dermatitis.</p>	<p>Topical hydrocortisone or corticosteroids are usually the most effective treatment.</p>
	<p>Impetigo is a common crusty, weeping, superficial bacterial infection seen most often in children.</p>	<p>Impetigo responds well to antibiotics, either applied as an ointment to the skin surface or as a syrup given by mouth for a few days. Staphylococcal scalded skin</p>

		<p>syndrome lesions are treated with Neo-Polycin or other antibiotic ointment with Sulfur, ppt. 4% for 3 days after the lesions apparently have disappeared. Systemic antibiotic therapy with oral penicillin or erythromycin in children and doxycycline in adults for 10 days would be effective.</p>
	<p><b>Acne vulgaris</b> is a very common skin condition of adolescents and young adults due to hormones. It is characterized by any combination of comedones (blackheads), pustules, cysts, and scarring of varying severity on the face and neck and, less commonly, on the back, the chest, and the arms.</p>	<p>Affected areas should be washed twice a day with a washcloth and Dial soap. Benzoyl peroxide gel (5% or 10%) (Benzagel, Desquem-X, Panoxyl, Persa-Gel, and others). Resulin lotion (Almay), Sulfacet-R (Dermik), Komed lotion (Barnes-Hind), Acne-Aid Cream (Stiefel), Acno lotions (Baker-Cummins), and Rezamid lotion (Dermik). Tretinoin gel (0.025%) (Retin-A) q.s. 150 applied locally once a day. Isotretinoin (Accutane), for severe, scarring, cystic acne is given 1.0 mg/kg/day given for 4 to 5 months. The hormonal combination most commonly prescribed for acne is Dianette, starting 5 days after the period has begun and continuing for 21-22 days.</p>
	<p>Keratosis, actinic or senile, appear mainly after the age of 50 due to chronic sun and wind exposure. Prickle cell epitheliomas arise in an appreciable percentage of actinic keratosis.</p>	<p>5-Fluorouracil solution (Efudex 2% or 5%, fluoroplex 1%) applied to all sun-damaged area for 2 to 4 week. Complete blocking of the sun rays is desired for prevention. Moisturizer is the mainstay treatment of aging skin.</p>

<p>Hives (Urticaria)</p>  <p>Red, itchy, raised areas of skin © 2007 MedicineNet, Inc.</p>	<p>Hives (Urticaria) are vascular dermatoses. Poison oak, ivy or sumac should be highly suspected. Penicillin is a common cause of acute hives, but any other drug, can cause the reaction. Common food allergies are seafood, strawberries, chocolate, nuts, cheeses, pork, eggs, wheat, and milk.</p>	<p>Treat with Hydrocortisone 1/2% and prednisone, 5 mg or other corticosteroid</p>
 <p>Copyright © 2000. All Rights Reserved. UBC Dermatology <a href="http://www.derm.ubc.ca">http://www.derm.ubc.ca</a></p>	<p>Bullous diseases such as Erythema multiforme bullosum has no known cause, clinically one sees large vesicles and bullae usually overlying red, irislike macules. It can last from days to months. Fresh tissue biopsies must be examined for deposits of immune reactants, immunoglobulins (ig) and complement components, at or near the basement membrane zone.</p>	<p>Corticosteroids orally and by injection are the single most effective drugs in use today.</p>
	<p>Aphthous stomatitis (Canker sores) are common, painful, superficial ulcerations of the mucous membranes of the mouth. One or more lesions develop at the same time and heal without scarring in 5 to 10 days. They can recur at irregular intervals. Common conditions are infectious diseases, herpes simplex and Fordyce condition. Chocolate, nuts and fruits can precipitate the lesions.</p>	<p>Herpes is treated with Acyclovir. Kenalog in Orabase (prescription needed) applied locally before meals will relieve some of the pain. Doxycycline 100 mg therapy, in oral suspension with water, swished in the mouth for 2 minutes and then swallowed, daily, is quite healing.</p>

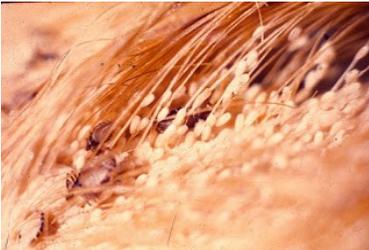
	<p><b>Furuncle</b> (boil) is an extensive infection of the hair follicle, usually due to <i>Staphylococcus</i>. A <b>carbuncle</b> is an extensive infection of several adjoining hair follicles that drains with multiple openings onto the skin surface. Fatal cases were not unusual in the preantibiotic days.</p>	<p>It is treated with Burow's solution hot packs, incision and drainage, oral antistaphylococcal penicillin, such as dicloxacillin, for 5 to 10 days. Oral doxycycline therapy 100 mg for weeks, as for acne patients, is very effective in breaking the cycle of recurrent cases.</p>
	<p><b>Leprosy</b> or Hansen's disease is to be considered in the differential diagnosis of any skin granulomas. It is endemic in the southern part of the United States and in semitropical and tropical areas the world over. The causative organisms is <i>Mycobacterium leprae</i>.</p>	<p>Dapsone (diaminodiphenyl sulfone, DDS), rifampin, and isoniazid are all quite effective</p>
	<p><b>Herpes simplex</b> An acute, moderately painful, viral eruption of a single group of vesicles that commonly occurs around the mouth or the genitalia. Type 1 HSV is associated with most nongenital herpetic infections. Type 2 HSV occurs chiefly in association with genital infection and is venereally transmitted.</p>	<p>Treatment is Acyclovir (Zovirax) therapy 200 mg 5 capsules a day for 5 days, in divided doses every 4 hours while awake. Zovirax ointment (5%), Neo-Synalar or other antibiotic-corticosteroid ointment and Burow's solution wet compress for 20 minutes three times a day to relieve much of the pain and irritation</p>
	<p>Chickenpox and zoster are thought to be caused by the same virus. New crops of vesicles may appear for 3 to 5 days. The vesicles then dry up and form crusts, which take 3 weeks, on the average, to disappear. The general health is seldom affected, except for low-grade fever and malaise. Recurrences are rare.</p>	<p>Treatment consists of alcoholic white shake lotion that may be (0.25%) menthol. triamcinolone, 4 mg, 1 tablet for 6 days, then 2 tablets every morning. Prednisone, 10 mg, 2 tablets every morning for 6 days, then decrease dose slowly as symptoms subside. Benadryl hydrochloride elixir 1 teaspoon for moderately severe itching</p>



Warts, or **verrucae** are very common small tumors of the skin. The human papillomavirus (HPV) is a DNA virus. There are 30 to 40 types of HPV that will affect an estimated 75% of 80% of males and females in their lifetime. For most, HPV clears on its own, but, for others HPV could cause cervical cancer in females and other types of HPV could cause genital warts in both males and females.

Single small (under 6 mm) warts are best removed by electrosurgery. No dressing should be applied. The site will heal in 5 to 14 days with only minimal bacterial infection and scar formation. Warts around the nails have a high recurrence rate, and cure usually requires removal of part of the overlying nail. Liquid nitrogen therapy is simple, effective but moderately painful, admonished to freeze lightly and not deeply. Alternatively, Salicylic acid (10%) in flexible collodion 30.0 may be applied to warts every night for 5 to 7 nights. The dead tissue can then be removed with scissors. Another form of treatment for multiple warts or warts in children is a mild corticosteroid cream 150.0 applied in very small quantity to each wart at night, then cover the wart with Saran Wrap or Blenderm tape. Gardasil helps protect against 4 types of HPV. In girls and young women ages 9 to 26 Gardasil helps protect against 2 types of HPV that cause about 75% of cervical cancer cases, and 2 more types that cause 90% of genital warts cases. In boys and young men ages 9 to 26 Gardsasil helps protect against 90% of genital warts cases.

	<p>Athlete's foot (tinea pedis) Most vesicular, acute fungal infections are due to <i>Trichophyton mentagrophytes</i> and respond readily to treatment with clotrimazole athlete's foot crème. The chronic scaly type of infection is usually due to <i>T. rubrum</i> and is exceedingly difficult, if not impossible, to cure.</p>	<p>Treatment involves hygiene, debridement, the skipping off the tips of the blister enabling pus to drain out and medication to reach the organisms. The edges of any blister should be kept trimmed, since fungi spread under these edges. Neosporin or other antibiotic ointment and sulfur (antifungal) ppt. 5% may be applied locally to feet after soaking. Subsequent treatment should include an antifungal crème such as clotrimazole, Lotrimin, Monistat-Derm, Loprox, Spectazole, Tinactin, Halotex, Desenex, Mycelex and so on. A corticosteroid, such as Lotrisone cream (Schering) can be beneficial.</p>
	<p><b>Tinea versicolor</b> is a moderately common skin eruption the skin does not tan when exposed to sunlight. The causative agent is a lipophilic yeast, <i>Pityrosporum orbiculare</i>, which as a hyphae form called <i>Pityrosporum</i> or <i>Malassezia furfur</i>. A scraping of the scale is placed on a microscopic slide, covered with a 20% solution of potassium hydroxide and a coverslip will show the hyphae very thin mycelia filaments are seen under low power.</p>	<p>Treated with Selenium Suspension 2 ½% 120.0 applied after bathing and drying. Bathe again in 24 hours and wash off the medicine. Repeat procedure again at weekly intervals for four treatments. Recurrences can be re-treated. Depigmented spots may remain after the tinea is cured, but if desired, can be tanned by gradual exposure to sunlight or ultraviolet light</p>

 <p>Gastrointestinal (GI) candidiasis</p>	<p><b>Candidiasis</b> is a fungal infection caused by <i>Candida albicans</i> that produces lesions in the mouth (thrush or perleche, vagina, skin, nails, lungs or the gastrointestinal tract or occasionally a septicemia, in patients on long-term, high dose antibiotic therapy and in those who are immunosuppressed. Since <i>C. albicans</i> exists commonly as a harmless skin inhabitant, the laboratory findings of this organism is not adequate proof of its pathogenicity and etiologic role.</p>	<p>For infections of the GI and mouth OTC anticandidal remedies are usually sufficient and without ill effect. For chronic mucocutaneous candidiasis, ketoconazole can heal dramatically. Mycostatin vaginal tablets 100,000 units inserted into the vagina. Or Monostat-Derm lotion or Sulfur, ppt. 5%, Hydrocortisone 1% and Mycostatin cream 30.0. Apply antifungal imidazole type solution (Lotrimin or Mycelex Solution 1%) to base of nail for several weeks.</p>
	<p><b>Pediculosis</b>, lice infestation, affects persons of all ages because of lack of cleanliness and infrequent changes of clothing or STD. Three clinical entities are produced (1) infestation of the hair by the head louse <i>Pediculus humanus capitis</i>, (2) infestation of the body by <i>P. humanus corporis</i> and (3) infestation of the pubic area by the pubic louse <i>Phthirus pubis</i>. Since lice bite the skin and live on the blood. Storage of headwear for 30 days will destroy the lice and the nits.</p>	<p>Treatment for <i>Pediculosis capitis</i> and <i>P. pubis</i> is lindane shampoo (Kwell or Scabene) 60.0 shampoo and comb hair thoroughly, leave on the hair for 4 minutes. Shampoo again in 3 days. For secondary scalp infections trim hair as much as possible, shampoo once a day with an antiseborrhea-type shampoo. Neosporin or other antibiotic ointment. Change and clean bedding and headwear after 24 hours of treatment. <i>Pediculosis corporis</i> is treated with phenol (0.5%) in calamine lotion 120.0 applied locally for itching.</p>
	<p><b>Scabies</b> is a parasitic infestation of burrows caused by the female of the mite <i>Sarcoptes scabiei</i> measures approximately 2 mm in length and can be hidden by the secondary eruption. Itching is intense, particularly at night. The mite can persist for months and years (seven-year itch) in untreated, unclean individuals. The</p>	<p>Apply lindane lotion (Kwell or Scabene) to the entire body from the neck down. Old clothes may be reworn. Do not bathe for 12 to 24 hours after application. After 24 hours bathe carefully and change to clean clothes and bedding. Itching may persist for a few days or even for 2 to 3 weeks in spite of the destruction of the mite. For</p>

	<p>female scabies mite, ova and fecal pellets may be seen in curreted burrows examined under the low-power magnification of the microscope.</p>	<p>itching apply sulfur (4%), camphor (1%) in Alcoholic white shake lotion or Eurax cream that has scabicial power and antipruritic action</p>
	<p><b>Psoriasis</b> is a common, chronically recurring papulosquamous disease, characterized by varying sized whitish, scaly patches seen most commonly on the elbows, knees and scalp. The scale is usually thick and silvery and bleeds from minute points when it is removed by the fingernail. Psoriasis is notoriously chronic and recurrent. It is not contagious.</p>	<p>Psoriasis is treated with Fluorinated Corticosteroid Cream or Ointment q.s. 30.0 . For scalp lesions Pragmatar ointment 15.0 applied to scalp in water-washable base such as Unibase, Neobase, Dermovan, and so on). Selsun Suspensin 120.0, or a tar shampoo, twice a week. Triamcinolone (Kenalog) Spray 63 g applied to scalp with plastic tube applicator at night. Methotrexate therapy is used in cases of severe psoriasis, for instance psoriasis covering &gt;65% of the body surface, with good results.</p>
	<p><b>Discoid lupus erythematosus</b> is red, scaly, patches on the face, mainly in "butterfly" area, but also on scalp, ears, arms and chest, may not be symmetrical. Aggravated by intense sun exposure or radiation therapy. Twice as common in females. Laboratory findings are negative. <b>Systemic lupus erythematosus</b> produces red, mildly scaly, diffuse, puffy lesions, purpura is also seen. Systemic complications of nephritis, arthritis, epilepsy, pancarditis, hepatitis, and so on make life difficult. Leukopenia, anemia, albuminuria, increased sedimentation rate, positive ANA test, and biologic false-positive serologic test for</p>	<p>Treatment of discoid lesions includes the application of Fluorinated corticosteroid cream locally to lesions, but not on the face for long periods because atrophy and telangiectasia can develop. Sunscreen cream with SPF 15. Most cases of systemic lupus erythematosus respond rapidly to corticosteroid and supportive therapy, but the prognosis for life is poor</p>

	<p>syphilis are found.</p> <p><b>Chloasma</b> (Melasma) is an irregular hyperpigmentation of the skin that varies in shades of brown. The lesions usually occur on the sides of the face, forehead and sides of the neck. The disorder is slowly progressive, but remissions do occur. It is more obvious in the summer. The differential diagnosis must rule out drug eruption, hyperpigmentation due to hormones and secondary melanoderma.</p>	<p>Sunlight intensifies the pigmentation so a sunscreen should be used. Melanex solution 3% (Neutrogena) 30.0 or Eldopaque Forte Cream (elder) 30.0 can be applied locally. Stop if irritation develops. The treatment with either of these hydroquinone preparations should be at least 3 months. A salve containing 5% ammoniated mercury in white petrolatum can be prescribed is allergic contact reactions to hydroquinones occurs.</p>
	<p><b>Vitiligo</b> is irregular areas of depigmented skin with a hyperpigmented border. Most commonly the lesions occur on the face and the dorsum of hands and feet, but they can occur on all body areas. The disease is slowly progressive but remissions are frequent. It is more obvious during the summer. The cause is unknown, heredity is a factor in some cases.</p>	<p>The use of covering or staining preparation is recommended such as Covermak, Vitadye (Elder); walnut juice stain or potassium permanganate solution in appropriate dilution. Corticosteroid cream therapy is effective for early cases of vitiligo, especially when one is mainly concerned with face and hand lesions. Betamethasone valerate cream 0.1% (Valisone cream) can be prescribed for use on the hands for 4 months or so and for use on the face for only 3 months.</p>
	<p><b>Basal cell carcinoma</b> is the most common malignancy of the skin that occurs from the basal layer of the skin. Fortunately, it is not a metastasizing tumor, and the cure rate can be 100% if these lesions are treated early and adequately. There are four clinical types of basal cell epitheliomas (1) noduloulcerative, (2) pigmented, (3) fibrosin (sclerosing), and (4)</p>	<p>Surgical excision, electrodesiccation and curettage, cryotherapy and microscopically controlled "fresh-tissue" surgery are the available modalities. If the tumor is large a flap or skin graft may be necessary. <b>Curettage and cryotherapy</b> are most useful for small (&lt;10 mm diameter) BCC that is located on flat surfaces or tumors having depth no greater than the dermis or at</p>

	<p>superficial. The noduloulcerative basal cell epithelioma is the most common type. It begins as a small waxy nodule that enlarged slowly over the years. A central depression forms that eventually progresses into an ulcer surrounded by the pearly or waxy border.</p>	<p>most the upper subcutaneous layer. It appears that <b>cisplatin</b> has antitumor activity, singly or in combination with bleomycin or doxorubicin, has produced major regression of tumor in selected cases. <b>Premalignant lesions</b> of the skin are all amenable to treatment before invasive cancer develops. Actinic keratoses can be removed by excision, curettage or cryotherapy. For patients with multiple lesions, topical <b>5-fluorouracil (5-FU)</b> is effective, 1% to 5% 5-FU cream or gel is applied twice daily for 10 to 21 days or longer until marked erythema and crusting develop in the treated skin; the lesions are then allowed to slough and re-epithelialize.</p>
 <p data-bbox="201 1335 589 1373">Squamous Cell Carcinoma</p>	<p><b>Squamous cell carcinoma</b> is a rather common skin malignancy that can arise from an actinic keratosis or leukoplakia in the squamous layer of the skin. The grade of malignancy and metastasizing ability varies from grade I (low) to grade IV (high). Other terms for this tumor include prickle cell epithelioma and epidermoid carcinoma. Squamous cell carcinoma present as a rapidly growing nodule that soon develops a central ulcer and an indurated raised border with some surrounding redness. This type of lesion is the most malignant. The least malignant form has the clinical appearance of a warty, piled up growth, which may not ulcerate.</p>	<p>Treatment is the same as basal cell carcinoma</p>

	<p><b>Malignant melanoma</b> has four types. The most common is the <b>superficial spreading melanoma</b> which develops from an in situ lesions, it grows slowly with a resulting good prognosis. <b>Nodular melanomas</b> grow quite rapidly and have a poorer prognosis. <b>Acral lentiginous melanoma</b>, occurs on the palms, soles and around the nails, is the most common type seen in black patients, ulcerates and metastasizes rapidly, so that it has the poorest prognosis. <b>Lentigo maligna melanoma</b>, the least frequent type, develops from a lentigo maligna, occurs on the exposed areas of the body in the elderly, mainly on the forearms and face, grows slowly peripherally, and has a high survival rate.</p>	<p>Surgical resection is necessary. Eight-year survival varies with thickness in the following manner: 99% +/- 1% (&lt;0.85 mm); 93% +/- 2% (0.85 mm – 1.69 mm); 69% +/- (1.7 mm – 3.6 mm); and 38% +/- 6% (&gt;3.6 mm).</p>
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Credit: Google Images

Although many skin problems are immediately obvious to the trained eye and easy to diagnose, some can be more difficult to identify accurately. Sometimes a skin problem is an external sign of an internal illness such as liver disease or a cancerous tumor or a vitamin or mineral deficiency. For example, dry skin accompanied by hair loss might indicate an underactive thyroid gland; jaundice and spider nevi (red bumps with lines radiating out, resembling a spider's legs) may be symptoms of liver disease. Blood tests done in general practice include tests for anemia and kidney, liver and thyroid function and tests to blood for autoimmune diseases. If infection is suspected tiny samples of skin may be sent to the laboratory to fine out whether there are bacteria, viruses or fungi present. There are two main types of skin biopsies: punch biopsy and scalpel biopsy. Before either test, the area around the site of the biopsy is anesthetized using a local anesthetic injection such as lidocaine. A punch biopsy involves removing a cylinder of skin a tenth of an inch wide with a sharp instrument that bores a small hole into the skin. The sample is lifted and put into a preservative, then sent to a histopathologist for analysis. The cut on the skin is stitched or sealed with a diathermy needle. A scalpel biopsy is performed when a sample of tissue is required that is large enough to enable a comparison of normal and abnormal tissue. An ellipse of skin (shaped like an oval) that includes the area in question is removed, and the skin edges are then stitched together. A shave biopsy is very common and is performed by taking a very superficial slice of skin with a scalpel or razor blade. No stitches are required. Immunologic testing helps to determine exactly what is causing an allergic reaction (Davenport '03: 108, 109).

There are three types of skin tests: (1) intracutaneous, (2) scratch, and (3) patch. The intracutaneous tests and the scratch tests can have two types of reactions: (1) an immediate wheal reaction and (2) a delayed reaction. The patch test is left on for 48 to 72 hours, when the test is removed, the patient is considered to have a positive patch test if there is any redness or vesiculation under the site of the testing agent. A method of testing for allergy when food is suspected is to use the Rowe elimination diet. The procedure is to limit the diet to the following basic foods, which are known to be hypoallergenic: lamb, lemon, grapefruit, pears, lettuce, spinach, carrots, sweet potato, tapioca, rice and rice bread, cane sugar, maple syrup, sesame oil, gelatin, and salt. The patient is to remain on this basic diet for 5 to 7 days. Fungus examinations are a simple office laboratory procedure. They are done by scraping the diseased skin and examining the material directly under the microscope, culturing the material directly under the microscope, culturing the material and examining the grown culture under the microscope. The skin scrapings are obtained by abrading a scaly diseased area with a knife blade. The material is deposited on a slide and covered with a 20% aqueous potassium hydroxide solution and a coverslip, with Parker Super Quink, Permanent Black ink. The preparation on the slide can be heated, or allowed to stand for 15 to 60 minutes, to allow the keratin particles to dissolve and reveal the fungi more clearly. Using Sabouraud's media in 1 to 2 weeks a whitish or variously colored growth will be noted. The species of fungus can be determined grossly by the color and the characteristics of the growth in the culture tube.

**Biopsy** of questionable skin lesions is an important laboratory procedure in which benign and malignant lesions are preemptively removed, biopsied under a microscope. Biopsies may be done by surgical incision, punch biopsy (often without stitches) and scissors biopsy (the easiest). The biopsy specimen must be placed in appropriate fixative solution, usually 10% formalin. The stain most routinely used is hematoxylin and eosin. With this stain, the nuclei stain blue and collagen, muscles and nerves stain red. The cervical Papanicolaou smear is the most common form of cytodiagnosis. In dermatology, cytodiagnosis, known as the Tzanck test, is useful in bullous diseases (pemphigus), vesicular virus eruptions (herpes, and basal cell epitheliomas. In the case of a blister, remove the top with a scalpel or sharp scissors. Blot the excess fluid with a gauze pad. Then gently scrape the floor of the blister with a scalpel blade. Try not to cause bleeding. Make a thin smear of the cells on a clean glass slide. If you are dealing with a solid lesion, squeeze the material between two slides. The slide may be air dried, but it can also be fixed by dipping it four to five times in 95% ethanol. Stain the slide with Wright's stain, Giemsa's stain or hematoxylin and eosin. In addition to skin testing, fungus examination, biopsies and cytodiagnosis, there are certain tests for specific skin conditions (Sauer '85: 9-13).

The aim of **Tissue Processing** is to remove water from tissues and replace with a medium that solidifies to allow thin sections to be cut. Biological tissue must be supported in a hard matrix to allow sufficiently thin sections to be cut, typically 5  $\mu\text{m}$  (micrometres; 1000 micrometres = 1 mm) thick for light microscopy and 80-100 nm (nanometre; 1,000,000 nanometres = 1 mm) thick for electron microscopy. For light microscopy, paraffin wax is most frequently used. Since it is immiscible with water, the main constituent of biological tissue, water must first be removed in the process of dehydration. Samples are transferred through baths of progressively more concentrated ethanol to remove the water. This is followed by a hydrophobic clearing agent (such as xylene) to remove the alcohol, and finally molten paraffin wax, the infiltration agent, which replaces the xylene. Paraffin wax does not provide a sufficiently hard matrix for cutting very thin sections for electron microscopy. Instead, resins are used. Epoxy resins are the most commonly employed embedding media, but acrylic resins are also used, particularly where immunohistochemistry is required. Thicker sections (0.35 $\mu\text{m}$  to 5 $\mu\text{m}$ ) of resin-embedded tissue

can also be cut for light microscopy. Again, the immiscibility of most epoxy and acrylic resins with water necessitates the use of dehydration, usually with ethanol. After the tissues have been dehydrated, cleared, and infiltrated with the embedding material, they are ready for external embedding.

During this process the tissue samples are placed into molds along with **liquid embedding material** (such as agar, gelatine, or wax) which is then hardened. This is achieved by cooling in the case of paraffin wax and heating (curing) in the case of the epoxy resins. The acrylic resins are polymerized by heat, ultraviolet light, or chemical catalysts. The hardened blocks containing the tissue samples are then ready to be sectioned. Because **Formalin-fixed, paraffin-embedded (FFPE)** tissues may be stored indefinitely at room temperature, and nucleic acids (both DNA and RNA) may be recovered from them decades after fixation, FFPE tissues are an important resource for historical studies in medicine. Embedding can also be accomplished with **cryogenics** using frozen, non-fixed tissue in a water-based medium. Pre-frozen tissues are placed into molds with the liquid embedding material, usually a water-based glycol, OCT, TBS, Cryogel, or resin, which is then frozen to form hardened blocks. Sectioning can be done in limited ways. Vertical sectioning perpendicular to the surface of the tissue is the usual method. Horizontal sectioning is often done in the evaluation of the hair follicles and pilosebaceous units. Tangential to horizontal sectioning is done in Mohs surgery and in methods of CCPDMA.

**Chemical fixatives** are used to preserve tissue from degradation, and to maintain the structure of the cell and of sub-cellular components such as cell organelles (e.g., nucleus, endoplasmic reticulum, mitochondria). The most common fixative for light microscopy is 10% neutral buffered formalin (4% formaldehyde in phosphate buffered saline). For electron microscopy, the most commonly used fixative is glutaraldehyde, usually as a 2.5% solution in phosphate buffered saline. These fixatives preserve tissues or cells mainly by irreversibly cross-linking proteins. The main action of these aldehyde fixatives is to cross-link amino groups in proteins through the formation of methylene bridges (-CH<sub>2</sub>-), in the case of formaldehyde, or by a C<sub>5</sub>H<sub>10</sub> cross-links in the case of glutaraldehyde. This process, while preserving the structural integrity of the cells and tissue can damage the biological functionality of proteins, particularly enzymes, and can also denature them to a certain extent. This can be detrimental to certain histological techniques. Further fixatives are often used for electron microscopy such as osmium tetroxide or uranyl acetate. Formalin fixation leads to degradation of mRNA, miRNA and DNA in tissues. However, extraction, amplification and analysis of these nucleic acids from formalin-fixed, paraffin-embedded tissues is possible using appropriate protocols. Frozen section (**cryosection**) is a rapid way to fix and mount histology sections. It is used in surgical removal of tumors, and allow rapid determination of margin (that the tumor has been completely removed). It is done using a refrigeration device called a cryostat. The frozen tissue is sliced using a microtome, and the frozen slices are mounted on a glass slide and stained the same way as other methods. It is a necessary way to fix tissue for certain stain such as antibody linked immunofluorescence staining. It can also be used to determine if a tumor is malignant when it is found incidentally during surgery on a patient.

For **light microscopy**, a steel knife mounted in a microtome is used to cut 4-micrometer-thick tissue sections which are mounted on a glass microscope slide. For **transmission electron microscopy**, a diamond knife mounted in an ultramicrotome is used to cut 50-nanometer-thick tissue sections which are mounted on a 3-millimeter-diameter copper grid. Then the mounted sections are treated with the appropriate stain. Frozen tissue embedded in a freezing medium is cut on a microtome in a cooled machine called a cryostat. It should use only microtome to ensure

the thickness of 1-10 um or micrometer. Biological tissue has little inherent contrast in either the light or electron microscope. **Staining** is employed to give both contrast to the tissue as well as highlighting particular features of interest. Where the underlying mechanistic chemistry of staining is understood, the term histochemistry is used. An example of staining in light microscopy are Carmine staining of a monogenean (parasitic worm). Hematoxylin and eosin (**H&E stain**) is the most commonly used light microscopical stain in histology and histopathology. Hematoxylin, a basic dye, stains nuclei blue due to an affinity to nucleic acids in the cell nucleus; eosin, an acidic dye, stains the cytoplasm pink. A commonly performed histochemical technique is the Perls Prussian blue reaction, used to demonstrate iron deposits in diseases like hemochromatosis. Uranyl acetate and lead citrate are commonly used to impart contrast to tissue in the electron microscope. There are hundreds of various **other techniques** that have been used to selectively stain cells and cellular components. One of the major applications involves marking peripheral tumors or surgical margins, in which a certain color of dye is applied to the posterior border of a sample, another to the anterior, etc., so that one can identify the location of a tumor or other pathology within a specimen. Other compounds used to color tissue sections include safranin, Congo red, fast green FCF, silver salts, and numerous natural and artificial dyes that were usually originated from the development dyes for the textile industry.

#### Common laboratory stains

Stain	Common use	Nucleus	Cytoplasm	Red blood cell (RBC)	Collagen fibers	Specifically stains
Haematoxylin	General staining when paired with eosin (i.e. H&E)	Orange, Cyan Blue or Green	Blue/Brown/Black	N/A	N/A	Nucleic acids—blue ER (endoplasmic reticulum)—blue
Eosin	General staining when paired with haematoxylin (i.e. H&E)	N/A	Pink	Orange/red	Pink	Elastic fibers—pink Collagen fibers—pink Reticular fibers—pink
Toluidine blue	General staining	Blue	Blue	Blue	Blue	Mast cells granules—purple
Masson's trichrome stain	Connective tissue	Black	Red/pink	Red	Blue/green	Cartilage—blue/green Muscle fibers—red
Mallory's trichrome stain	Connective tissue	Red	Pale red	Orange	Deep blue	Keratin—orange Cartilage—blue Bone matrix—deep blue Muscle fibers—red
Weigert's elastic stain	Elastic fibers	Blue/black	N/A	N/A	N/A	Elastic fibers—blue/black
Heidenhain's AZAN trichrome	Distinguishing cells from extracellular	Red/purple	Pink	Red	Blue	Muscle fibers—red Cartilage—blue Bone matrix—blue

stain	components					
Silver stain	Reticular fibers, nerve fibers, fungi	N/A	N/A	N/A	N/A	Reticular fibers—brown/black Nerve fibers—brown/black Fungi—black
Wright's stain	Blood cells	Bluish/purple	Bluish/gray	Red/pink	N/A	Neutrophil granules—purple/pink Eosinophil granules—bright red/orange Basophil granules—deep purple/violet Platelet granules—red/purple
Orcein stain	Elastic fibers	Deep blue	N/A	Bright red	Pink	Elastic fibers—dark brown Mast cells granules—purple Smooth muscle—light blue
Periodic acid-Schiff stain(PAS)	Basement membrane, localizing carbohydrates	Blue	N/A	N/A	Pink	Glycogen and other carbohydrates—magenta

Source: Wikipedia; Michael H. Ross, Wojciech Pawlina, (2006). *Histology: A Text and Atlas*. Hagerstown, MD: Lippincott Williams & Wilkins

Histology samples have often been examined by radioactive techniques. In **historadiography**, a slide (sometimes stained histochemically) is X-rayed. More commonly, **autoradiography** is used to visualize the locations to which a radioactive substance has been transported within the body, such as cells in S phase (undergoing DNA replication) which incorporate tritiated thymidine, or sites to which radiolabeled nucleic acid probes bind in *in situ* hybridization. For autoradiography on a microscopic level, the slide is typically dipped into liquid nuclear tract emulsion, which dries to form the exposure film. Individual silver grains in the film are visualized with dark field microscopy. Recently, **antibodies** have been used to specifically visualize proteins, carbohydrates, and lipids. This process is called **immunohistochemistry**, or when the stain is a fluorescent molecule, immunofluorescence. This technique has greatly increased the ability to identify categories of cells under a microscope. Other advanced techniques, such as nonradioactive *in situ* hybridization, can be combined with immunochemistry to identify specific DNA or RNA molecules with fluorescent probes or tags that can be used for immunofluorescence and enzyme-linked fluorescence amplification (especially alkaline phosphatase and tyramide signal amplification). **Fluorescence microscopy** and confocal microscopy are used to detect fluorescent signals with good intracellular detail. Digital cameras are increasingly used to capture histological and histopathological image.

## 2. Surgery

For centuries surgery has been the principal mode of therapy for cancer. Cancer is treated by surgery, radiation and chemotherapy. If tumors are relatively small, detectable, and in convenient sites, then surgeons can remove them, much as Leonides of Alexandria performed mastectomies for breast cancer in AD 180. That excision alone can eradicate the problem in some cases is not in doubt. But clearly it can and does fail. The real problem in cancer treatment comes from the spread of disease throughout and between tissues. Once a cancer clone has evolved to this stage of territorial exploration, the knife is redundant and the blunter instruments of ionizing radiotherapy and chemotherapy are used (Greaves '00: 239). Surgical treatment can result in a complete cure if the surgeon is able to remove every single cancer cell, this is easiest to achieve if the cancer is completely confined to a single tumor. In many cases, surgery is a very effective way of treating cancer, especially if the cancer is located in an accessible part of the body, so that the surgeon can reach all of the cancer and can safely remove a generous amount of the surrounding normal tissue, just to be certain. Cancer of the breast is often treated this way. Sometimes a cancer may be inoperable because of where it is growing. Tumors that have metastasized widely are also inoperable. Under such circumstances it is impossible to surgically remove all the cancerous tissue. A third condition that can make cancer inoperable is that the patient's general health is not adequate to survive the ordeal of major surgery.

In theory even a single cancer cell remaining in the body after surgery may be sufficient for the cancer to start growing again. It is therefore very common to follow surgical treatment of cancer with some other type of treatment that is designed to kill any remaining cancer cells. The two most widely used nonsurgical treatments involve the use of X-rays and chemicals to kill cancer cells. Earlier efforts were directed toward the destruction of the lesion rather than removal of the tumor. With improvements in surgical instrument and techniques and the introduction of anesthesia, surgery entered an era of remarkable achievements. However, these operations were accompanied by unacceptably high morbidity and mortality rates. It was only with the discovery of antibiotics to combat infection, a better understanding of fluid requirements in the surgical patients, and the widespread use of blood transfusions that surgery became an acceptable risk.

Indeed, the ready availability of surgery led to a period of increasingly radical surgery, while not all of these procedures have been totally discarded, it has become clear with the passage of time that survival rates for many cancers have not been improved by extending the scope of the operation and frequently the quality of the patient's remaining life has been markedly impaired by unduly radical procedures. Because of these shortcomings there has been a gradual retreat from radicalism in surgery. Additional weight has been given to a more conservative surgical approach by the growing benefits to be derived from other treatment modalities, i.e. radiation therapy and chemotherapy. A significant number of common cancers can be cured by surgical removal of the lesion. Failure to produce a higher cure rate is due to at least 4 recognized conditions: first, that the lesion has already manifested distant metastasis at the time the patient is first seen; second, that the cancer may be multicentric; third, that we may be unable to detect micrometastasis; and fourth, that there was inadequate removal of the tumor (Cole '86: 269, 270).

**Nonmelanoma skin cancers** are the most curable malignant tumors of human beings. Most tend to remain localized. Although basal cell carcinomas (BCC) are capable of metastasis only about 400 cases late in the course of inadequately controlled local disease have been reported. Squamous cell carcinoma (SCC) behaves more variably. The usual SCC arising in light-exposed areas of skin damaged by chronic ultraviolet exposure has a low incidence of metastasis. By

contrast SCC in shaded parts of the anatomy are much more likely to metastasize. SCC after radiation metastasizes in about 20% to 25% of cases. There is no staging system for nonmelanoma skin cancers because metastasis is so rare. The goal of therapy ought to be the expeditious removal of all viable tumor in a manner that ensures a satisfactory cosmetic result. Surgical excision, electrodesiccation and curettage, cryotherapy and microscopically controlled "fresh-tissue" surgery are the available modalities. If the tumor is large a flap or skin graft may be necessary. **Curettage and cryotherapy** are most useful for small (<10 mm diameter) BCC that is located on flat surfaces or tumors having depth no greater than the dermis or at most the upper subcutaneous layer. It appears that **cisplatin** has antitumor activity, singly or in combination with bleomycin or doxorubicin, has produced major regression of tumor in selected cases. **Premalignant lesions** of the skin are all amenable to treatment before invasive cancer develops. Actinic keratoses can be removed by excision, curettage or cryotherapy. For patients with multiple lesions, topical **5-fluorouracil** (5-FU) is effective, 1% to 5% 5-FU cream or gel is applied twice daily for 10 to 21 days or longer until marked erythema and crusting develop in the treated skin; the lesions are then allowed to slough and reepithelialize. Bowen's disease may be treated in a similar fashion, however, if 5-FU is employed it must be of longer duration and under occlusion. Leukoplakia occurring in the setting of chronic tobacco usage should probably be treated with **isotretinoin** (13-cis-retinoic acid), 1 mg to mg/kg/day for 3 months significantly decreases the number and size of leukoplakia lesions in such patients. Because of a potential side-effects an experienced physician is recommended, pregnancy is an absolute contraindication (Witte & Sober '90: 329-331).



**Rapid and adequate therapy** after diagnosis and staging of malignant melanoma after sun avoidance has proven ineffective is wide surgical excision and lymph node dissection; chemotherapy and immunotherapy are of limited effectiveness (Sauer '85: 319, 320). Any skin lesion undergoing change in the size, color or texture of a nevus or freckle, especially if a lesion bleeds or scales. A critical prognostic discriminant of malignant melanoma is the vertical extension of the primary lesion. A level I lesion is confined to the

epidermis and does not have metastatic potential, whereas a level V lesion permeates the subcutaneous fat with a grave prognosis. The thickness of the melanoma is measured from the stratum corneum to the deepest penetration of the tumor rather than the level of the invasion. Eight-year survival varies with thickness in the following manner: 99% +/- 1% (<0.85 mm); 93% +/- 2% (0.85 mm – 1.69 mm); 69% +/- (1.7 mm – 3.6 mm); and 38% +/- 6% (>3.6 mm). Surgical resection is necessary. The safety of conservative margins was demonstrated in a review of 1151 patients with lesions less than 1 mm thick. Sixty-two percent had resected margins of 2 cm or less. Only 8% recurred locally, and the median survival of this group was 3 years. In another study of 118 patients, the survival of patients with lesions less than 2 mm thick was not influenced by the extent of resection and there was no apparent survival advantage for lesions 2 mm or more in thickness by increasing the margins of resection to more than 3 cm. Survival was substantially decreased if these deeper lesions were excised with margins less than 2 cm. As a general guideline, lesions that are 1.69 mm or less can be safely excised with margins of 1 cm to 2 cm, whereas thicker lesions should be excised with 3 cm margins (Creagan '90: 323-328).

The view that many cancers may be cured by surgical excision is based on the widely held concept that at some time in the growth of a malignancy it is possible to completely encircle the lesion with the scalpel. To accomplish this, it is important that the lines of excision be far

enough away from the edges of the tumor to allow for a margin of normal tissue to be included with the lesion. Cancer frequently presents with microscopic invasion of adjacent tissue that is imperceptible to the operating surgeon and multiple frozen sections at the margins may be required to satisfactorily resolve the issue. Tumors can be dislodged into the vasculature during surgical procedure leading to the seeding of distant metastatic deposits. Therefore the blood supply leading to and from the tumor is interrupted early in the course of the dissection and manipulation of the cancer is kept to a minimum. Adequate removal of the tumor is intended to include those tissues adjacent to the lesion that harbor lymph vessels and their accompanying nodes. Furthermore, the primary lesion and the adjacent tissue should be removed *en bloc* to prevent mechanical seeding of tumor cells by instruments coming into direct contact with viable cancer cells (Cole '86: 270). The mainstays of treatment for localized or regionalized cancer remain surgical extirpation and radiotherapy. For systemic disease, either actual or suspected, systemic chemotherapy is necessary. The principle of surgery has been total ablation of the tumor when possible, or debulking of the mass when removal is not possible. Similarly, radiotherapy aims to kill all of the sensitive cells which the beam can reach. Partial debulking of the tumor may at some times not allow for wound healing. Similarly, radiotherapy that only decreases the mass may result in a necrotic draining foul-smelling residual tumor. Neither of these situations results in true palliation. Recurrent cancer may not allow further therapy with the same modality. Tissue tolerance may have been reached with the first dose of radiotherapy, or all of the tissue which could be safely sacrificed may have been resected during the initial treatment (Robson '86: 272).

The role of surgery in the diagnosis of cancer is well-established. With few exceptions, cancer diagnosis is based on a histological interpretation of tissue removed by surgical methods. The procedure may range in scope from the excision of a small fragment of a superficial tumor of the skin to an abdominal laparotomy or craniotomy to obtain sufficient tissue for pathological examination. In general, excisional rather than incisional biopsies of the primary tumors are to be preferred whenever possible. Excisional biopsy also minimizes the risk of disseminating tumor cells and, should the lesion prove benign, obviates the need for further surgery. Surgery or needle biopsy is also often required to establish the diagnosis of cancer recurrence or the presence of distant metastasis. Surgery may also be used to remove precancerous conditions such as leukoplakia of the buccal mucosa, carcinoma in situ of the cervix and chronic ulcerative colitis. The combination of various therapeutic modalities in the treatment of certain cancers has led to considerable improvement in their survival rates. The ultimate place of surgery in the multimodality approach to cancer treatment remains to be precisely defined. Generally speaking, surgery should be reserved for those patients presenting with solitary metastasis, where a considerable period of time has elapsed since resection of the primary lesion and the patient is otherwise in good health. To improve treatment other surgical techniques of cancer therapy have evolved, such as Mohs' chemosurgery, cryosurgery and electrosurgery (Cole '86: 270, 271).

**Mohs' chemosurgery** is a procedure which began using zinc chloride to fix tissues in situ. Mohs described a technique of removing a lesion in a bloodless field and microscopically controlling his resection with immediate frozen sections. This technique has been modified to a fresh-tissue technique so that in situ fixation is no longer practiced, and therefore, chemosurgery is a misnomer. The principle is to tangentially excise the tissue in layers, carefully code and map the specimens, and examine them microscopically. This allows one to follow the irregular contours of the cancer and to excise unidirectional pseudopod extensions, without excising great amounts of normal tissue unnecessarily. Mohs' chemosurgery is extremely useful for skin cancers which are recurrent after another treatment modality. It is also extremely useful in areas

where it is desirable to sacrifice only a minimal amount of normal tissue. Because the margin of resection is so narrow, tumors with a high metastatic incidence are not good choices for this technique. Also, the lesions which are multicentric are poor choices since the method relies on identification of contiguous cells. Complications were originally pain and tissue loss due to the chemical fixative resulting in a granulating wound often with infection. These complications have been avoided with the fresh tissue technique. The wound can now be immediately reconstructed or may leave a distorting scar (Robson '86:273, 274). In over 9,000 cases of basal cell carcinoma treated by Dr. Mohs with fixed tissue technique from 1955-1976, the 5 year cure rate is 99%. For Grade III squamous cell carcinoma the 5 year cure rate was 73% and for Grade IV it was 45%. Drs. Mohs and the statistics concede that fixed and fresh tissue techniques yield the same cure rate. When treating difficult, recurrent, invasive and destructive basal cell carcinomas, radiation therapy, electrodesiccation and curettage or surgical excision results in cure rates of only 50%. In primary tumors of the orbital region of the brain with radiation therapy the recurrence ranges up to 17.5% and with surgical excision up to 23%. In this region, Mohs' chemosurgery of primary tumors provides a 1% recurrent rate (Robinson '86: 279).

**Cryosurgery** usually involves the application of 2 or 3 rapid freeze-spontaneous thaw cycles to tumors easily accessible to a freezing apparatus, be it spray or probe. Ischemia appears to potentiate the cell damage caused by the freeze-thaw cycles. Cryonecrosis has been shown to be enhanced with the local administration of epinephrine. Skin cancers have been reported to have cure rates of 97-98% for small lesions and in the range of 90% or larger lesions. Invasive malignant melanoma, tumors of the scalp, sclerosing lesions and cancers of the nose are less amenable to freezing. Cryosurgery is particularly well suited for oral cavity cancers because of their relatively easy accessibility the fact that it can be performed under local anesthesia, and it can be repeated if necessary in the same or adjacent areas. It may be the most useful treatment for local recurrences after radiotherapy, especially in areas where surgical excision would be difficult. The immediate complications seen are pain, edema, and blister formation, airway obstruction, trismus, aspiration or insufflation of soft tissue. Delayed complications include a prolonged inflammatory response, a toxic febrile response and hemorrhage. Scarring can lead to hypopigmentation, hyperpigmented, atrophic or hypertrophic scars. These scars must be weighed against a neat to incisional scar left by a scalpel.

**Electrosurgery**, mostly involving CO<sub>2</sub> lasers, are another modality. The use of heat to treat malignancies is older than the use of cold. Electrosurgery was popularized in the 1920s. The concept originally thought to favor heat in the treatment of cancer is that the heat will seal lymphatics and blood vessels as the extirpation proceeds, thus minimizing the need for local implantation or spread of cancer, but these concepts have not withstood scientific scrutiny. Heat can act both to cut and to coagulate tissue. Slowly heating tissue will result in coagulation and heat damage. Rapid heating in excess of 100°C will cause vaporization of intracellular water resulting in an incision. The incision will be essentially bloodless, which is the major advantage of thermal knives. In large bulky vascular tumors, blood loss can be a major problem. Thermal knives can minimize blood loss. It is also useful in the resection of vascular organs such as the liver and palliative deblocking of unresectable lesions. The major complication is that excessive heat destroys more tissue than is necessary. The burned tissue must become necrotic and slough and this will always cause a delay in normal wound healing and repair and delayed hemorrhage can occur. Proper grounding of equipment and the patient are mandatory and proper credentialing is wise with the use of lasers (Robson '86: 274). Any lesion which can be exposed can be excised with a steel scalpel, the only advantage of lasers and electrosurgical units is the control of blood loss (Glover et al '86: 290).

The many **surgical treatments** for diseases and disorders of the skin can be broadly divided into two categories: those designed to treat large areas and those that enable pinpoint accuracy in order to remove tiny growths and other lesions without damaging the skin around them. Creams and lotions can cover extensive areas, as can phototherapy. When skin has been badly damaged, skin grafting is sometimes required. Doctors freeze, scrape, shave or burn off many types of benign growths and markings – or even vaporize them with a laser. For malignant melanomas, the preferred option is to cut out the tumor and surrounding tissue with a scalpel and 2 to 3 cm margin (Davenport et al '03: 111). A basic **cutaneous surgical pack** includes the following: (1) Webster or neurosurgery needle holder, (2) Adson forceps with teeth, (3) Frazier skin hook (two), (4) Metzenbaum dissecting scissors, (5) Stevens curved scissors, (6) Galde scissors, (7) Utility scissors, (8) Halsted mosquito hemostats (four), (9) Backhaus towel clips, 3 ½ inch (four), (10) Round toothpicks for marking skin, (11) Gauze sponges, (12) Cotton tipped applicators for point control of bleeding.

**Sutures** may be divided into two general groups, absorbable and nonabsorbable. The absorbable sutures are plain gut, chromic gut, polyglycolic acid (Dexon), polyglactin 910 (Vicryl), and polydioxanone (PDS). Gut sutures undergo degradation by phagocytosis, and the synthetic sutures (Dexon, Vicryl, and PDS) are hydrolytically degraded in the tissues. Plain gut maintains its tensile strength for 14 days, chromic gut for 21 to 25 days, and Dexon and Vicryl from 21 to 25 days. The newest absorbable suture, PDS, maintains tensile strength for 6 to 8 weeks. The frequently used nonabsorbable sutures are silk and nylon. Sutures of 6-0 silk are preferred for eyelids and lips so that there are no sharp irritating ends. The monofilament nylons such as Ethilon are general purpose sutures. Prolene, a polypropylene type of monofilament sutures, has the characteristics of an increased "memory" and high tensile strength. Usually 5-0 and 6-0 size sutures are used on the face. For very fine, delicate work 7-0 nylon may be indicated. With 7-0 nylon, it is easiest to use a Castroviejo needle holder. A number of different **stitches** are used, the buried subcutaneous stitch, simple stitch, vertical mattress stitch, horizontal mattress stitch, corner stitch (tip stitch, half-buried mattress), running intradermal stitch and running simple stitch. Sutures should be tied to coat the wound edges but not to strangulate. Most individuals err by tying too tightly. In tying vessels, use the smallest size suture that is practical.

It is absolutely necessary to take no aspirin or aspirin-containing products for 2 weeks before surgery since they interfere with blood clotting. Refrain from alcohol for 1 week before surgery. For electrocoagulation, a biterminal device such as a Bovie is used so that a current enters the patient through an active or coagulating electrode. Where tissue contact is made, heat is generated and coagulation occurs. Most cutaneous surgeries require only local infiltrative or regional block anesthesia. The standard agent, 1% lidocaine, is an effective and safe anesthetic in which allergic reactions are virtually unknown. By the addition of epinephrine, systemic absorption of lidocaine is lessened, the duration of action is markedly prolonged, and a local hemostatic effect is achieved. The available commercial preparations usually combine lidocaine with 1:100,000 epinephrine. The maximum recommended dosage of lidocaine with epinephrine is 500 mg, the equivalent of 50 ml of 1% solution (Sauer '85: 53, 54, 55).

**Incisions** should be planned so that they are parallel to or within wrinkle and smile lines. Another guide for camouflaging scars is to place incision lines at the boundaries of aesthetic and anatomical units. Incisions should be made vertical to the skin surface. An exception to the rule of vertical incisions is adjacent to the eyebrows where the incision should be angled away from the brow to avoid transecting hair follicles. The standard excision is the fusiform shape this is

often referred to as an ellipse. If the length-to-width ratio of the fusiform is less than 4:1 or if one side is longer than the other, redundant tissue will develop at the corner of the closure. The wound is closed along the lines of least tension. If the wound is too large for direct linear closure, reconstruction with flaps or grafts may be carried out. In the first hours, a coagulum forms over the wound. Between 12 and 72 hours, there are two spurts of mitotic activity and epidermal cells begin migrating across the wound. However, the dried crust over the wound is a barrier and the epidermal cells must form a new plane below the crust. This forms a shallow, linear depression in the healed incision. To prevent wound crusting and the resultant linear trough in the healed wound, an occlusive dressing is used. For such a dressing, either Dermicel tape or Vigilon is available. For most sized wounds, Dermicel is adequate. Benzoin is applied to the surrounding skin. A 1-inch wide strip of Dermicel is then applied over and along the incision. The adhesive on Dermicel tape also has bacteriostatic properties. The tape is left in place for 3 days. Guidelines for suture removal follow: Face 3 to 5 days, neck 6 to 8 days, back 10 to 14 days, abdomen 7 to 10 days, extremities 10 to 18 days. It is prudent to examine wounds 4 to 5 days after surgery, since this is when a wound infection is most likely to occur (Sauer '85: 58, 59).

Surgery is an essential part of the treatment plan for all patients with third-degree burns and for some patients with second-degree burns. The **burn wounds** must be covered with new skin both to prevent infection and to limit scarring, which may interfere with the person's ability to function. The principal surgical operation performed on burn patients is skin grafting. In this procedure, a sliver of the patient's skin is removed from a healthy, unburned area (the donor area) and attached to the area destroyed by the burn (the recipient area) by stitches, staples, or adhesive paper strips or simply by dressings. The recipient area must be prepared to accept the donor skin. This may be done either surgically, by excision, or by allowing the heat-damaged skin (the eschar) to separate naturally from the underlying, healthy tissue. **Excision** is performed on the areas of the burn that are not expected to heal on their own. In excision, the eschar is removed either tangentially or fascially. Tangential excision involves removing the eschar with a long razor blade in layers until all dead tissue is gone and the surface consists of healthy tissue. Excision down to the fascia involves removing the entire layer of damaged skin and underlying at down to the fascia – the tough covering over the underlying muscle. Excision promotes early healing and eliminates a source of infection. Despite its advantages, this technique is sometimes used reluctantly because the final appearance after removal of fat can be less pleasing, and the blood loss is disconcerting. Natural separation of the eschar takes three to five weeks. Once the eschar is removed, if there is not enough remaining dermis, which contains regenerating elements (epidermal cells in hair follicles and sweat glands), new skin will not grow. Multiple trips to the operating room are often required before all the eschar is removed and the entire burn wound is grafted (Munster '93: 21- 23).

Skin must be transferred from an unburned part of the body. The patient donates their own skin (**autograft**) in a surgical procedure in which the surgeon removes skin from unburned areas. Only a partial layer of skin is removed from the donor site, so the dermis that remains on the donor site will generate new epidermis. Donor sites can be any part of the body, but since they heal with scarring, inconspicuous areas are used first, such as the thigh, abdomen, trunk and scalp. The donor sites are treated with gauze dressings (dry or medicated, such as Xeriform and Scarlet Red) or plastic dressings (Opsite, Tegaderm, and others) or synthetic gauzes (Biobrane). Donor site healing is usually complete within 7 to 10 days. Once the donor site has healed, new skin grafts can be obtained or "harvested" from the same area. The skin from the donor site may be stretched to allow it to cover a larger area than it came from, a procedure called meshing. This

involves making small slits in the skin which allow it to expand like fish netting. Meshing allows blood and body fluids to drain from under the skin grafts and allows the skin to stretch over a greater area. Meshing works well but on widely meshed skin the mesh marks may be visible forever on the healed burn. When the burn wound covers a large area, the available donor areas (autograft) may not provide enough skin to cover the entire excised wound. An allograft or homograft is human skin donated from a deceased person which is stored after undergoing rigorous testing for transmittable disease in compliance with the standards of the American Association of Tissue Banks. These standards state that the donor's medical history must be screened and the donor tested for HIV and hepatitis virus. The skin is frozen and stored at - 80°C, to provide additional protection against contaminants. Eventually allografts will be rejected by the patient's immune system, but before this they will actually adhere to the wound as in the normal healing process. Allografts keep the wound closed until donor sites have healed sufficiently to allow re-harvesting or until cultured skin is available. Cultured skin, or cultured autograft, is a relatively new and expensive method of healing the wound that is used when the patient's own available skin graft donor sites are insufficient. To produce cultured autograft, a tiny piece of skin is taken from an unburned area of the patient's body and its cells are grown in layers in laboratory petri dishes. The skin grows in small sheets that are then applied to the burn. This method expands the patient's own epidermis from a 1-inch sample up to more than 250 yards of skin – a 10,000 fold increase – over a 30 day period. Cultured skin takes three weeks to grow, it is quite fragile and very expensive. Healed cultured skin is often very fragile, too, it is easily damaged and subject to blistering, since there is no underlying layer of dermis, but only epidermis covering the tissues underneath.

There is no true **artificial skin** yet. There are however many good temporary artificial wound coverings but all of them eventually must be replaced with autograft. The best of the artificial skins developed so far is two-layered product, the inside layer being biologic (that stays on the patient) and the outside being plastic (this part is replaced by autograft). The autograft replacing the plastic is much thinner than conventional autograft so that the donor site heals in 3 to 5 days instead of 7 to 10 days. Commercially processed pigskin and human fetal membranes are used by some surgeons as a temporary covering for the burn wound. Closing wounds with these dressings has the advantages of reducing the loss of protein fluid and electrolytes from the wound, decreasing pain in the wound, and facilitating the healing of partial-thickness burns. Furthermore, if the biologic dressing becomes adherent, it is a sign that the wound is ready to support an autograft. Grafts, auto or allo, are either left open to the air or are wrapped in dressings, sometimes with antibiotic solutions or creams applied. "Take down" is the first dressing change after the grafting procedure and occurs usually two to five days after the procedure. At this point "take" the amount of graft that is viable and adherent is estimated. The take is often expressed as a percentage of the grafted area. A take of more than 85 percent means the procedure was a success. Small open areas can heal in from the surrounding edges. If the take is less than 60 percent, another patching procedure usually must be performed. Grafted areas need to be protected from rubbing by clothing or activity. The healed or grafted skin may also be itchy and dry. Frequent application of moisturizers such as lanolin and Eucerin help make up for the absence of normal oil glands in the skin graft. Grafted skin will always look different from normal skin, healed skin grafts are redder or darker than surrounding skin and have irregular raised areas. Skin that has healed by itself or with skin grafting is less sensitive to touch and will always be somewhat more easily damaged than normal skin. The length of stay in the hospital can be as short as a few hours or as long as many months. The average length of stay in U.S. hospitals is 14 days (Munster '93: 23-27).

The body repairs itself by forming **scar tissue**. When an injury first occurs, certain of the body's blood cells are attracted to the wound to help rid it of dead and damaged tissue, foreign substances (such as dirt), and any bacteria that may have entered the wound. This initial phase of healing lasts for five to seven days and is called the inflammatory phase. Scar tissue is made up of collagen, a protein that is manufactured and deposited in the healing wound by a cell called a fibroblast. As the first phase of healing ends, fibroblasts migrate into the wound and start laying down collagen to form scar tissue. This second phase is called the proliferative phase. Particularly during the first six to eight weeks after injury, a large amount of collagen is formed, resulting in thick scars. Even as the collagen is being laid down, an enzyme called collagenase begins breaking down the collagen. Although this process starts soon after injury occurs, only after two or three months does a balanced state develop, in which the amount of collagen being removed is equal to the amount of collagen being formed. The stage in which the scar fades is known as the maturation phase, it can last up to two years following the injury. Some scars become pathological and cause physical problems for the burn patient early on and even after the body has tried to remodel the scar tissue during the maturation phase of healing. Most common pathological scar is the hypertrophic scar, that are raised, red and hard. The application of pressure causes the collagen to lay down more normally within the scar and results in a softer, flatter scar. Keloids are similar but grow beyond the bounds of the original wound. A third type of pathological scar occurs across a joint, limiting the movement of that joint. If non-operative treatments do not correct the problem a surgeon will cut across the contracture and extend the joint. Scars that remain an abnormal color for a long period of time are also considered pathological. Burn scars usually differ in color from normal skin early in the healing process and even long after the scar matures, frequently as long as 18 to 24 months. Gradually the color of the burn scar approximates the normal skin color, but it seldom completely matches. Dark-skinned individuals often have persistent depigmentation, resulting in patches of whiteness, or hyperpigmentation, resulting in extra-dark scars. A final category of pathological scars consists of those that are inadequate, most commonly scars that are thin and fragile, resulting in chronic reopening of the wound following minor trauma. Correcting the problem usually requires cutting away the inadequate scar and covering the area with split-thickness skin grafts or flaps in its place. Unless scars pose an urgent functional problem or endanger a vital structure, reconstructive surgery for functional problems is deferred for 6 to 12 months, and reconstructive surgery for the correction of disfigurement is delayed as long as 12 to 18 months after burn injury. Surgery performed on mature scars produces the best results, and the waiting period allows for scar maturation (Munster '93: 116-120, 122).

**Reconstructive surgery** is the aspect of plastic surgery whose goal is correction of dysfunction an disfigurement resulting from injury. Reconstructive surgery is surgery that deals with the repair or replacement of lost or damaged parts of the body. Reconstructive surgery for burn injuries usually consists of replacing the skin lost or disfigured by the injury in order to correct the pathological scars. Deforming scars are cut out (excised) and the wound is either closed (if sufficient skin exists) or covered with new skin, a procedure called resurfacing. Also in reconstructive surgery, contractures are released (cut across) and skin is placed in the resulting wound after the joint is extended. A graft is tissue that is completely removed from the body, disconnected from its blood supply, and replaced on a wound, where it lives by absorbing nutrients from the wound. The area from which tissue is taken is called the donor site. The recipient site is the wound in need of closure. Blood vessels from the wound generally grow into the graft within three or four days, resulting in the "take" of the graft. Whereas most burn wounds that need to be closed by skin graft surgery are covered with split-thickness skin grafts during acute burn recovery period, full-thickness grafts, composite grafts, and flaps are generally

used for reconstructive surgery. When a split-thickness graft is taken, only a portion of the dermis is removed with the epidermis, a full-thickness graft involves removing the entire thickness of the skin for use as a graft. Composite grafts contain more than one type of tissue, most commonly skin and cartilage from the ear, and are sometimes used to reconstruct facial features such as the nose, eyebrows, and upper lip. Split-thickness donor sites heal by epithelialization, but when a full-thickness or composite graft is taken, the donor site must be closed with sutures or, sometimes, a split-thickness graft. A flap is a tissue that maintains its blood supply when moved to another area of the body, they do not contract. A local flap is a flap that is moved to an area adjacent to its original donor site. A distant flap is a piece of tissue which is moved to an area that is not adjacent to the donor site. The most common way of maintaining the blood supply to a distant flap is to disconnect the blood supply to the flap from the original donor site and connect the flap's blood vessels into blood vessels close to the recipient site using microvascular surgery. This is called free flap (Munster '93: 122-124).

In **reconstructive surgery** burn scars are commonly moved to that they are hidden in the contours or resting skin tension lines (RSTL) of the face or body. Scars lying within or parallel to the RSTL are generally better hidden than scars that run perpendicularly to the RSTL. Local flaps are used whenever possible, because they provide the best color match, skin texture, and skin thickness for reconstruction. A Z-plasty is one of the most commonly used local flaps. With a Z-plasty, a long, straight line scar is broken into multiple broken lines. This makes the scar less visible and often reorients the scar into the natural lines of the skin. Another method of breaking along scar into multiple broken lines is a W-plasty, which is performed in broad, open areas of skin where there is an excess of tissue, such as the cheek. The limbs of the resulting W are aligned better with the RSTL of the face than the original scar and is less noticeable. A new technique for increasing the amount of local tissue available for flaps is tissue expansion, in which a deflated silicone balloon called a tissue expander is placed under normal skin next to the areas to be reconstructed. The balloon is inflated by injecting a saltwater solution into a valve on the balloon which can be felt through the skin. The inflation stretches the skin, and the body responds to this stretching by growing new skin. The procedure may be repeated several times, more saltwater being injected into the expander each time, until enough new skin is grown to reconstruct the adjacent defect after the tissue expander is removed. When the areas of burn scarring are extensive, full-thickness or split-thickness skin grafts are used to resurface large areas. These grafts also provide the best means of preserving fine facial features. Thick split-thickness skin is generally used for reconstructing the eyelid, for example, unless full-thickness eyelid skin is available from the eyelid on the opposite side. As a rule, the more dermis the graft contains, the less likely it is that the graft will change postoperatively. For most surgery performed to release contractures, full-thickness grafts are the first choice. Because the skull has no blood supply on its surface to support a skin graft, a flap that has its own vascular system must be placed in this area. This procedure is generally performed early in the course of recovery to prevent infection of the skull bone (Munster '93: 129, 124-128, 130).

**Skin replacement** of the face should be performed in aesthetic units, that is, grafts and flaps should be placed so that scars are located within naturally occurring lines of the face. The forehead is a surprisingly large expanse of skin, and although the lines run horizontally a vertical scar in the center of the forehead is often acceptable. When the patient has large forehead scars, the forehead must be resurfaced, generally by placing a thick split-thickness graft as an aesthetic unit (with the scars in the hairline). A hair-bearing full-thickness graft from the temple or behind the ear may yield an acceptable result for reconstruction of an eyebrow, but hair growth is usually sparse and unsatisfactory. The sparseness can be augmented using eyebrow pencil or by

medical tattooing. To allow the upper eyelids to move freely, artificial lubricants are applied to protect the patient's corneas until reconstructive surgery can be performed. To reconstruct eyelids, full-thickness skin from the eyelid of the other eye is the ideal replacement. More often, thick split-thickness skin is used to release contractures of the eyelids. The release of the eyelid will be overcorrected in surgery, and frequently this will make the eyelids appear large and droopy, but this overcompensation will correct itself in time, and the eyelids will appear more normal. Scars across the corners of the eyelid can restrict movement, they are corrected using Z-plasty flap techniques or skin grafts. False eyelashes or tattooed eyeliner can be used to substitute for eyelashes. Ear reconstruction is often difficult because of burn scarring next to the ear. When nearby normal skin is available this is used for reconstruction. Portions of the remaining ear can be used to reconstruct the general form of the ear. When the ear is totally missing, a vascularized deep tissue flap from under the scalp is used to cover a framework of rib cartilage, or sometimes plastic. This flap is subsequently covered with a skin graft. Prostheses that look very much like real ears are often the best solution when the entire ear is lost. As with the ear, reconstruction of the nose is difficult. Reconstruction involves releasing the scar contracture, making up the tissue, making up the tissue deficit caused by the burn, replacing the nasal lining in its anatomic location, and resurfacing the nose with local flaps, full-thickness grafts, or sometimes, a composite graft of skin and cartilage. When the nose is missing, skin for the forehead or from other areas of the body is placed over the cartilage framework to shape a new nose. Nasal prostheses are also available (Munster '93: 131, 132)

The mouth is a dynamic structure. Small linear contractures can be released by Z-plasty techniques. When large portions of the upper or lower lip are scarred, these areas must be replaced by skin graft applied as an aesthetic unit. Technically the area around the mouth consists of five aesthetic units. The upper lip consists of the dimple in the middle of the lip flanked by two lateral aesthetic units extending out to the nasolabial crease (the groove between the nose and the corners of the mouth). The lower lip is an inverted U-shaped aesthetic unit surrounding the prominence of the chin itself, which is the fifth aesthetic unit. The contour of the dimple in the upper lip can be duplicated by using a composite graft of ear skin and cartilage. When the cheeks are scarred, the skin may be discolored and the person may lose facial expression. When tightness occurs as a result of contractures, and when large areas of hypertrophic scarring are present, the cheek is often resurfaced using a full-thickness skin graft or a flap of skin from the neck or shoulder. A tissue expander may be used to expand donor tissue. Small hypertrophic scars and contractures can be corrected or improved through excision of the scars and subsequent closure with Z-plasty or W-plasty (Munster '93: 132, 133).

Burn scar contractures can develop across any of the major joints of the body, though they are most common in the neck, across the shoulder joint, or armpit area (axilla) and on the hands, wrists, elbows, knees and feet. Early burn physical therapy strives to prevent these contractures. If the contractures are significant between 6 and 12 months after the burn, reconstructive surgery is performed to release the contractures. A neck contracture is most frequently released through a simple incision and skin grafting that allows the neck to extend, although Z-plasties and other local flap techniques are also used. The skin graft is placed over the resulting wound, with the size of the graft usually being quite large. Grafts generally take well in neck tissues, with the exception of grafts over the larynx, the movement of which interferes with the healing of the graft. The appearance of tracheostomy scars can be improved through reconstructive surgery. Loose skin on the back of the hand and sensitive, thicker skin on the palm cover the tendons, ligaments, nerves, muscles, bones and joints. Contractures of these many joints and loss of skin sensitivity can interfere with the interactions that allow the hand to function as a fine instrument.

Contractures of the fingers are released using grafts and flaps, and sometimes the ligaments around the joints must be released as well, in a surgical procedure called a capsulectomy, in which a portion of the joint capsule is removed. Amputation of fingers is often necessary. The most common effect of burn scars on the feet is contracture of the dorsum (the top or back) of the foot, which causes the toes to be pulled back, resulting in an unnatural gait. When a child's feet have been burned the growth of the foot may be disturbed. Release and grafting usually correct the contracture and the hyperextension of the toes, leaving webbing between the toes. The webbing rarely interferes with function and can be left in place until the child is much older and desires reconstructive surgery. Scar contractures of the trunk can interfere with movement. These contractures are released using grafts or local flaps. When hypertrophic scarring develops over the large areas of the chest, back and abdomen, resurfacing is not possible, since it would require too large a skin graft. Cultured skin autografts are already being used for the treatment of severely burned patients (Munster '93: 133-136).

A chemical peel employs a caustic chemical to destroy the epidermis. The peeling solution is painted onto the skin and then removed after a precisely timed interval. Over the next few days, the dead skin peels away; the skin then heals and the overall result is to give the skin a smoother, tighter, less scarred appearance. **Trichloroacetic acid (TCA)** at a concentration of 10 percent left on the skin for several minutes will result in tingling and a little discomfort, some facial redness, and the subsequent sloughing of skin cells from the uppermost layer of the skin. TCA at 30-50 percent provides a medium-depth chemical peel. The deeper penetration of the dermis results in greater bruising, swelling and redness. Treatment at this level of concentration is an effective way of treating a variety of skin lesions and markings including warts, liver spots, acne scars, and xanthelasma – fatty deposits around the eyes. **Alpha hydroxy acids (AHAs)** are peels that produce a superficial peel in lower concentrations and a medium chemical peel in higher concentrations. Phenol produces a deep chemical peel that gives the most dramatic results but requires the longest recovery time and removes pigmentation, so the treated skin will be permanently paler than untreated skin. **Dermabrasion** involves abrasion of the skin to remove superficial lesions or to soften depressed scars (Davenport et al '03: 126).

The use of cold to kill tissue is known as **cryotherapy** or cryosurgery. The most common freezing agent used today is liquid nitrogen. The liquid nitrogen is applied for 10 to 209 seconds to the site of the lesion, using either a spray gun from a distance of about a half-inch or a cotton swab. Typical conditions that can be treated this way are warts, freckles, liver spots on the back of hands and some skin precancers and cancers. Cryotherapy can be painful and will cause inflammation and in some cases blistering. Occasionally, cryotherapy can cause mild scarring or a permanent change in color of the treated skin especially in dark-skinned patients.

Another technique that allows the removal of simple skin lesions is **curettage**. A local anesthetic is injected into the skin, and then the skin lesion is scraped off with a sharp-edged curette spoon. The base of the skin, now raw and oozing or bleeding, is sealed by cauterization. Curettage is only possible if the material being scraped off is more frail than the surrounding skin or when there is a natural cleavage plane between the lesion and the normal tissue that surrounds it. Curettage may be used on multiple lesions in a short period of time. Electrosurgery involves the use of an electric current to cut or burn tissue in a controlled manner. When removing a mole or other growth from the surface of the skin by means of surgical excision the ellipse drawn by the surgeon is generally about three times as long as it is wide. The skin is cleaned and local anesthetic is administered. The surgeon uses a scalpel to cut along the two curved lines that make up the ellipse, as far down as the layer of subcutaneous fat. The growth and the skin

surrounding it are removed and the two cut surfaces are stitched together; generally only a few stitches are needed (Davenport et al '03: 119, 120).

The type of **laser** and its optimal wavelength dictate its use: Alexandrite and ruby lasers, for example, target melanin so are used to treat pigment problems; carbon dioxide lasers vaporize tissue and are used in skin resurfacing or cutting; bromide and argon lasers target hemoglobin and are used to treat problems in blood vessels or to heat-seal vessels. Ablative lasers are destructive, they vaporize or remove skin and can also cut tissue quickly and precisely. They can treat blood vessel problems and excess pigmentation, remove warts and skin tags, or resurface the skin following acne, sun damage, or signs of aging. Healing may take up to six months. The skin can be left with prolonged redness and discoloration and cannot go to work. Non-ablative lasers do not vaporize the skin. These lasers are used at a lower wavelength so don't produce heat. They can treat facial lines caused by aging and sun damage and also soft scarring. They act by stimulating collagen production thereby "plumping" the skin up to that slight irregularities are softened and the skin's appearance is improved. Improvements in appearance may take longer but there is no recovery time. Lasers are now available to treat pigmented growths such as seborrheic keratoses (basal cell papillomas), to remove tattoos as well as pigment changes. Laser tattoo removal has mixed results: a tattoo that is primarily black or blue is fairly easy to remove completely, whereas reds and yellows are more difficult (Davenport et al '03: 126, 127).

### 3. Radiation

**Radiation therapy** has been used for cancer treatment since the discovery of X-rays by Roentgen in 1895 and radium by Madam Marie Curie in 1898. By 1899, a cure of basal cell carcinoma of the skin with X-ray treatment has been reported. Initial reports were optimistic but later it was learned that tumor recurrences developed and there was significant normal tissue damage. Patients often died of acute effects of irradiation and those who survived frequently had major complications. If radiation is deemed appropriate, a technical specialist plans dose delivery. Planning begins with simulation which is accomplished with a fluoroscopic-radiographic unit capable of imitating the geometric conditions of the treatment machine. The actual area of treatment is designated using previous X-ray studies, information from surgical procedures and the extent of disease. Once the target volume has been delineated, the tumor dose is prescribed by the radiation oncologist, and dose calculations are performed by the physicist or the dosimetrist. Custom made beam shaping devices, immobilization devices, shielding devices, masks or compensating filters are often constructed to conform the beam profile to the treatment volume and spare as much normal tissue as possible. Prior to the first treatment and during the course of treatment, radiographs (portal films) are obtained using the treatment machine beam compared to the simulator radiographs. Depending on the clinical situation, a course of radiation may consist of only a few treatments or may last for many weeks with one or more treatments daily (Ahuja et al '86: 257).

Two **ionizing radiations** are of importance in external beam radiation, X-rays and  $\gamma$ -rays. X-rays are created through interactions of electrons, whereas  $\gamma$ -rays originate in the atomic nucleus during radioactive decay, although they are physically identical. The unit of radiation absorbed dose is the "rad" and is defined as the absorption of 100 ergs/g of matter. The international unit of absorbed dose is the "Gray" (1 Joule/kg). One Gray is equal to 100 rad. The Gray is the established unit for reporting radiation dosages. The higher the energy of the beam, the more penetrating it is. Oxygen is a potent radiation sensitizer. The **oxygen enhancement ratio** (OER) is the ratio of the dose for anoxic cells to the dose for oxygenated cells to achieve the

same biologic effect. For X-rays, the OER is 2.5 to 3.0 times greater for anoxic cells than for oxygenated cells. Within a tumor the center may be necrotic and anoxic, without blood or oxygen. Well-oxygenated tumor cells may be responsive to irradiation and die, yet decreasing oxygen deep within the tumor may enhance cell survival. This allows more oxygen to diffuse further into the tumor and the previously hypoxic cells become better oxygenated so these cells are more radio-responsive than during the first radiation dose. During fractionated radiotherapy, this process of re-oxygenation occurs after each dose. Standard radiotherapy protocols call for a prescribed dose over a given period of time, usually in 5 increments weekly.

Another factor that influences cellular response to radiation is the **linear energy transfer** (LET) which defines the density of ionizing events resulting from specific radiation. In general, particle beams (neutrons, protons, stripped nuclei, etc.) have higher LET than photons (X-rays). Because of this increased energy transfer, cells are more damaged than they would be from the passage of lower LET photons. Relative biologic effectiveness (RBE) values are the ratio calculated by comparing a source of radiation to a 250 kVp X-ray beam as the standard radiation comparison, usually approximately 3. Cells in mitosis are far more sensitive to radiation damage than cells in interphase and cell sensitivity in S-phase (DNA synthetic phase) is lower than phase G1 or G2 (Ahuja et al '86: 258, 259).

**Irradiation** is used as a single modality with curative intent in many diseases such as medulloblastoma, skin cancer, gynecologic cancers, early head and neck tumors, breast cancer, retinoblastomas, Hodgkin's disease, non-Hodgkin's lymphoma, etc. Lymphoma cells are exquisitely radiosensitive and doses of 3500 to 4000 cGy (centigray) can achieve 95% local control. For medulloblastoma, a brain tumor that usually occurs before age 15, where complete resection is usually not possible because of critical location, that is prone to spread throughout the neuraxis, a postoperative irradiation is delivered to the brain and spinal cord – a minimum dose of 3500 cGy is given to the entire neuraxis while the posterior fossa receives 5000 to 5500 cGy. Additional boost doses of 1000 to 1500 cGy may be delivered to gross disease. Studies show comparable local control and 10-year survival in patients with breast cancer (less than 5 cm) treated with lumpectomy (lumpectomy) and primary irradiation. A dose of 4500 to 5000 cGy is delivered to the breast and nodes followed by a boost of 1500 to 2000 cGy to the tumor bed. Hodgkin's disease is one of the most radio-curable malignancies. Patients with early-stage disease (Stages I, II and III-A) are often treated exclusively with radiation. For higher stage disease, radiation is commonly given to areas of bulky disease for consolidation after chemotherapy induction. In early cervical cancer (Stage I and II-A) surgery and irradiation achieve equally good results. In more advanced cases, irradiation is clearly the treatment of choice. Initially, external radiation therapy is often delivered to a dose of 4000 to 5000 cGy to the pelvis. Often this is accomplished in 2 sessions of approximately 48 hours each, with an interval of 10 to 14 days. A commonly used dose specification point lies 2 cm above and 2 cm lateral to the cervical os (point A, where the ureter crosses the uterine artery). Usually point A receives a total dose of 8500 to 9000 cGy and the pelvic sidewalls are treated to doses as high as 6500 cGy. Early laryngeal carcinoma is often best treated by irradiation because of high success rate and preservation of voice. Small 5 x 5 or 6 x 5 cm opposing lateral fields are commonly used to deliver 6600 to 7000 cGy over 6 ½ to 8 weeks. For early lesions, the success rate is generally in excess of 90% (Ahuja et al '86: 259-261).

Radiation can often provide pain relief for patients with metastatic bone disease, control bleeding from advanced malignancy, relieve bronchial obstruction and palliate symptoms of brain metastasis. Rapid treatment schedules are often used (267 cGy x 15 or 300 cGy x 10 or 400 cGy

x 5). The goal is to significantly improve the quality of life. Preoperative radiation is often delivered in doses ranging from 3000 cGy in 2 weeks to 5500 cGy given in 6 weeks. Preoperative irradiation can compromise the healing process unless adequate nutritional support is provided. Skin incisions must be planned with the irradiated vasculature in mind. For example a post-radiation radical neck dissection incision should be "U" or "J" shaped instead of the traditional trifurcated "Y" incision. Postoperative radiation is delivered within 6 weeks of surgery to the tumor bed in doses of 4000 to 5500 cGy in standard fractionation to reduce the potential for local recurrence of cancer. A boost dose up to 2000 cGy should be considered if there is known residual disease or extensive scar formation. In sandwich therapy, peri-operative, intra-operative and postoperative irradiation can be combined. In rectal carcinoma post-operative irradiation of 4500 to 5500 cGy decreased local re-occurrence from 40% to 6%. Low dose preoperative radiation (500 cGy) was found to increase survival from 20% to 40%. 500 cGy to the pelvis preoperatively and 45000 cGy over 5 weeks postoperatively results in a 78% tumor free survival rate at 3 years (Ahuja et al '86: 261-263).

Radiation may be administered via an external beam, intracavitary placement, or interstitial implantation of radioactive sources, or systemic administration of radioactive isotopes. For the production of X-rays, the cathode ray tube is acceptable for energies up to about 300,000 electron volts (orthovoltage). A filament within an evacuated glass tube is energized by a current producing free electrons. The electrons are accelerated toward a target by high voltage across the filament and target. Once the electrons strike the (tungsten) target, X-rays are produced and radiate through a thin (beryllium) window. Maximum dose is delivered at the skin surface, and the dose is approximately 50% of maximum at 6 cm within the tissue. Except when treating relatively superficial tumors the dose delivered to the surrounding normal structures, when compared to the dose delivered to the tumor is unacceptably high.

The development of supervoltage machines and isotope tele-therapy units allowed for skin-sparing effects and deeply penetrating beams. Cobalt 60 units were first used clinically in 1951 and their use is widespread today. Development of high-energy X-ray machines of various types (linear accelerator, betatron) has continued. In the linear accelerator, a radio-frequency wave of about 3000 MHz is produced and is fed into the accelerator wave guide which increases the velocity. Electrons injected by the electron "gun" are accelerated towards the target on the microwave beam. By removing the target, electrons can be used directly for therapy. The betatron is an accelerator or generating X-ray and electron beams of high energies. A filament and electron injector provide electrons in an evacuated "donut". The electrons are constrained to move within the circular path of the donut at an equilibrium established by a magnetic field permeating the donut.

Because of a phenomenon known as "electron buildup" the maximum dose deposited by a high-energy X-ray beam is delivered at some depth below the surface of the skin and the percentage dose delivered to the skin is much lower. Much higher tumor doses can be delivered with high-energy beams without normal tissue complications. Placement of radioisotopes into the body cavities is referred to as intracavitary radiotherapy. Early stage tumors of the uterine cervix are well-treated with radiation therapy, usually with intracavitary irradiation playing a major role. Survival is equal to that of radical surgery but the complication rate is usually lower for radiation. Such treatment in vaginal and endometrial cancers preoperatively or postoperatively can reduce the local recurrence rate to less than 2%. Currently systemic radioisotope administration is largely limited to the management of disseminated thyroid cancer with

radioiodine. Occasionally, radiophosphorus is given for widespread osseous lesions from prostate or breast cancer (Ahuja et al '86: 263-266).

### Radiation Complications

	Organ	Injury	CD5/5 (cGy)	CD5/50 (cGy)	Portion of organ
<b>Potentially severe or fatal radiation injury</b>	Bone marrow	Pancytopenia, aplasia	250 3,000	450 4,000	Whole Segment
	Liver	Hepatitis	2,500	4,000	Whole
	Stomach	Ulcer, hemorrhage	4,500	5,500	100 sq cm
	Intestine	Ulcer, perforation	4,500	5,500	400 sq cm
	Rectum	Stricture, ulcer	6,000	8,000	100 sq cm
	Brain	Infarct, necrosis	6,000	7,000	Whole
			7,000	8,000	25%
	Spinal cord	Infarct, myelitis, necrosis	4,500	5,500	10 cm
	Heart	Pericarditis	4,500	5,500	60%
	Lung	Pneumonitis	3,000	3,500	100 sq cm
	Kidney	Nephrosclerosis	1,500	2,500	Whole
Fetus	Death	200	400	Whole	
<b>Potentially mild or moderately severe radiation injury</b>	Bladder	Contracture	6,000	8,000	Whole
	Testes	Sterilization	100	200	Whole
	Ovary	Sterilization	200-	625-	Whole
			300	1,200	
	Lens	Cataract	500	1,200	Whole/part
	Vagina	Ulcer, fistula	9,000	10,000	Whole/part
	Breast (child)	No development	1,000	2,500	Whole
Breast (adult)	Atrophy, necrosis	>5,000	>10,000	Whole	

Source: Ahuja et al '86: Table 20.3 pg. 267

Whenever radiation is administered, the normal tissues in the target volume and the transit tissues are at risk for both early and late radiation effects. Radiation tolerance is studied in terms of CD/5 the dose level for a 5% complication rate and CD/50 the dose level for a 50% complication rate. Common complications involve the skin, oral cavity, esophagus and stomach, small bowel, liver and kidneys, testis and ovaries, lungs, eyes and spinal cord. Immediately after high-dose irradiation, the skin may appear flushed, but this usually disappears after a few hours. Hair loss starts in 10 to 14 days, and with larger doses, there is an erythematous reaction in the third week of treatment. 4 to 5 weeks after a single large dose of radiation large scaly fragments of epidermis shed which "new skin" underneath. Long-term effects on the skin may appear as epilation, achromia, atrophy, fibrosis and telangiectasia.

Acute **radio-dermatitis** is divided into three degrees of severity. The first degree is manifested by the slow development of erythema, hyperpigmentation and usually hair loss. A single dose of x-rays necessary to produce these changes is called an "erythema dose". All of the changes in the first degree are reversible. The second degree is characterized by vesicle formation, erosions, hair loss, secondary infection and delayed healing. Atrophic and telangiectasis are the end results. The third degree of radiodermatitis includes ulceration, infection and greatly delayed healing. Epitheliomatous changes are very common in the chronic ulcer or scar. Chronic radiodermatitis can follow acute radiation injury or develop slowly, following repeated small

radiation exposures. The dosage of ionizing radiation on the skin is cumulative; the effects of previous radiation therapy is never erased by the passage of time. When a complete course of radiation therapy has been given to a particular body area, no further radiation should be administered to this area at any future time. Acute cases of radiodermatitis can be treated symptomatically with bland local measures (Sauer '85: 279-282).

The effects on the mucosal membranes in the oral cavity, esophagus and gastrointestinal tract are similar to that of the skin but occur in half the time and the mucosa is rapidly covered with a whitish membrane. High-dose irradiation of the salivary glands may cause decreased salivation, and the saliva thickens, the resulting xerostomia can cause dental caries and periodontal problems years after treatment. Dysphagia and odynophagia are frequently noticed in patients who receive irradiation of the mediastinum due to epithelitis of the esophagus, that may occasionally lead to necrosis and stenosis. The mucosa of the small bowel is ery radiosensitive and very early changes occur in the basal cells of the crypts of Lieberkühn between the villi. Overproduction of mucus, hyperemia and edema may lead to diarrhea with malnutrition and cachexia. Sometimes progressive obstruction and ulceration may result. If a surgical procedure precedes abdominal or pelvic irradiation, it may increase the risk of complication.

The liver and kidneys are relatively radiosensitive organs. The whole liver may tolerate a dose of 2500 cGy in standard fractionation. Radiation hepatitis appears a few months following the irradiation, and include hepatomegaly, ascites, pain, jaundice and weight gain. The tolerance dose of the kidney is 2000 cGy. Irradiation of the testis can diminish their size. The spermatozoa completely disappear between 4 and 8 weeks after radiation. Sterilization may be temporary or permanent, depending on the total dose. Irradiation of ovaries in younger women may cause arrest of menstruation and development of menopausal symptoms, including hot flashes, sweating and anxiety. Acute radiation pneumonitis usually begins 4 to 6 weeks following treatment and is limited to the area of the treatment field. Symptoms may present as fever, cough, bloody sputum, chills and malaise. Late irradiation fibrosis of the lungs may occur 3 months to a year after treatment and is often asymptomatic.

Irradiation of the eye often results in conjunctivitis, with or without ulceration or permanent opacity, depending on the dose. Interstitial keratitis can also occur. There is a 50% incidence of cataract formation with doses of 750 to 1000 cGy delivered in 3 weeks to 3 months. Most of these cataracts can be avoided by adequately blocking the lens out of the field of treatment. Radiation cataracts can easily be removed surgically, but often no treatment is necessary. One of the most serious complications of irradiation is spinal cord injury. The tolerance of the spinal cord is often quoted as 4500 cGy delivered over 4 ½ to 5 weeks. At lower doses, a transient myelopathy may develop with a resultant feeling of electric current or "pins and needles" down the spine into the lower extremities. This usually subsides but may herald transverse myelitis, which is irreversible. Many medications, including "over the counter" preparations will potentiate or mask radiation reactions, wherefore during the course of radiation therapy incidental medication should be prescribed by the radiation oncologist on call (Ahuja '86: 266-268).

**Ionizing radiation** is hazardous. In recent years there has been an increasing awareness in the medical profession of the potential danger of radiation from X-ray treatments, and steps have been instituted to limit the radiation dose. A small percentage (around 1-5%) of patients with leukemia, Hodgkin's disease, ovarian and other cancers have developed so-called secondary leukemias or, less often, other cancers, that can be attributed to their prior therapeutic exposures.

One of the most tragic examples of this is the very high accumulated or overall risk of breast cancer in women who received broad-field chest X-rays of Hodgkin's disease when they were aged between 13 and 16 years. The figure is around 40 percent, or 4 out of 10 exposed. Most of these women will have developed breast cancer 20 to 30 years after the initial mutational event. Marie Curie and her daughter Irene both died of radiation induced bone marrow failure. Marie Curie herself was so hot that her letters are radioactive to this day. By 1902, just seven years after Röntgen's discovery of X-rays, it became clear that exposure caused not only painful erythema and dermatitis, but, in some individuals, malignant skin cancer. The widespread vogue for therapeutic and diagnostic use of radiation during the 1930s and 1950s did not appear to have appreciated the risk involved.

Skin cancer has been known to develop as an unintentional consequence of treating psoriasis with UV light plus photo-activated compounds (psoralen). The acute or single dose of gamma radiation received by those who developed leukemia as estimated, in units called Grays, to be from 1 to 4. This is approximately the same as some therapeutic doses in medicine but around 1000 times our natural environmental exposure level per year. A total body exposure to 5 Grays is usually lethal (Greaves '00: 206-208). As the safety limit, the National Academy of Sciences has recommended, that the average person receive not more than ten roentgens (equivalent to 8.77 cGy (centiGray) or 0.087 Gray), of man-made radiation to the reproductive organs from conception to the age of 30. The roentgen is a unit measurement of radiation dose. One roentgen of air kerma deposits 0.00877 gray (0.877 rad = 0.877 centiGray cGy commonly used to describe radiation therapy) of absorbed dose in dry air, or 0.0096 gray (0.96 rad) in soft tissue. One roentgen (air kerma) of X-rays may deposit anywhere from 0.01 to more than 0.04 gray (1 to 4 cGy) in bone depending on the beam energy (Gerson '90: 87, 88). The primary worry about radiation therapy is that concealed in the confusing radiation metrics is the fact that the normal therapeutic dose of about 5,000 cGy delivered to a specific area is ten times higher than the 500 cGy lethal whole body dose. Patients whose cancer is likely to have been caused by radiation poisoning, including probable occupational exposures, such as to the lasers on damaged CD-ROM and DVD drives on computers, are highly discouraged from exposing themselves to yet another potentially lethal dose of radiation. The teeth fallout and the patient dies.

Radiation-induced cancer is difficult to detect. There are three major reasons for this. Variable background radiation dose makes increased cancer risk from small exposures impossible to detect. Cancer rate and cancer mortality are highly variable in different human populations making it very difficult to pinpoint excess radiation-induced cancer. At the present time there are no specific biological markers for radiation-induced cancer so they cannot be identified or assigned a cause. The linear-no-threshold hypothesis is that there is an increase in cancer risk for every unit of radiation exposure. 0.1Gy or 100 mSv are thought to be the minimum threshold of radiation toxicity (Brooks et al '07).

**Ionizing radiation** is hazardous. Approximately one-half of all ionizing radiation currently received by individuals in the United States comes from natural background sources. These include: (a) cosmic rays; (b) naturally occurring elements in the earth such as uranium, thorium and radium, and (c) emission within the body from such isotopes as potassium-40 and carbon-14. These sources deliver about 80 millirems or ionizing radiation per year to a person living at sea level. Background dose received may be approximately doubled at high altitudes, or where concentrations of radium in the ground are unusually high. Approximately 43% of all ionizing radiation is currently received from medical sources, largely from diagnostic X-rays. These result in an annual exposure of about 92/millirems/year (0.092 cGy; 1 millirem = 0.001 cGy) for the average United States citizen. Most other exposure is from mining and processing

radioactive ores (2% to 3%), fallout from nuclear weapons (2% to 4%) and such consumer products as television sets, smoke detectors and relatively high levels of radiation are emitted by laser products such as DVD players and CD-ROM drives for computers (1% to 4%). The average person living at sea level in the United States thus receives about 180 millirems (0.18 cGy) of ionizing radiation per year. This is roughly equivalent to that received during an upper or lower gastrointestinal series. Mammography results in up to 3 times this amount of radiation to the breast, whereas only about 10 millirems (0.01 cGy) are received from a chest X-ray. It has been estimated that approximately 1% of all cancers in the United States may be attributable to irradiation from other than background sources (Thomas '86: 14, 15). As the safety limit, the National Academy of Sciences has recommended, that the average person receive not more than ten roentgens (8.696 cGy) of man-made radiation to the reproductive organs from conception to the age of 30. In recent years there has been an increasing awareness in the medical profession of the potential danger of radiation from X-ray treatments, and steps have been instituted to limit the radiation dose (Gerson '90: 87, 88).

### Radiation Exposure Due to Medical Tests

Medical Tests	Effective Dose cGy	Medical Tests	Effective Dose cGy
Radiographs X-rays	0.0004 (dental bitewing) – 0.083 (pelvis, hips)	Coronary angiogram	0.46 – 1.58
Intravenous pyelogram 6 films of kidneys	0.25	Mammogram	0.013
Barium	swallow 0.15, meal 0.3, follow-up 0.3, enema 0.7	Nuclear Medicine scan	0.15 – 1.70
Computed tomography (CT) scan	Head 0.2, chest 0.8, abdomen 1, pelvis 1, head and chest 1.1	Annual dose allowed radiation workers	5
Thallium cardiac stress test	0.75 – 5.7	Detectable health effect on annual basis, vomiting if exposed in one dose.	10

Source: 1 milliSievert = 0.1 cGy

A small percentage (around 1-5%) of patients with leukemia, Hodgkin's disease, ovarian and other cancers have developed so-called secondary leukemias or, less often, other cancers, that can be attributed to their prior therapeutic exposures. One of the most tragic examples of this is the very high accumulated or overall risk of breast cancer in women who received broad-field chest X-rays when they were aged between 13 and 16 years. The figure is around 40 percent, or 4 out of 10 exposed. Most of these women will have developed breast cancer 20 to 30 years after the initial mutational event. Marie Curie and her daughter Irene both died of radiation induced bone marrow failure. Marie Curie herself was so hot that her letters are radioactive to this day. By 1902, just seven years after Röntgen's discovery of X-rays, it became clear that exposure caused not only painful erythema and dermatitis, but, in some individuals, malignant skin cancer. The widespread vogue for therapeutic and diagnostic use of radiation during the 1930s and 1950s did not appear to have appreciated the risk involved. Skin cancer has been known to develop as an unintentional consequence of treating psoriasis with UV light plus

photoactivated compounds (psaloran). The acute or single dose of gamma radiation received by those who developed leukemia as estimated, in units called Grays, to be from 1 to 4. This is approximately the same as some therapeutic doses in medicine but around 1000 times our natural environmental exposure level per year. A total body exposure to 5 Grays is usually lethal (Greaves '00: 206-208).

As the safety limit, the National Academy of Sciences has recommended, that the average person receive not more than ten roentgens (equivalent to 8.77 cGy (centiGray) or 0.087 Gray), of man-made radiation to the reproductive organs from conception to the age of 30. The roentgen is a unit measurement of radiation dose. One roentgen of air kerma deposits 0.00877 gray (0.877 rad = 0.877 centiGray cGy commonly used to describe radiation therapy) of absorbed dose in dry air, or 0.0096 gray (0.96 rad) in soft tissue. One roentgen (air kerma) of X-rays may deposit anywhere from 0.01 to more than 0.04 gray (1 to 4 cGy) in bone depending on the beam energy (Gerson '90: 87, 88). The primary worry about radiation therapy is that concealed in the confusing radiation metrics is the fact that the normal therapeutic dose of about 5,000 cGy in 500 cGy fractions delivered to a specific area is ten times higher than the 500 cGy lethal whole body dose. Patients whose cancer is likely to have been caused by radiation poisoning, including probable occupational exposures, such as due to defective lasers in DVD players and CD-ROM drives on computers, are highly discouraged from exposing themselves to yet another potentially lethal dose of radiation in attempt to treat their radiation caused cancer.

Acute **radiodermatitis** is divided into three degrees of severity. The first degree is manifested by the slow development of erythema, hyperpigmentation and usually hair loss. A single dose of x-rays necessary to produce these changes is called an "erythema dose". All of the changes in the first degree are reversible. The second degree is characterized by vesicle formation, erosions, hair loss, secondary infection and delayed healing. Atrophic and telangiectasis are the end results. The third degree of radio-dermatitis includes ulceration, infection and greatly delayed healing. Epitheliomatous changes are very common in the chronic ulcer or scar. Chronic radiation dermatitis can follow acute radiation injury or develop slowly, following repeated small radiation exposures. The dosage of ionizing radiation on the skin is cumulative; the effects of previous radiation therapy is never erased by the passage of time. When a complete course of radiation therapy has been given to a particular body area, no further radiation should be administered to this area at any future time. Acute cases of radio-dermatitis can be treated symptomatically with bland local measures (Sauer '85: 279-282).

The effects on the mucosal membranes in the oral cavity, esophagus and gastrointestinal tract are similar to that of the skin but occur in half the time and the mucosa is rapidly covered with a whitish membrane. High-dose irradiation of the salivary glands may cause decreased salivation, and the saliva thickens, the resulting xerostomia can cause dental caries and periodontal problems years after treatment. Dysphagia and odynophagia are frequently noticed in patients who receive irradiation of the mediastinum due to epithelitis of the esophagus, that may occasionally lead to necrosis and stenosis. The mucosa of the small bowel is very radiosensitive and very early changes occur in the basal cells of the crypts of Liberkun between the villi. Overproduction of mucus, hyperemia and edema may lead to diarrhea with malnutrition and cachexia. Sometimes progressive obstruction and ulceration may result. If a surgical procedure precedes abdominal or pelvic irradiation, it may increase the risk of complication. The liver and kidneys are relatively radiosensitive organs. The whole liver may tolerate a dose of 2500 cGy in standard fractionation. Radiation hepatitis appears a few months following the irradiation, and include hepatomegaly, ascites, pain, jaundice and weight gain. The tolerance dose of the kidney

is 2000 cGy. Irradiation of the testis can diminish their size. The spermatozoa completely disappear between 4 and 8 weeks after radiation. Sterilization may be temporary or permanent, depending on the total dose. Irradiation of ovaries in younger women may cause arrest of menstruation and development of menopausal symptoms, including hot flashes, sweating and anxiety.

Acute radiation pneumonitis usually begins 4 to 6 weeks following treatment and is limited to the area of the treatment field. Symptoms may present as fever, cough, bloody sputum, chills and malaise. Late irradiation fibrosis of the lungs may occur 3 months to a year after treatment and is often asymptomatic. Irradiation of the eye often results in conjunctivitis, with or without ulceration or permanent opacity, depending on the dose. Interstitial keratitis can also occur. There is a 50% incidence of cataract formation with doses of 750 to 1000 cGy delivered in 3 weeks to 3 months. Most of these cataracts can be avoided by adequately blocking the lens out of the field of treatment. Radiation cataracts can easily be removed surgically, but often no treatment is necessary. One of the most serious complications of irradiation is spinal cord injury. The tolerance of the spinal cord is often quoted as 4500 cGy delivered over 4 ½ to 5 weeks. At lower doses, a transient myelopathy may develop with a resultant feeling of electric current or "pins and needles" down the spine into the lower extremities. This usually subsides by may herald transverse myelitis, which is irreversible. Many medications, including "over the counter" preparations will potentiate or mask radiation reactions, wherefore during the course of radiation therapy incidental medication should be prescribed by the radiation oncologist on call (Ahuja '86: 266-268). Under no circumstances should cancer caused by radiation be treated with radiation. Independent studies have confirmed radiation treatment for cancers that were caused by radiation and radioactive elements is swiftly fatal. Patients must beware of the radiation hazard posed by lasers in defective CD-ROM and DVD drives, as well as accumulated radiation exposure, over their lifetime, that might preclude radiation treatment.

#### **4. Chemotherapy**

**Chemotherapy**, the management of disease with chemical substances, is used to manage primary as well as recurrent cancers. Neo-adjuvant or induction chemotherapy is delivered before radiation therapy or induction chemotherapy is delivered before radiation therapy or a surgical procedure to attempt to decrease the tumor burden and make it more amendable to the primary therapy. Concomitant chemotherapy is given simultaneously with the definitive form of therapy. Adjuvant chemotherapy is given after radiation or surgical treatment to help control remaining microscopic disease. In some malignant diseases such as leukemia and lymphoma, chemotherapy may be the primary therapy, whereas in head and neck cancer chemotherapy is provide in conjunction with a primary therapy. Despite response rates exceeding 75% with the use of induction chemotherapy, it has not been shown to improve survival rates. Chemo-prevention is the administration of drugs to prevent the development of invasive carcinoma. Because second primary cancers develop at an annual rate of 5% it is desirable to find a way of decreasing or suppressing these new cancers. Isotretinoin activity in suppressing premalignant lesions showed fifty-five percent to 100% of leukoplakic lesions showed regression during therapy with the retinoid drugs. Most lesions that initially responded to therapy progressed after the medicine was stopped. Despite continual advancement in chemotherapeutic management of head and neck cancer, overall survival rates have not changed significantly during the past 30 years (Schwartz, Har-E; & DiPillo '04: 459, 462).

**Chemotherapeutic drugs** exert their effects by interfering with cell proliferation or the processes of DNA, RNA or protein synthesis. Most anticancer drugs indiscriminately attack rapidly dividing cells and damage both normal host tissues and cancer cells. Many chemotherapeutic drugs act at specific phases during the cell cycle and are termed cycle-specific agents. Agents that interfere with DNA synthesis are called S-phase specific, and those that interfere with microtubules to disrupt mitosis are called M-phase specific. DNA-alkylating drugs are considered cell-cycle nonspecific because they damage cells whether or not they are dividing, making these agents more effective against slow-growing and solid tumors. A chemotherapeutic agent will not affect tumor cells if the drug does not reach the cells, the cells are not in the proper phase of the cell cycle for the drug to work, or the cells are resistant to the effects of the drug. Cancer cells can gain resistance by reducing drug uptake, enhancing the repair of its DNA, producing altered drug-resistant enzymes, decreasing the amount of prodrug converted into active drug, and inactivating agents working within the cells. Also, multi-drug resistance can develop and may be caused by a cellular pump that decreases drug levels.

Every time any new cell is formed, it goes through a usual process to become a fully functioning (or mature) cell. The process involves a series of phases and is called the **cell cycle**. Chemotherapy drugs target cells at different phases of the cell cycle. Understanding how these drugs work helps doctors predict which drugs are likely to work well together. Doctors can also plan how often doses of each drug should be given based on the timing of the cell phases. Cancer cells tend to form new cells more quickly than normal cells and this makes them a better target for chemotherapy drugs. However, chemo drugs can't tell the difference between healthy cells and cancer cells. This means normal cells are damaged along with the cancer cells, and this causes side effects. Each time chemo is given, it means trying to find a balance between killing the cancer cells (in order to cure or control the disease) and sparing the normal cells (to lessen side effects). The good news is that most normal cells will recover from the effects of chemo over time. But cancer cells are mutated (not normal) cells, and they usually do not recover from the effects of chemo. This is why chemo is good at killing many types of cancer cells. Chemo drugs can be grouped by how they work, their chemical structure, and their relationships to other drugs. Some drugs work in more than one way, and may belong to more than one group. Knowing how the drug works is important in predicting side effects from it. This helps doctors decide which drugs are likely to work well together. If more than one drug will be used, this information also helps them plan exactly when each of the drugs should be given (in which order and how often). Other drugs to treat cancer work differently, such as targeted therapy, hormone therapy, and immunotherapy (Ihde '89: 198).

**Alkylating agents** keep the cell from reproducing (making copies of itself) by damaging its DNA. These drugs work in all phases of the cell cycle and are used to treat many different cancers, including cancers of the lung, breast, and ovary as well as leukemia, lymphoma, Hodgkin disease, multiple myeloma, and sarcoma. Because these drugs damage DNA, they can affect the cells of the bone marrow which make new blood cells. In rare cases, this can lead to leukemia. The risk of leukemia from alkylating agents is "dose-dependent," meaning that the risk is small with lower doses, but goes up as the total amount of the drug used gets higher. The risk of leukemia after getting alkylating agents is highest about 5 to 10 years after treatment. Examples of alkylating agents include: Altretamine, Bendamustine (nitrogen mustard), Busulfan (alkyl sulfonate), Carboplatin (platinum), Carmustine (nitrosurea), Chlorambucil (nitrogen mustard), Cisplatin (platinum), Cyclophosphamide (nitrogen mustard), Dacarbazine (triazine), Estramustie (nitrogen mustard with 17-beta-estradiol), Ifosfamide (nitrogen mustard), Lomustine (nitrosurea), Mechlorethamine (nitrogen mustard), Melphalan (nitrogen mustard), Oxaliplatin

(platinum), Temozolomide (triazine), Thiotepea (aziridine), Trabectedin, Treosulfan.

**Nitrosoureas** are a group of alkylating agents that have a special action. The other alkylating agents listed above cannot travel into the brain, but nitrosoureas are able to do so. They can enter the brain because they are able to cross through the area known as the blood-brain barrier, a special area that keeps most drugs out of the brain. This action makes these drugs useful in treating certain types of brain tumors. Examples of nitrosoureas include: Carmustine. Lomustine, Streptozocin.

**Antimetabolites** interfere with DNA and RNA by acting as a substitute for the normal building blocks of RNA and DNA. When this happens, the DNA cannot make copies of itself, and a cell cannot reproduce. They are commonly used to treat leukemias, cancers of the breast, ovary, and the intestinal tract, as well as other types of cancer. Examples of antimetabolites include: Azacitidine (pyrimidine analogue), 5-fluorouracil (5-FU) (pyrimidine analogue), 6-mercaptopurine (6-MP) (purine analogue), Capecitabine (Xeloda)(purine analogue), Cladribine (pyrimidine analogue), Clofarabine, Cytarabine (Ara-C)(pyrimidine analogue), Decitabine, Floxuridine, Fludarabine, Gemcitabine (Gemzar)(pyrimidine analogue), Hydroxyurea, Methotrexate (folate analogue), Nelarabine, Pemetrexed (Alimta)(folate analogue), Pentostatin, Pralatrexate (folate analogue), Thioguanine (purine analogue), Trifluridine/tipiracil combination (pyrimidine analogue/thymidine phosphorylase inhibitor).

**Methotrexate** 2.5 mg, available online without prescription, is reportedly as effective as higher toxic doses without any side-effects at doses less than 7.5 mg a week, and at 70 cents a pill, once a week, less cost. During the 1940s in New York, the Lederle Pharmaceutical company were testing various compounds known as anti-folates or folate analogues which inhibit the body's use of folic acid, a vitamin essential for cell growth. These compounds exert their effects by blocking the reduction of folic acid to tetrahydrofolic acid (citrivorum factor), preventing synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins. The first of these anti-folates (or anti-metabolites) that showed potential as a chemotherapy drug was aminopterin, which was first reported in 1948 to produce temporary remission of acute leukemia of children. Clinical trials showed that, aminopterin, methotrexate was effective in causing remission in childhood leukemia and also in the fast growing, pregnancy related cancer, choriocarcinoma, via its inhibition of the metabolism of rapidly dividing cells. Between 1949 and 1954, the first clinical trials that tested combinations of chemotherapy drugs methotrexate and corticosteroids, (and unfortunately 6-MP) for childhood acute lymphoblastic leukemia (ALL) were carried out. Patients lived longer with these new combinations of chemotherapy drugs, but all still died, usually within a year. Because ALL tended to come back in the central nervous system, a major advance was made by aggressively treating the brain and spinal fluid with radiation and drugs that markedly decreased this form of relapse so, one-half of the patients were cured of leukemia. The cure rate now approximates 80 percent and methotrexate is available by prescription for oral consumption (Simone '08). In 1988 methotrexate was approved by the U.S. Food and Drug Administration for use in adults for the treatment rheumatism (Baker '08: 53-55).

**Microtubule inhibitors** are also called plant alkaloids. They are compounds derived from natural products, such as plants. They work by stopping cells from dividing to form new cells, but can damage cells in all phases by keeping enzymes from making proteins needed for cell reproduction. Examples of mitotic inhibitors include the taxanes and vinca alkaloids. **Taxanes** include: Cabazitaxel (taxane), Docetaxel (taxotere), Eribulin, Ixabepilone, Paclitaxel regular and nanoparticle, albumin-bound)(taxane). **Vinca alkaloids** include: Vinblastine, Vincristine,

Vincristine liposomal and Vinorelbine. They are used to treat many different types of cancer including breast, lung, myelomas, lymphomas, and leukemias. These drugs may cause nerve damage, which can limit the amount that can be given. **Topoisomerase inhibitors** are also called plant alkaloids. They interfere with enzymes called topoisomerases, which help separate the strands of DNA so they can be copied. (Enzymes are proteins that cause chemical reactions in living cells.) Topoisomerase inhibitors are used to treat certain leukemias, as well as lung, ovarian, gastrointestinal, colorectal, and pancreatic cancers. Topoisomerase inhibitors are grouped according to which type of enzyme they affect: **Topoisomerase I inhibitors** (also called camptothecins) include: Irinotecan, Irinotecan liposomal, Topotecan. **Topoisomerase II inhibitors** (also called epipodophyllotoxins) include: Amsacrine, Etoposide (VP-16), Mitoxantrone (also acts as an anti-tumor antibiotic), and Teniposide. Topoisomerase II inhibitors can increase the risk of a second cancer.

**Anti-tumor antibiotics** are not like the antibiotics used to treat infections. They work by changing the DNA inside cancer cells to keep them from growing and multiplying.

**Anthracyclines:** Anthracyclines are anti-tumor antibiotics that interfere with enzymes involved in copying DNA during the cell cycle. They bind with DNA so it cannot make copies of itself, and a cell cannot reproduce. (Enzymes are proteins that start, help, or speed up the rate of chemical reactions in cells.) They are widely used for a variety of cancers. Examples of anthracyclines include: Danorubicin, Doxorubicin (Adriamycin), Doxorubicin (pegylated liposomal), Epirubicin, Idarubicin, Valrubicin. A major concern when giving these drugs is that they can permanently damage the heart if given in high doses. For this reason, lifetime dose limits (also called cumulative dose) are often placed on these drugs. Anti-tumor antibiotics that are not anthracyclines include: Bleomycin, Dactinomycin, Mitomycin-C, Mitoxantrone (also acts as a topoisomerase II inhibitor). Some **other chemotherapy drugs** act in slightly different ways and do not fit well into any of the other categories. Here are some examples: All-trans-retinoic acid, Arsenic trioxide, Asparaginase, Hydroxyurea, Ixabepilone, Mitotane, Omacetaxine, Pegaspargase, Procarbazine, Romidepsin, Vorinostat.

**Angiogenesis** is the formation of new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. The process of angiogenesis is controlled by chemical signals in the body. These signals can stimulate both the repair of damaged blood vessels and the formation of new blood vessels. Other chemical signals, called angiogenesis inhibitors, interfere with blood vessel formation. Normally, the stimulating and inhibiting effects of these chemical signals are balanced so that blood vessels form only when and where they are needed. Angiosarcomas are usually treated with paclitaxel (Taxol), docetaxel (Taxotere), sorafenib (Nexavar), or bevacizumab (Avastin). Bevacizumab was the first **angiogenesis inhibitor** that was shown to slow tumor growth and, more important, to extend the lives of patients with some cancers. The FDA has approved other drugs that have antiangiogenic activity, including sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), and everolimus (Afinitor). Sorafenib is approved for hepatocellular carcinoma and kidney cancer, sunitinib and everolimus for both kidney cancer and neuroendocrine tumors, and pazopanib for kidney cancer. Angiogenesis inhibitors are unique cancer-fighting agents because they tend to inhibit the growth of blood vessels rather than tumor cells. In some cancers, angiogenesis inhibitors are most effective when combined with additional therapies, especially chemotherapy.

**Lymphangiosarcomas** are more difficult to treat. Chemotherapeutic drugs such as paclitaxel, doxorubicin, ifosfamide, and gemcitabine exhibit antitumor activity. Recently, there has been

interest in evaluating the effectiveness of anti-angiogenic drugs in the treatment of lymphangiosarcoma. Early evidence suggests that treatment with one such drug, Bevacizumab, may be effective in treating lymphangiosarcoma. Investigation of bevacizumab in combination with other chemotherapy agents is underway. Interferon-alfa was the first drug specifically approved for the treatment of Kaposi's. It is of particular interest because of its anti-proliferative, antiviral (anti-HIV), anti-angiogenic, and immune-modulating properties. A number of natural substances have been identified that block the proliferation of new blood vessels. One of the most potent anti-angiogenic chemicals is thalidomide. Compounds like thalidomide operate by interfering with with particular chemical signals – one called TGF $\alpha$ , in particular, and these molecules are not only important for blood vessel formation but for other vital functions including the immune response (Greaves '00: 253).

**Other drugs and biological treatments** are used to treat cancer, but aren't considered chemotherapy. They often have different side effects than chemotherapy. Many are used along with surgery, chemo, or radiation therapy. **Hormone therapy** drugs work on different actions of hormones that make some cancers grow. These drugs are used to slow the growth of certain breast, prostate, and endometrial (uterine) cancers, which normally grow in response to natural sex hormones in the body. They work by making the cancer cells unable to use the hormone they need to grow, or by preventing the body from making the hormone. **Corticosteroids**, often simply called steroids, are natural hormones and hormone-like drugs that are useful in the treatment of many types of cancer, as well as other illnesses. When these drugs are used as part of cancer treatment, they are considered chemotherapy drugs. Examples of corticosteroids include: Prednisone, Methylprednisolone, Dexamethasone and hydrocortisone crème. Steroids are also commonly used to help prevent nausea and vomiting caused by chemo. They are used before some types of chemo to help prevent severe allergic reactions, too. **Immunotherapy** is a type of treatment that uses drugs to boost or alter a person's immune system. These drugs are used with certain types of cancer to help a patient's immune system recognize and attack cancer cells. **Targeted therapies** work by finding specific substances called proteins or receptors that some cancer cells have. The protein or receptor is precisely targeted by the drug, so normal cells are not affected by the drugs. This is different than how traditional chemotherapy drugs work. Targeted drugs can be used as the main treatment for a cancer, or they may be used after treatment to keep the cancer under control or keep it from coming back (ACS '20).

**Hormone therapy** is often used to treat hormone-sensitive cancer. Hormone therapy for cancer is also called endocrine therapy. Hormone therapies associated with menopause and aging seek to increase the amount of certain hormones to compensate for age or disease related hormonal declines. Hormone therapy, as a cancer treatment, either reduces the level of specific hormones in the body or alters the cancer's ability to use these hormones to grow and spread. Cancers that are most likely to be hormone-receptive include breast cancer, prostate cancer, ovarian cancer and endometrial cancer. Various drugs can alter the body's production of estrogen and testosterone. **Anti-hormone drugs**, such as tamoxifen (Nolvadex) and toremifene (Fareston) for breast cancer, and the anti-androgens flutamide (Eulexin) and bicalutamide (Cadodex) for prostate cancer, block cancer cell's ability to interact with the hormones that propel cancer growth without reducing the body's production of hormones.

Hormonal therapies. **Anti-estrogens** oppose the effects of estrogen. Tamoxifen is a partial estrogen antagonist (antagonist on breast tissue, agonist on endometrium, bone and lipids). Fulvestrant is a full estrogen antagonist (no agonist activity). Many women who've had surgery for breast cancer take tamoxifen only for five years because taking it for a longer period doesn't

offer any further benefit and may actually increase the risk that cancer will recur. **Anti-androgens** oppose the effects of androgens. Apalutamide, bicalutamide, enzalutamide (more affinity for androgen receptors and Plus inhibits more steps in the androgen inhibition than other agents in this class), flutamide, nilutamide. **Androgens**- testosterone may be used in breast cancer androgen therapy. **Corticosteroids** are thought to act via apoptosis induction, eg. Dexamethasone and prednisone. **Somatostatin analogues** inhibit exocrine and endocrine secretion of hormones, which is useful for hormone-secreting tumors (e.g. neuroendocrine). Additional mechanisms include modulation of biliary/GI motility and apoptosis inductions, eg. Lanreotide and octreotide. **Thyrotropin Stimulating Hormone Agonist** is a recombinant thyrotropin used for serum thyroglobulin testing in thyroid cancer – thyrotropin alpha. **Aromatase inhibitors** (AIs) prevent the final step in the conversion of androgens to estrogens in peripheral tissues, some examples are anastrozole, exemestane, letrozole. Aromatase inhibitors (AIs), such as letrozole (Femara), anastrozole( Arimidex) and exemestane (Aromasin), target enzymes that produce estrogen in postmenopausal women, thus reducing the amount of estrogen available to fuel tumors. **Luteinizing Hormone Releasing Hormone (LHRH) Agonists** (also known as gonadotropin releasing hormone analogues) initially stimulate the release of luteinizing hormone, which leads to an increase in sex hormones (testosterone, estradiol). Chronic use leads to down regulation of the LHRH receptors, leading to decreased testosterone in men and estrogen in women, buserelin, goserelin, and leuprolide. Luteinizing hormone-releasing hormone) LH-RH) agonists and antagonists reduce the level of hormones in the body by altering the mechanisms in the brain that tell the body to produce hormones. LH-RH agonists include Leuprolide (Lupron, Viadure, Eligard) for prostate cancer, Goserelin (Zoladex) for breast and prostate cancers and Triptorelin (Trelstar) for ovarian and prostate cancers. One LH-RH antagonist currently approved for men with prostate cancer is abarelix (Plenaxis) that is also under investigation for use in women with breast cancer. **Luteinizing Hormone Releasing Hormone (LHRH) Antagonist** (also known as gonadotropin releasing hormone antagonist) reduce the release of luteinizing hormone, follicle-stimulating hormone, and consequently testosterone by the testes – degarelix. **Progestins** suppress the release of luteinizing hormone from the pituitary gland and subsequently decrease estrogen levels. Additional mechanisms include binding to progesterone, glucocorticoid and androgen receptors, resulting in decreased number of estrogen receptors and decreased estrogen and progesterone levels peripherally in target tissues – medroxyprogesterone, megestrol. **Prolactin Lowering Agents** are dopamine antagonists that decrease hormone production and the size of prolactin-dependent pituitary adenomas by inhibiting the release and synthesis of prolactin from the anterior pituitary – bromocriptine, cabergoline, quinagolide (Mooney '07: 56-62).

Immunotherapies. **Cytokines** are proteins that are involved in the cell signaling that leads to immune responses at sites of inflammation, infection and trauma. They induce various cellular responses, such as suppression of cell proliferation and augmentation of the cytotoxicity of lymphocytes – aldesleukin, interferon and peginterferon. **Vaccine therapy** – bacillus calmette-guerin (CBG) a live, attenuated bacteria (*Mycobacterium bovis*) that exerts a variety of anti-tumor actions, including induction of a local granulomatous reaction, activation of histiocytes, and other direct and indirect stimulation of immune responses. The result is a local inflammatory response that destroys tumor cells. **Immunomodulatory Drugs** (IMiDs) have multiple mechanisms of action including inhibition of proliferation of certain hematopoietic tumor cells, enhancing numbers and activity of T, NK and NKT cells and inhibition of angiogenesis – lenalidomide, pomalidomide, thalidomide. **Differentiating Agents** are vitamin A derivatives. Their proposed mechanism of action is to overcome impaired cellular differentiation - acitretin, bexarotene, tretinoin. **Other immunotherapies** – mimiquimod – TLR7 agonist.

**Cancer vaccines** are the new cutting-edge treatment that trains the immune system to attack cancer cells. Although cancer vaccines are still being tested, and are not yet FDA approved, early studies show promise that cancer vaccines can be a viable treatment for certain types of cancer. Cancer is a term for more than 100 diseases characterized by the uncontrolled, abnormal growth of cells. The immune system doesn't recognize cancer cells as foreign. Cancer vaccines try to get the immune system to overcome its tolerance of cancer cells so that it can recognize them and attack them. In 1991 the first human cancer antigen was found in cells of a person with melanoma. The two main approaches for cancer vaccines are whole-cell vaccines and antigen vaccines. Whole-cell vaccines may take whole cancer cells from a patient or sometimes several patients, or use human tumor cell lines derived in a laboratory. Antigen vaccines try to trigger an immune response by using only certain antigens from cancer cells. One major strategy involves combining vaccines with additional substances called adjuvants, which act as chemical messengers that help T cells work better. An example of one type of adjuvant, called cytokine, is interleukin-2, a protein made by the body's immune system that can also be made in a lab. Cancer vaccines have shown promise in clinical trials with many types of cancer – skin cancer (melanoma, kidney cancer (renal cell), lymphoma, myeloma and solid tumors such as lung cancer. Less than 3 percent of U.S. adults with cancer participate in clinical trials (Mooney '07" 63-70).

In general, a gene cannot be directly inserted into a person's cell. It must be delivered to the cell using a carrier, or "vector" The vectors most commonly used in gene therapy are viruses. Viruses have a unique ability to recognize certain cells and insert their DNA into the cells. In some gene therapy clinical trials, cells from the patient's blood or bone marrow are removed and grown in the laboratory. The cells are exposed to the virus that is carrying the desired gene. The virus enters the cells and inserts the desired genes into the cells' DNA. The cells grow in the laboratory and are then returned to the patient by injection into vein. This type of gene therapy is called *ex vivo* because the cells are grown outside the body. The gene is transferred into the patient's cells while the cells are outside the patient's body. In other studies, vectors (often viruses) or liposomes (fatty particles) are used to deliver the desired gene to cells in the patient's body. This form of gene therapy is called *in vivo*, because the gene is transferred to cells inside the patient's body. Many gene therapy clinical trials rely on retroviruses to deliver the desired gene. Other viruses used as vectors include adenoviruses, adeno-associated viruses, lentiviruses, poxviruses and herpes viruses (Mooney '07: 50-55).

**Targeted therapies** target receptors, ligands, or intracellular molecules involved in the signal transduction of cancer cells. The relative affinity to particular targets is not always clear for each agent, and may differ when used in different indications. Monoclonal antibodies, particularly those that inhibit CTLA-4, PD-1 or PD-L1 (Checkpoint Inhibitors), or IL-6 are suspected of abusively causing pain to a specific anatomical area when the 'anti-body conjugated with cytotoxic' is leaked into the environment and some passing person is exposed. The last letters in the drug names provide information about the classification of the drug – mab = monoclonal antibody, zomib = proteasome inhibitor, nib = kinase inhibitors, olimus = MTOR inhibitor. Abemaciclib (CDK 4/6). Afatinib (EGFR, HER2, HER4). AGS-16C3F (MMAF)(anti-body conjugated with cytotoxic). Alectinib (ALK). Alemtuzumab (CD52), atezolizumab (PD-L1). Avelumab (PD-L1). Axitinib (VEGFR 1, 2, 3). Bevacizumab (VEGF). Belantamab mafodotin (antibody conjugated with cytotoxic). Blinatumomab (CD3 & CD19). Bortezomib 26S proteasome). Brentuximab vedotin (CD30)(antibody conjugated with cytotoxic). Cabozantinib (MET, VEGF, FLT3). Carfilzomib (26S proteasome). Carotuximab (aka TRC105)(CD105).

Cemiplimab (PD-1). Ceritinib (ALK). Cetuximab (EGFR). Cobimetinib (MEK). Crizotinib (ALK, HGFR, C-Met, ROS1). Dabrafenib (BRAF). Dacomitinib (EGFR). Daratumumab (CD38). Dasatinib (BCR-ABL, LYN, HCK, c-kit, EPH, PDGF $\beta$ ). Denosumab (RANKL). Dinutuximab (GD2). Durvalumab (PD-L1). Erlotinib (EGFR). Everolimus (MTOR). Gefitinib (EGFR). Gemtuzumab ozogamicin (antibody conjugated with cytotoxic). Ibrutinib (BTK). Idelalisib (P13K $\delta$ ). Imatinib (BCR-ABL, PDGF, c-KIT). Inotuzumab ozogamicin (CD22) (antibody conjugated with cytotoxic). Ipilimumab (CTLA-4). Lapatinib (EGFR, HER2). Lenvatinib (VEGFR, FDFE, PDGFR $\alpha$ , KIT, RET). Midostaurin (FLT-3, KIT, PDGFR). Nilotinib (BCR-ABL, c-KIT, PDGFR). Nivolumab (PD-1). Obinutuzumab (CD20). Ofatumumab (CD20). Olaparib (PARP-1, PARP-2, PARP-3). Olaratumab (PDGFR $\alpha$ ). Osimertinib (EGFR). Panitumumab (EGFR). Palbociclib (CDK 4/6). Pazopanib (VEGFR 1, 2, 3, c-KIT, PDGFR $\alpha$ - $\beta$ , FGFR-1 and 3, IL-2, and c-Fms). Pembrolizumab (PD-1). Pertuzumab (HER2). Polatuzumab vedotin (monoclonal antibody). Ramucirumab (VEGFR2 and VEGF A, C, and D). Regorafenib (VEGFR-1, 2, & 3, TIE2, KIT, RET, RAF-1, BRAF, BRAV600E, PDGFR, FGFR). Ribociclib (CDK 4/6). Rituximab (CD20). Ruxolitinib (JAK 1 & 2). Siltuximab (IL-6). Sorafenib (c-Raf, B-Raf, V600E, b-Raf, KIT, FLT-3, VEGFR-2, 3 & beta). Sunitinib (VEGFR 1, 2, & 3, PDGFR $\alpha$ - $\beta$ , KIT, FLT-3, CSF-1R, RET). Temsirolimus (MTOR). Tocilizumab (IL-6). Trametinib (MEK 1 & 2). Trastuzumab (HER2). Trastuzumab emtansine (HER2) (antibody conjugated with cytotoxic). Vandetanib (VEGFR-2, EFR, RET). Vemurafenib (BRAF). Venetoclax (BCL-2). Vismodegib (Hh) (Kalyn '18).

ALK Anaplastic Lymphoma Kinase translocations in this gene lead to oncogenic fusion proteins that play a role in many cancers, including non-small cell lung cancer. BCL-2 B-cell chronic lymphoma 2 is an anti-apoptotic protein. BCR-ABL Breakpoint Cluster Region-Abelson is the fusion protein created by the abnormal Philadelphia chromosome, which characterizes chronic myeloid leukemia. BRAF Serine-Threonine Kinase plays a role in cell growth, differentiation and survival. BTK Bruton's Tyrosine Kinase is involved in tumor proliferation, migration and survival. CD Cluster of Differentiated Antigens are a group of antigens present on the surface of all cells in different combinations which makes them useful for classifying cells, CD3 is found on T cells, CD19 is found on B cells, CD 20 is found on B cells, CD30 is expressed on Hodgkin's Lymphoma and anaplastic large cell lymphoma cells, CD 38 is highly expressed on myeloma cells, but is expressed at low levels on normal lymphoid and myeloid cells, CD52 is found on the surface of B cells and T lymphocytes, most monocytes, macrophages and NK cells, and certain granulocytes, CD105 (endoglin) expression is required for vascular endothelial cell proliferation, targeting CD105 is a novel approach to inhibiting angiogenesis in cancer cells. CDK 4/6 Cyclin-dependent kinases form complexes with cyclin D to promote phosphorylation of retinoblastoma (Rb) protein, which allows cell cycle progression. C-Kit Stem cell factor receptor is involved in oncogenesis, 95% of GIST cells have c-Kit mutations. CTLA-4 Cytotoxic T Lymphocyte-Associated Antigen 4 acts as an immune response checkpoint by switching off T-cells, agents that target CTLA-4 are referred to as Checkpoint inhibitors. EGFR epidermal growth factor receptor is involved in cancer cell proliferation, blocking apoptosis, mobilizing cells to promote metastasis and angiogenesis. EPH Ephrin receptor may be involved in the development of resistance to imatinib. EGFR Fibroblast Growth Factor Receptor contributes to the maintenance of the tumor microenvironment. HER Human Epidermal Growth Factor (also known as EGFR) is over-expressed in about 20% of breast cancers, which leads to increased cell proliferation, cancer spread, and apoptosis inhibition. Hh Hedgehog Pathway is normally dormant in adult tissues, but basal cell carcinomas have gene mutations that activate the Hh pathway, which promotes tumor survival and cancer spread. JAK Janus associated kinase mediates the signaling pathway of cytokines and growth factor for hematopoiesis. LYN Lck/Yes

novel tyrosine kinase is involved in BCR-ABL signaling. MEK Mitogen-Activated Extracellular Signal-Regulated Kinase MEK 1 and MEK2 are involved in cell growth, differentiation, inflammation and apoptosis. MTOR Mammalian target of Rapamycin inhibits cell proliferation and angiogenesis. PARP poly (ADP-ribose) polymerase binding to PARP inhibits single stranded DNA base excision repair and creates PARP-DNA complexes that lead to double-stranded DNA breaks, ultimately causing cell death. PD-1 and PD-L1 Programmed Death Receptor 1 & 2 are located on T-cells, when ligands bind to PD-1 receptors, they switch off T-cells, which fight cancer. Agents that target PD-1 are referred to Checkpoint Inhibitors. PDGF Platelet-Derived Growth Factor contributes to maintenance of tumor microenvironments, P13K $\delta$  Phosphoinositide 3-kinase activate in the signaling pathways of B-cell malignancies. Proteasome degrades cellular proteins targeted for destruction, inhibition of the proteasome results in cell cycle arrest and apoptosis. RANKL Receptor Activator of Nuclear Factor activates osteoclasts, leading to bone resorption. RET Neurotrophic Factor Receptor is involved in oncogenesis. TLR7 Toll-like receptor 7 stimulates innate and cell-mediated immunity to induce anti-tumor effects, including the increased production of inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\alpha$  and interleukin-12. VEGF and VEGFR Vascular Endothelial Growth Factor and Receptor are involved in the development of tumor blood supply (angiogenesis).

In 1960, Peter Nowell and David Hungerford, working in Philadelphia, described a shortened chromosome in the blood and bone marrow of patients with CML. This was the first consistent chromosomal abnormality associated with a human cancer. Then, in 1973, Janet Rowley showed that this abnormal chromosome, now called the **Philadelphia chromosome**, came about because of an exchange of genetic material between two chromosomes. In the 1980s, it was demonstrated that the consequence of this chromosome exchange was the production of an abnormal gene called *BCR-ABL* fueling the excess growth of white blood cells in CML. With the target identified, a drug discovery program was started, aimed at developing a drug to shut down the activity of *BCR-ABL*. The compound that became known as **imatinib** (Gleevec) was developed in 1992, and studies showed that this compound killed CML cells without harming normal cells. In 1998, the drug was tested in patients with CML who had exhausted standard treatment options and whose life expectancy was limited. Within six months of starting the clinical trials of imatinib, all of the patients had their blood counts return to normal. Remarkably, this once-a-day pill had minimal side effects. These unprecedented results were confirmed in much larger clinical trials, and imatinib was approved by the U.S. Food and Drug Administration (FDA) in 2001, less than three years from the start of the clinical trials. With longer follow-up, this once routinely fatal leukemia now has a five-year survival rate of 95 percent. Newer drugs (dasatinib and nilotinib) have been developed that can shut down most of the mutated forms of *BCR-ABL*, and have significant activity in patients with resistance to imatinib; these drugs are also FDA-approved (Druker '08).

Combination therapy, a treatment modality that combines two or more therapeutic agents, is a cornerstone of cancer therapy (Bayat et al '17). **Breast:** Cyclophosphamide, Doxorubicin and Fluorouracil (CAF, FAC). Cyclophosphamide, Methotrexate and Fluorouracil (CMF). Docetaxel and Capecitabine (DC). Docetaxel and Carboplatin (AUC=6)(DC). Docetaxel and Cisplatin (DP). Docetaxel, Doxorubicin and Cyclophosphamide (TAC). Dose Dense Doxorubicin and Cyclophosphamide Followed by Paclitaxel. Doxorubicin and Cyclophosphamide. Doxorubicin and Cyclophosphamide followed by Docetaxel. Doxorubicin and Docetaxel. Fluorouracil, Epirubicin and Cyclophosphamide (FEC50)(FEC)(FEC100)(FEC).

Gemcitabine and Capecitabine. Ixabepine and Capecitabine. Lapetinib and Capecitabine. Paclitaxel and Gemcitabine. Pemetrexed and Carboplatin (PC)(Solimando & Waddell '12).

**Gastrointestinal:** Gemcitabine and Capecitabine (Biliary, Gallbladder). Irinotecan and Cisplatin (IP) (Gastroesophageal). Colon/Colorectal: Capecitabine plus Oxaliplatin (XelOx/CapOx). Fluorouracil, Leucovorin and Irinotecan (FOLFIRI). High-Dose Fluorouracil and Leucovorin. Irinotecan, Fluorouracil and Leucovorin. Leucovorin, Fluorouracil and Oxaliplatin (FOLFOX4). Leucovorin, Fluorouracil and Oxaliplatin (FOLFOX 6 & 7). Protracted Venous Infusion Fluorouracil. Weekly Fluorouracil and Leucovorin. Gastric: Docetaxel and Capecitabine (DC). Docetaxel and Cisplatin (DP). Docetaxel, Cisplatin and Fluorouracil (DCF). Epirubicin, Cisplatin and Capecitabine (ECX). Epirubicin, Cisplatin and Fluorouracil (ECF). Fluorouracil, Doxorubicin and Mitomycin (FAM). Irinotecan and Cisplatin. Esophageal: Docetaxel and Capecitabine (DC). Docetaxel and Cisplatin (DP). Irinotecan and Cisplatin (IP). Pancreatic: Fluorouracil, Doxorubicin and Mitomycin (FAM). Gemcitabine and Capecitabine (Solimando & Waddell '12). The first-line treatment for metastatic colorectal cancer appears to be the fluorouracil + folinic acid combination (LV-5FU2 protocol) plus either oxaliplatin (FOLFOX protocol) or irinotecan (FOLFIRI protocol)(Prescrire '05).

**Genitourinary:** Docetaxel and Cisplatin (DP(Urothelial)). Gemcitabine and Capecitabine (Renal Cell). **Bladder:** Intravesical Doxorubicin. Intravesical BCG. Intravesical Gemcitabine. Intravesical Mitomycin. Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC). **Prostate:** Docetaxel and Capecitabine (DC). Docetaxel and Estamustine. Docetaxel and Prednisone (DP). Gemcitabine and Capecitabine. Mitoxantrone and Prednisone (MP). Taxanes and Estramustine. **Testicular:** Bleomycin, Etoposide and Cisplatin (BEP). Cisplatin and Ifosfamide with either Vinblastine or Etoposide (VIP). Etoposide and Cisplatin. **Gynecologic:** Docetaxel and Carboplatin (AUC=6)(DC)(Cervical). Gestational Trophoblastic Neoplasm: Etoposide, Methotrexate, Actinomycin, Cyclophosphamide and Vincristine (EMA/CO). Hydroxyurea, Dactinomycin, Vincristine, Leucovorin, Cyclophosphamide, and Doxorubicin (Modified Bagshawe Regimen). **Ovarian:** Docetaxel and Carboplatin (AUC=6)(DC). Docetaxel and Carboplatin (AUC=5)(DC). Docetaxel and Cisplatin (DP). Liposomal Doxorubicin. Pemetrexed and Carboplatin (PC). **Head and Neck:** Cisplatin and Continuous Infusion Fluorouracil (CF). Docetaxel and Carboplatin (AUC=6)(DC). Docetaxel and Cisplatin (DP). Docetaxel, Cisplatin and Fluorouracil (DCF). Docetaxel, Cisplatin and Fluorouracil (TCF). **Lung:** Carboplatin and Etoposide (CE). Cisplatin and Pemetrexed. Docetaxel and Capecitabine (DC). Docetaxel and Cisplatin (DP). Etoposide and Cisplatin (GC). Irinotecan and Carboplatin (IC). Irinotecan and Cisplatin (IP). Paclitaxel and Carboplatin (PC or TC). Pemetrexed and Carboplatin (PC). Vinorelbine and Cisplatin (VC)(Solimando & Waddell '12). **Central Nervous System:** Temozolomide. Procarbazine, lomustine CCNU, and vincristine (PCV). Recurrent glioma: Bevacizumab monotherapy. Bevacizumab and irinotecan

Leukemias. **Acute Lymphocytic (ALL):** Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone Alternating with Methotrexate and Cytarabine (Hyper-CVAD). Prednisone, Asparaginase, Vincristine, Daunorubicin, Cyclophosphamide, Cytarabine, Thioguanine, Mercaptopurine and Methotrexate (Hoelzer Regimen). Prednisone, Vincristine, Daunorubicin, and Asparaginase (PVDA). **Acute Myelogenous (AML):** Cytarabine and Daunorubicin (7 plus 3). Cytarabine and Idarubicin (7+3). Fludarabine, Cytarabine and Filgrastim (FLAG). High-Dose Cytarabine (HIDAC). High-Dose Cytarabine (HDAC) Plus Daunorubicin. **Chronic Lymphocytic (CLL):** Cyclophosphamide, Fludarabine, and Rituximab (CFR, FCR). Cyclophosphamide, Vincristine and Prednisone (Solimando & Waddell '12).

Lymphomas. **Hodgkin Lymphoma:** Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone (BEACOPP baseline and escalated). Doxorubicin, Bleomycin, Vinblastine and Dacarbazine (ABVD). Mechlorethamine, Vincristine, Procarbazine and Prednisone (MOPP). MOPP/ABVD and Selected MOPP/ABV(D) Hybrid Regimens. Mechlorethamine, Doxorubicin, Vinblastine, Vincristine, Bleomycin, Etoposide and Prednisone (Stanford V). **Non-Hodgkin Lymphoma:** Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP). Dexamethasone, Cytarabine and Cisplatin (DHAP). Etoposide, Prednisone, Vincristine, Cyclophosphamide and Doxorubicin (EPOCH). Etoposide, Methylprednisolone, Cytarabine and Cisplatin (ESHAP). Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone Alternating with Methotrexate and Cytarabine (Hyper-CVAD). Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP)(Solimando & Waddell '12).

**Melanoma:** Bleomycin, Vincristine, Lomustine, and Dacarbazine (BOLD) with Interferonb. Carmustine, Cisplatin, Dacarbazine, and Tamoxifen (Dartmouth Regimen). **Myeloma:** Bortezomib and Dexamethasone (BD). Liposomal Doxorubicin and Bortezomib. Melphalan and Prednisone (MP). Melphalan, Prednisone and Thalidomide (MPT). Thalidomide and Dexamethasone (TD). Vincristine, Doxorubicin and Dexamethasone (VAD). **Sarcomas.** **Osteosarcoma:** Cisplatin, Doxorubicin, and High-Dose Methotrexate. Doxorubicin and Cisplatin. Doxorubicin, Cisplatin, High-Dose Methotrexate and Ifosfamide. **Sarcomas:** Mesna, Doxorubicin, Ifosfamide and Dacarbazine (MAID). **Soft-Tissue Sarcomas:** Cyclophosphamide, Vincristine, Doxorubicin and Dacarbazine (CYVADIC). Gemcitabine and Docetaxel (GD). Ifosfamide, Carboplatin and Etoposide (ICE). **Solid Tumors:** Docetaxel and Capecitabine (DC). Docetaxel and Carboplatin (AUC=6)(DC). Docetaxel and Cisplatin (DP). Gemcitabine and Capecitabine. Irinotecan and Cisplatin (IP). Pemetrexed and Carboplatin (PC). **Tumors of Unknown Origin:** Docetaxel and Cisplatin (DP) (Solimando & Waddell '12).

Cancer cells tend to grow fast, and chemo drugs kill fast-growing cells. But because these drugs travel throughout the body, they can affect normal, healthy cells that are fast-growing, too. Damage to healthy cells causes side effects. The normal cells most likely to be damaged by chemo are blood-forming cells in the bone marrow; hair follicles; and cells in the mouth, digestive tract, and reproductive system. Some chemo drugs can damage cells in the heart, kidneys, bladder, lungs, and nervous system. In some cases, medicines can be given with the chemo to help protect the body's normal cells. Normal cells usually recover when chemotherapy is over, so most side effects gradually go away after treatment ends, and the healthy cells have a chance to grow normally. Most people have no serious long-term problems from chemotherapy. However, on some occasions, chemotherapy can cause permanent changes or damage to the heart, lungs, nerves, kidneys, reproductive or other organs. And certain types of chemotherapy may have delayed effects, such as a second cancer, that show up many years later. Virtually all chemotherapeutic regimens can cause **depression of the immune system**, often by paralyzing the bone marrow and leading to a decrease of white blood cells, red blood cells, and platelets. Anemia and thrombocytopenia, when they occur, are improved with blood transfusion. Neutropenia (a decrease of the neutrophil granulocyte count below  $0.5 \times 10^9$ /litre) can be improved with synthetic G-CSF (granulocyte-colony-stimulating factor, e.g., filgrastim, lenograstim). In very severe **myelosuppression**, which occurs in some regimens, almost all the bone marrow stem cells (cells that produce white and red blood cells) are destroyed, meaning *allogenic* or *autologous* bone marrow cell transplants are necessary.

## Toxicity profile for selected chemotherapeutic agents

Chemotherapeutic agent	Common toxic profile
Methotrexate	Bone marrow suppression, gastrointestinal ulcers, hepatotoxicity, pulmonary infiltration, mucositis, neutropenia-thrombocytopenia, anemia, diarrhea, stomatitis
5-Fluorouracil	Nausea, vomiting, diarrhea, bone marrow suppression, photosensitivity, cerebellar toxicity, mucositis, neutropenia-thrombocytopenia, skin reaction, alopecia
Cisplatin	Bone marrow suppression, tinnitus and hearing loss, nausea and vomiting, renal failure, potassium and magnesium wasting, peripheral neuropathy, anemia, anorexia
Bleomycin	Pulmonary fibrosis, pneumonitis, little immunosuppression or bone marrow suppression, erythema, hyperpigmentation, ulceration, fever, chills, allergic reaction
Mitomycin-C	Bone marrow depression, gastrointestinal, renal and pulmonary toxicity, alopecia, stomatitis, nausea and vomiting, diarrhea, potential for hemolytic-uremic syndrome

Source: Schwartz, Har-E; & DiPillo '04: 462 Table 53-2

**Typhlitis** is a "life-threatening gastrointestinal complication of chemotherapy which may manifest itself through symptoms including nausea, vomiting, diarrhea, a distended abdomen, fever, chills, or abdominal pain and tenderness. Nausea and vomiting occur commonly in the cancer patient receiving chemotherapy. The worst offenders in order of decreasing emetic potential are as follows: cisplatin, dacarbazine, actinoycin-D, cyclophosphamide, nitrogen mustard, lomustine, doxorubicin, mitomycin C, methotrexate, 5-fluourouracil (5-FU), vincristine, and bleomycin. Other etiologies such as enteritis, intestinal obstruction and psychological cause may also contribute. Drug-induced vomiting usually occurs 1 to 2 hours after chemotherapy in previously untreated patients. Drugs that may also produce delayed vomiting after administration are cyclophosphamide (12 hours) and cisplatin (1-4) days. **Hair loss (Alopecia)** can be caused by chemotherapy that kills rapidly dividing cells; other medications may cause hair to thin. These are most often temporary effects: hair usually starts to regrow a few weeks after the last treatment, and sometimes can change color, texture, thickness and style. Sometimes hair has a tendency to curl after regrowth, resulting in "chemo curls." Severe hair loss occurs most often with drugs such as doxorubicin, danorubicin, paclitaxel, docetaxel, cyclophosphamide, ifosfamide and etoposide. Permanent thinning or hair loss can result from some standard chemotherapy regimens.

**Cardiotoxicity** (heart damage) is especially prominent with the use of anthracycline drugs (doxorubicin, epirubicin, idarubicin, and liposomal doxorubicin). The cause of this is most likely due to the production of free radicals in the cell and subsequent DNA damage. Other chemotherapeutic agents that cause cardiotoxicity, but at a lower incidence, are cyclophosphamide, docetaxel and clofarabine. Interstitial **lung disease** can be caused by bleomycin and pulmonary infiltrates can be caused by methotrexate. **Hepatotoxicity** (liver damage) can be caused by many cytotoxic drugs. The susceptibility of an individual to liver damage can be altered by other factors such as the cancer itself, viral hepatitis, immunosuppression, (food) poisoning and nutritional deficiency. The liver damage can consist of damage to liver cells, hepatic sinusoidal syndrome (obstruction of the veins in the liver),

cholestasis (where bile does not flow from the liver to the intestine) and liver fibrosis.

**Nephrotoxicity** (kidney damage) can be caused by tumor lysis syndrome and also due direct effects of drug clearance by the kidneys. Different drugs will affect different parts of the kidney and the toxicity may be asymptomatic (only seen on blood or urine tests) or may cause acute renal failure.

**Ototoxicity** (damage to the inner ear) is a common side effect of platinum based drugs that can produce symptoms such as dizziness and vertigo. Some types of chemotherapy are gonadotoxic and may cause **infertility**, those with high risk include procarbazine and other alkylating drugs such as cyclophosphamide, ifosfamide, busulfan, melphalan, chlorambucil, and chlormethine. Drugs with medium risk include doxorubicin and platinum analogs such as cisplatin and carboplatin. On the other hand, therapies with low risk of gonadotoxicity include plant derivatives such as vincristine and vinblastine, antibiotics such as bleomycin and dactinomycin, and antimetabolites such as methotrexate, mercaptopurine, and 5-fluorouracil. Chemotherapy is potentially **teratogenic** during pregnancy, especially during the first trimester, to the extent that abortion usually is recommended if pregnancy in this period is found during chemotherapy. Second- and third-trimester exposure does not usually increase the teratogenic risk and adverse effects on cognitive development, but it may increase the risk of various complications of pregnancy and fetal myelosuppression. **Methotrexate 2.5 mg**, available online without prescription, is reportedly as effective as higher toxic doses without any side-effects at doses less than 7.5 mg a week, and at 70 cents a pill, once a week, less cost, but is teratogenic.

**Nausea and vomiting** occur commonly in the cancer patient receiving chemotherapy. The worst offenders in order of decreasing emetic potential are as follows: cisplatin, dacarbazine, actinomycin-D, cyclophosphamide, nitrogen mustard, lomustine, doxorubicin, mitomycin C, methotrexate, 5-fluorouracil (5-FU), vincristine, and bleomycin. Other etiologies such as enteritis, intestinal obstruction and psychological cause may also contribute. Drug-induced vomiting usually occurs 1 to 2 hours after chemotherapy in previously untreated patients. Drugs that may also produce delayed vomiting after administration are cyclophosphamide (12 hours) and cisplatin (1-4) days. Drug-induced nausea and vomiting should be treated with antiemetic drugs. The most effective agents are metoclopramide, droperidol and corticosteroids. An antianxiety agent such as lorazepam be can added. Commonly used emetic agents are Phenthiazine; prochlorperazine (Compazine) 5 mg-10 mg orally every 4 hours, thiethylperazine (Toecan) 10 mg orally twice daily, promethazine (Phenergan) 25 mg (orally, intramuscularly, or intravenously) every 4 hours; Butyrophenones, droperidol (Inapsine) 0.5 mg-2 mg intravenously every 4 hours, haloperidol (Haldol) 1 mg-2 mg (orally or intravenously) every 4 hours; Corticosteroids, dexamethasone (Decadron) 10 mg (intramuscularly, intravenously, or orally), methylprednisolone (Solu-Medrol) 250 mg intravenously very 6 hours; Cannabinoid, tetrahydrocannabinol (THC) 10 mg/m<sup>2</sup> orally; and Benzamide, metoclopramide (Reglan) 20 mg orally; 1 mg- 2 mg/kg intravenously (Thom & Daly '90: 498).

Development of **secondary neoplasia** after successful chemotherapy and/or radiotherapy treatment can occur. The most common secondary neoplasm is secondary acute myeloid leukemia, which develops primarily after treatment with alkylating agents or topoisomerase inhibitors (e.g., MOPP therapy for Hodgkin's disease). Survivors of childhood cancer are more than 13 times as likely to get a secondary neoplasm during the 30 years after treatment than the general population. Not all of this increase can be attributed to chemotherapy. Skin cancer can be caused by arsenic and inorganic arsenic compounds, Azathioprine, Coal-tar distillation, Coal-tar pitch, Cyclosporine, Methoxsalen plus ultraviolet A. Dieldrin, Digoxin, Estrogen menopausal

therapy are suspected of causing breast cancer. Tamoxifen is known to cause endometrial cancer. Benzidine, Chlornaphazine, Cyclophosphamide are known to cause bladder cancer. Azathioprine, Benzene, Busulfan, 1,3-Butadiene, Chlorambucil, Cyclophosphamide, Cyclosporine, Etoposide with cisplatin and bleomycin Lindane, Melphalan, MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture), Pentachlorophenol, Phosphorus-32, Rubber production industry, Semustine (methyl-CCNU), Thiotepa, and Treosulfan are known to cause leukemia and/or lymphoma. Bishloroethyl nitrosourea (BCNU), Chloramphenicol, DDT, Diazinon, Dichloromethane (Methylene-chloride), Ethylene oxide, Etoposide, Malathion, Mitoxantrone, Nitrogen mustard and Teniposide may cause leukemia and/or lymphoma. Cyclosporine and radiation are known to cause cancer to multiple sites and 2,3,7,8-Tetrachlorodibenzo-para-dioxin to all cancer sites (IRARC '20).

**Epsom salt baths** are an indispensable pain treatment that cure many diseases caused by methicillin resistant *Staphylococcus aureus* (MRSA) thereby avoiding the excruciating toxic shock syndrome that occurs in conjunction with *Streptococcus* spp. Swimming in a saline or chlorine pool or ocean has the same curative effect on the ubiquitous hospital and community acquired MRSA lesions. Drug therapy is the mainstay of treatment for the management of acute and chronic cancer pain. Three classes of analgesic drugs are used: (1) aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), (2) adjuvant analgesics, and (3) narcotic analgesics. **NSAIDs** include aspirin, ibuprofen, diflunisal and naproxen; they are used for mild to moderate pain. They have four major pharmacologic properties: analgesic, antipyretic, anti-platelet and anti-inflammatory actions. However, there is a ceiling effect to analgesia (i.e. increasing the dose of aspirin beyond 975 mg to 1300 mg per day will not increase the analgesia, but may increase the duration of analgesia. **Narcotic analgesics** are used to manage moderate to severe acute and chronic cancer-related pain. The typical starting dose for morphine ranges from 5 mg to 15 mg subcutaneously or intramuscularly or 30 mg to 60 mg orally every 3 to 4 hours. Among the more important side-effects are sedation, constipation, nausea, vomiting and respiratory depression. Respiratory depression may be fatal and is treated with the narcotic agonist Narcan. Tolerance to narcotics usually develops in the context of drug dependency. Physical dependence usually occurs after two weeks, but misbehavior when withdrawing from a short course of opioids is not uncommon. The syndrome of physical dependence is characterized by anxiety, nervousness, irritability, chills alternating with hot flashes, salivation, lacrimation, rhinorrhea, diaphoresis, piloerection, nausea, vomiting, abdominal cramps, insomnia and rarely, multifocal myoclonus (seizures). With short half-life drugs such as morphine or hydromorphone, the symptoms may appear in 6 to 12 hours and peak at 24 to 72 hours; for methadone and levorphanol (long half-life drugs) the symptoms may be delayed for several days and are typically less florid. About 25% of the previous daily dose is required to prevent withdrawal. **Adjuvant analgesics** are Anticonculsants, phenytoin and carbamazepine; Phenothiazine, methorimetprazine and fluphenzine; Tricyclic-antidepressants, amitryptaline, imipramine and doxepin; Dextroamphetamine; Antihistamines; and Corticosteroids, such as dexamethasone 16 mg – 96 mg/ daily, or equivalent is probably the most trouble-free short-term pain killer, but long-term use is compromised by osteoporosis and Cushing's disease. Benzodiazepines, sedative-hypnotic drugs (barbiturates), cannabinoids and cocaine are not worth the trouble as analgesic drugs (Payne '90: 474-483). Most patients with cancer require red blood cell (RBC) transfusion during the course of their disease to treat anemia (Lee & Schiffer '90: 543). In 1988 methotrexate was approved by the U.S. Food and Drug Administration for use in adults for the treatment rheumatism (Baker '08: 53-55).

Physical medicine embraces therapy with a variety of agents, which include massage, therapeutic exercise, water, air, radiations, heat, light, ultraviolet, x-rays, radium and lasers (vibrations, refrigeration, and electricity of various forms. Many of these agents are used in the treatment of skin diseases. The physical agent most commonly used for dermatoses is **hydrotherapy**, in the form of medicated or non-medicated wet compresses and baths. Distilled water and tap water are the vehicles and may contain any of the following chemicals in varying strengths: sodium chloride, aluminum acetate (Burow's solution), potassium permanganate, silver nitrate, tar, starch, oatmeal (Aveeno) and colloid (Soyaloid). Open **compresses** are used most frequently, since excessive maceration of tissue occurs when the dressings are "closed with wax paper or rubber sheeting. For most conditions, the area to be treated should be wrapped with two or three layers of clean sheeting or muslin. Then gauze 3 inches wide should be wrapped around the sheeting to hold it firmly in place. After that, the dressing can be moistened with the solution by pouring it on or by squirting it on with a bulb syringe. In most instances the dressing is wet with the solution before it is wrapped on the affected area. The indications for wet compresses are any oozing, crusting or pruritic dermatoses, regardless of etiology. **Medicated baths** should last from 15 to 30 minutes. Cool baths tend to lessen pruritis and are prescribed most frequently. Baths can be used for a multitude of skin diseases except those conditions where excessive dryness is to be avoided, such as for patients with atopic eczema, senile or winter pruritus, and ichthyosis (Sauer '85: 47). **Epsom salt** baths cure methicillin resistant *Staphylococcus aureus* (MRSA) and many other skin conditions.

Relieving the pain of hot and **sunburned skin** involves several moisturizers. Taking a lukewarm bath or shower can help cool the skin. Exposure to sun dries out the skin; smoothing an emollient onto the skin or adding one to the water in a bath helps soften the skin and conserve moisture within the epidermis. **Calamine lotion**, applied often and liberally to the burned area, will cool the skin as it dries, but it must not be used on broken skin. **Aloe vera** is also a very effective moisturizer. Lotions, sprays, or creams containing antihistamines or local anesthetics should not be used on the skin because they can cause the skin to become sensitized and develop an eczema like rash. **Topical steroids** will often reduce inflammation in sunburned skin (Davenport et al '03: 116, 117). People over the age of 40 or 50 require the application of moisturizer to keep the skin moist.

**5-Fluorouracil** solution (Efudex 2% or 5%, fluoroplex 1%) is probably the treatment of choice for actinic keratosis and should be applied to all sun-damaged area for 2 to 4 week, to chemically cauterize the lesion, or to the limits of tolerance, whichever is first. Complete blocking of the sun rays is desired for prevention and treatment of actinic keratoses, a flare-up or lupus erythematosus or a sun allergy reaction. Application of sun screen with a sun protective factor (SPF) of at least 15 cream or lotion is highly recommended if more than 20 minutes are to be spent in bright sun. Sensible and gradual sun exposure of the skin, and staying in the shade during the hottest part of the day, between noon and 3 pm, is the best preventative for sunburn. Sunburn should be treated with Burow's solution wet dressing in cool water. Menthol 0.25% in nonalcoholic white shake lotion may be applied locally to affected areas. Any moisturizer will help dramatically. A few days later to prevent secondary infection apply menthol 0.25%, Neosporin or other antibiotic ointment and white petrolatum (Sauer '85: 287, 281).

**Acne** responds to treatment relatively slowly and patients need to realize that it may take up to six months before they see a significant improvement in their condition. The affected areas should be **washed twice a day** with a washcloth and Dial soap. Topical therapies remain the mainstay for the treatment of mild acne. **Benzoyl peroxide** has antibacterial properties. Benzoyl

peroxide, sold as Benzoyl peroxide gel (5% or 10%) (Benzagel, Desquem-X, Panoxyl, Persa-Gel, and others) is applied locally once a day and treats inflamed and noninflamed skin effectively, but it can cause dryness of the skin, irritation and bleaching. Sulfur, ppt. (6%), **Resorcinol** (4%), Colored alcoholic shake lotion 60.0 should be applied locally at bedtime with fingers. Proprietary substitutions for the above ingredients include Resulin lotion (Almay), Sulfacet-R (Dermik), Komed lotion (Barnes-Hind), Acne-Aid Cream (Stiefel), Acno lotions (Baker-Cummins), and Rezamid lotion (Dermik). Tretinoin gel (0.025%)(**Retin-A**) q.s. 150 applied locally once a day. Patient toleration varies considerably, it is especially valuable for comedone acne. Isotretinoin (**Accutane**), for severe, scarring, cystic acne this therapy has proved beneficial. The usual dosage is 1.0 mg/kg/day given for 4 to 5 months. There are many minor and major side-effects with this therapy. Isotretinoin is effective in treating all mechanisms responsible for acne and also for pre-cancerous leukoplakia. It is only available from dermatologists and is used for severe and otherwise nonresponsive acne. The most important side effect is the possibility of abnormal development of a fetus, so fertile women must use adequate contraception while taking the drug and for four weeks after treatment. Other side effects include very dry lips and dry facial skin, which can be minimized by regular use of lip balms and oil-free moisturizers. Isotretinoin may also have psychological effects on patients, causing depression and mood changes. Topical **antibiotics** are helpful in reducing inflammatory acne lesions like papules (small raised bumps) and pustules. Clindamycin and erythromycin are common choices. Studies have shown that minocycline is the most effective drug, followed by doxycycline, trimethoprim, oxytetracycline and erythromycin. A major concern with the use of systemic antibiotics is the development of resistance of acne bacteria to the antibiotics. Combining topical benzoyl peroxide with oral antibiotics can reduce the risk of this. Hormonal therapy with the anti-androgen drug **spironolactone** is used because androgen hormones control sebum production. Spironolactone is also a diuretic used to treat heart failure, liver disease and high blood pressure (Davenport et al '03: 115, 116).

**Antibiotics** may be used when eczema is infected. The most commonly implicated organism is *Staphylococcus aureus* (staph), best treated with an Epsom salt bath, can be treated with oral antibiotics for 7 to 10 days. Short course of topical antibiotics cause no problems but prolonged use can lead to drug resistance. Flucloxacillin is effective in 90 percent of staph infections. Erythromycin is useful for people who are allergic to penicillin. Recurrent infections can be treated with antiseptic bath oils and emollients (Davenport et al '03: 113, 114). It does not matter than doxycycline and clindamycin for pregnant women and children under 8 are the drugs most indicated to treat MRSA. MRSA is best treated with an Epsom salt bath, or swim in saline or chlorine pool, or ocean. **Mycobacterial disease** such as leprosy and tuberculosis require special drugs. **Dapsone** (diaminodiphenylsulfone) was tested out on Jewish internees by Vonkennel (University of Leipzig at the concentration camp in Buchenwald in gruesome experiments in which they were subjected to poison gas, inducing severe burns, many of them dying in the process. Vonkennel, who was also the director of the SS Research Institute V, ran the only skin clinic in Germany whose research was still being funded by the Nazi government. In the early 1940s dapsone and related sulfones gained worldwide recognition for treating leprosy and other infectious diseases. Dapsone (diaminodiphenyl sulfone, DDS), rifampin, and isoniazid are all quite effective and used to this day for the treatment of leprosy (Baker '08: 41, 42, 45).

**Herpes simplex** causes the viral infection of the lips known as a cold sore, as well as genital herpes. The affected area should be kept clean by gentle washing with soap and water, then carefully dried. Antiviral creams such as **acyclovir** and penciclovir are sometimes effective when placed directly on blisters. They do not cure herpes simplex, but they shorten the duration

of symptoms by a few days. Herpes zoster is the virus that causes shingles. No drug can eliminate the virus, but antivirals such as acyclovir or famciclovir can be given by mouth for a short period of skin eruption. Human papillomavirus causes **warts**. Treatment depends on the location, type and severity of the wart, and how long it has been on the skin. Most common warts disappear without treatment within two years. Daily application of solutions or bandages containing **salicylic and lactic acids** soften the infected skin, which can be peeled off to make the wart disappear faster. A doctor can freeze the wart with liquid nitrogen or can use electrodesiccation or laser surgery. A wart can also be treated with the chemicals trichloroacetic acid, cantharidin salicylic acid or podophyllum resin in alcohol (25% solution) depending on the type of wart; the wart is destroyed, but sometimes new warts crop up around the edges of the old one (Davenport et al '03: 116, 117).

The **common wart**, single small (under 6 mm) warts in adults or older children are best removed by electrosurgery. The recurrence rate is minimal, and one treatment usually suffices. The technique is to cleanse the area, anesthetize the site with 1% procaine or other local anesthetic, destroy the tumor with any form of electrosurgery, nip off or curette out the dead tissue, and desiccate the base. Recurrences can be attributed to failure to remove the dead tissue. No dressing should be applied. The site will heal in 5 to 14 days with only minimal bacterial infection and scar formation. **Warts around the nails** have a high recurrence rate, and cure usually requires removal of part of the overlying nail. Liquid nitrogen therapy is simple, effective but moderately painful, admonished to freeze lightly and not deeply. Alternatively, **Salicylic acid** (10%) in flexible collodion 30.0 may be applied to warts every night for 5 to 7 nights. The dead tissue can then be removed with scissors. Another form of treatment for multiple warts or warts in children is a **mild corticosteroid cream** 150.0 applied in very small quantity to each wart at night. Then cover the wart with Saran Wrap or Blenderm tape and leave the occlusive dressing on all night or for 24 hours. Repeat nightly. This treatment has the advantage of being painless and quite effective. Salicylic acid (2% to 4%) can be added to the cream for further benefit. Vitamin A, 50,000 units, 1 tablet a day for no longer than 3 months, is safe, for the resistant case, and warts have disappears after such a course of treatment

The procedure for **plantar warts** follows, pare down the wart with a sharp knife, apply **trichloroacetic acid solution** (saturated) to the wart, then cover the area with plain tape. Leave the tape on for 5 days without getting it wet. Remove the tape and curette out the dead wart tissue. Usually, more wart will remain and the procedure is repeated until the wart is destroyed. Treatment may take several weeks. **Fluorinated corticosteroid-occlusive dressing therapy** is applied to the wart(s) at night and covered with Saran Wrap, Handi-Wrap, or Blenderm Tape. Leave on for 12 to 24 to 48 hours and reapply. This form of treatment is painless. **Cantharidin tincture** is applied by the doctor to the pared wart. Cover with adhesive tape and leave on for 12 to 24 hours. This treatment can cause pain and infection, but is quite effective. The resulting blister can be trimmed off in 1 week and the medicine reapplied, if necessary. **X-ray therapy** is a painless form of therapy that can be used for single small warts. The dose should never be repeated to that side. The cure rate is fairly high. **Filiform warts** can be snipped off without anesthesia, with a small scissors. Apply trichloroacetic acid solution (saturated) cautiously to the base. This method is fast and effective, especially for children. Alcoholic white shake lotion 60.0 has been effective. Electrosurgery or liquid nitrogen may be used. **Moist warts** (condylomata acuminata) are characteristic, single, or multiple, soft, non-horny masses that appear in the anogenital areas and, less commonly, between the toes and at the corners of the mouth. They are not always of a venereal nature. Treatment involves **Podophyllum resin in alcohol** (25% solution). Apply once to the warts, cautiously. Second or third treatments are

usually necessary at weekly intervals. To prevent excessive irritation, the site should be bathed within 3 to 6 hours after the application. **Gardasil** helps protect against 4 types of HPV. In girls and young women ages 9 to 26 Gardasil helps protect against 2 types of HPV that cause about 75% of cervical cancer cases, and 2 more types that cause 90% of genital warts cases. In boys and young men ages 9 to 26 Gardasil helps protect against 90% of genital warts cases (Sauer '85: 184, 186).

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 paste 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 acuminata*). 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. 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,  $\beta$ -glucuronidase, 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). Apricot pits are as tasty as almonds.

### Herbal Remedies for Cancer

<b>Vitamin</b>	<b>Indication</b>
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.
<b>Mineral</b>	<b>Indication</b>
Selenium	Antioxidant. Works with vitamin E to protect body from oxidation. Found in grains.
<b>Herb</b>	<b>Indication</b>
Asian Ginseng <i>Panax ginseng</i>	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. Interacts 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.
Garlic <i>Allium sativum</i>	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 colic.
Turmeric <i>Curcuma longa</i>	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 <i>Arctium lappa</i>	The root is part of a very well-known Native American anticancer formula called Essiac.
Red Clover <i>Trifolium pretense</i>	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 <i>Rhodiola rosea</i>	Increase cellular energy production, protein synthesis, serotonin, norepinephrine and dopamine. Support DNA repair, antioxidant, anticarcinogenic, anticancer. Improves oxygen utilization.
<i>Rhododendrum caucasicum</i>	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 <i>Eleutherococcus senticosus</i>	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: Brown, Richard P., M.D.; Gerbarg, Patricia L., M.D. *The Rhodalia Revolution: Transform Your Health with the Herbal Breakthrough of the 21<sup>st</sup> Century*. Rodale. 2004

**Topical antifungal agents** are in most cases the first-line treatment for superficial fungal infections. Topical therapies avoid the potentially serious side effects of systemic treatments. Creams include miconazole (sold as Micatin) and ketoconazole (Nizoral), and **clotrimazole** (\$1 athlete's foot crème) which cause the loss of fungal cell membrane integrity and activity and stop fungal growth. Topical terbinafine kills the fungus. The principal side effects of such topical agents are local irritation and sensitivity reactions. Treatment generally lasts 4 to 6 weeks and may need to be continued beyond the clearing of symptoms. Systemic therapy may be required for chronic infections. Oral therapy is the preferred treatment for fungal nail infections and for fungal infections of the scalp and beard area. The site of infection and type of fungus determines the choice of oral agent. The drug terbinafine is frequently prescribed; it accumulates well in skin tissue and kills fungi, is well-tolerated, and interacts with few other drugs. If the yeastlike fungus *Candida* is involved in the infection, then a drug such as fluconazole (Diflucan) is an appropriate oral agent. In cases that do not respond to fluconazole, itraconazole (Sporanox) may be effective. Griseofulvin is the oldest of the oral antifungal agents. It is now only used for ringworm of the scalp in children (Davenport et al '03: 116, 117). Hydrocortisone crème seems to be the cheapest and most highly effective treatment for mold infections above the shin, particularly *Aspergillus* spp.

**Topical corticosteroids** may be used in difficult cases for short periods. Topical corticosteroids are used to control flare-ups of eczema. They inhibit the production and action of chemicals that cause inflammation in the skin, thereby reducing inflammation and itching. **Oral corticosteroids** are occasionally prescribed to quickly control a severe flare-up of eczema. They are usually taken in high initial doses, which are then reduced every few days over a course of 3 to 4 weeks. As the dose is reduced, topical steroids are increasingly used to counteract the disease flare-up that can occur on withdrawal from the oral steroids (Davenport et al '03: 113, 114). Two new types of treatment for skin diseases became available after World War II; glucocorticosteroids and folate analogues. Despite its anti-inflammatory effects in RA, topical applications of **cortisone** for the treatment of skin diseases was not found to be beneficial, despite the fact that it penetrated the skin as well as clinically effective hydrocortisone and was converted to the latter in the skin. However, the availability of synthetic derivatives of corticosteroids hormones, at the beginning of the 1950s, revolutionized the treatment of skin diseases. These anti-inflammatory drugs were more potent than their natural counterparts and, administered topically in ointments and creams, avoided the side-effects experienced when the drugs were taken orally. In 1954-5 prednisolone and fluorocortisone were introduced. Prednisolone was 4 times as powerful as cortisone, whilst the replacement of the 9-hydrogen atom by halogen fluoride in fluorocortisone results in a 8-fold increase in its anti-inflammatory properties. Topical preparations of fluorocortisone, although clinically superior, were soon abandoned because of their effects on electrolyte balance.

The additional substitution of hydroxyl or methyl groups at position 16 on the steroid molecule was subsequently found to greatly reduce the unwanted side effects induced by the fluoride atom,, leading to the development of a wide variety of fluorinated steroids, including triamcinolone, dexamethasone and bethamethasone. Triamcinolone became available in 1958 and was administered systemically and topically in psoriasis with favorable results, over a period of 7-8 weeks, during which time the dose was reduced. Itching was relieved within 7 days, whilst clearance was observed within 3-7 weeks of commencing treatment in all but 2 of the

patients. A third of the patients remained clear 10 weeks after the end of treatment, minor side effects affected only two patients in this study but serious side effects such as "buffalo hump" hairy red face, decalcification of bone and hypertension were reported with higher doses of steroids and led to the discontinuation of the use of systemic steroids in psoriasis over the next few years. Triamcinolone acetonide was also used locally to treat psoriasis, either by intralesional injection, or combined with other treatments such as tar, which was more effective than steroid alone. However, together with increased potency came the increased likelihood of local side effects such as striae and atrophy of the skin, steroid-induced acne, purpura and glaucoma. Furthermore, systemic side effects could also be a problem (especially in children) if sufficient amounts of a potent steroid were absorbed (Baker '08: 51, 52).

### Equivalent doses of glucocorticoid drugs

Glucocorticoid	Approximate equivalent dose (mg)
Cortisone	25
Hydrocortisone	20
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
Betamethasone	0.6-0.75
Dexamethasone	0.75

Source: Bernatsky & Senécal '05: 49

Very powerful **corticosteroid** creams should only be used for a short period of time; a milder topical corticosteroid should be prescribed as the rash begins to respond to treatment. Like any medication, corticosteroids can cause side effects. Side effects are more likely to begin with doses of corticosteroids greater than the equivalent of about 7.5 mg of prednisone per day. The higher the dose and the more prolonged the treatment, the more likely it is that side effects will occur. **Side effects** of corticosteroids can include osteoporosis and osteonecrosis, facial changes and weight gain, moodiness, acne, facial hair, upset stomach, glaucoma and cataracts, adrenal insufficiency, high blood sugar (hyperglycemia), high blood pressure (hypertension), increased risk of infection and swelling or water retention necessitating salt elimination and calcium supplementation diet. **Stopping prednisone** suddenly when the body has become used to it, is very dangerous and could be fatal. Corticosteroids such as prednisone are very similar to the cortisone produced naturally by the body's adrenal glands. These two small glands, located close to the kidneys, produce hormones that regulate water and salt balance, along with many other functions. During corticosteroid treatment, because it notes the presence of prednisone, the body may "turn off" its own production of the hormones that drive the natural production of cortisone. Some difficulties can occur when the dose of prednisone is tapered below about 7.5 mg per day if the adrenal glands can't keep up. Difficulty can also occur when experiencing some very significant physical stressor, such as an infection or serious injury. In states of severe stress, the body normally produces doses of cortisone that equal at least about 15 mg of prednisone (Bernatsky & Senécal '05: 38, 48-52, 86).

## 5. Exercise

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).

The wide range of health and fitness levels observed among **older adults** make generic exercise prescription difficult. Major objectives in planning exercise for the aging adult and the person with dementing and disabling illness are to increase muscle tone to improve physical functioning, to increase flexibility and balance, to improve physical stamina or endurance, and to reduce stress and promote a feeling well-being. Aerobic activity, at least 3 times a week for 20 minutes, must be spaced throughout the week. If the person cannot tolerate 20 minutes of continual movement, recent research is showing that exercise can be broken into shorter blocks which total 20 to 30 minutes for the day. Usually walking, even slow walking, is aerobic for many aging adults. As age increases, the heart rate needed to perform aerobically decreases. A 10 second pulse rate between 15 and 19 will be more than adequate to sustain aerobic functioning in an adult between the ages of 70 and 90. Exercises designed to promote flexibility, range of motion and balance daily. Without stretching and utilizing all muscles, some will become stretched and others contracted, resulting in inability to utilize some muscles altogether. Typically, problems occur in the shoulders, arms, and legs. Caregivers must realize how extremely painful it is when muscles become weak, contracted, and out of alignment from lack of use (Bridges '98: 91-92). Poor athletic performance, like death, is not a natural part of aging, it is the result of disease and being out of shape. Unless a person, particularly males who so often die of laziness shortly after retiring, was a highly competitive athlete during their career, retirees should increase their daily exercise routine to an athletic level when they retire.

Optimal musculoskeletal function requires that an adequate range of motion be maintained in all joints. There are different types of **stretching techniques** that can be performed. Static stretching involves slowly stretching a muscle to the point of mild discomfort and then holding that position for an extended period of time (usually 10 to 30 seconds). Ballistic stretching uses the momentum created by repetitive bouncing movements to produce muscle stretch. Proprioceptive neuromuscular facilitation (PNF) stretching involves a combination of alternating contraction and relaxation of both agonist and antagonist muscles. As a rule stretches, with an emphasis on the lower back and thigh area, should be done at least 3 days week, to a position of mild discomfort, 10 to 30 seconds for each stretch, 3 to 5 repetitions. The maintenance or enhancement of muscular strength and muscular endurance enables an individual to perform such tasks with less physiological stress. **Resistance training** should be an integral part of adult

fitness and rehabilitative exercise programs to benefit increases in muscle strength and mass, bone mass, strength of connective tissue, modest improvements of cardiorespiratory fitness, reductions in body fat, modest reductions in blood pressure, improved glucose tolerance and improved lipoprotein profiles. Muscular strength and endurance are developed by the overload principle, by increasing the resistance to movement or the frequency or duration of activity to levels above those normally experiences (Mahler et al '95: 170-174).

A **standardized physical training session** consists of three essential elements: warm-up, activity, and cool-down. The body must be adequately warmed up to treat rheumatic complaints and prevent injury during running or other vigorous, strength exercises are more curative and protective than stretches. After vigorous exercise stretching affected muscles for ten or twenty seconds helps to prevent cramping and pain from overuse. The **military physical training prescription** takes approximately 45 minutes per day, and should be done everyday. Whether following walk-to-run guidelines or training at a higher level, the military program will help to ensure minimal standards of physical fitness. 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 as your fist. Do not perform exercises that cause indigestion that could lead to ulceration such as running, or sit-ups, immediately after a large meal, although push-ups may not cause discomfort and other slower exercises can actually aid digestion (TRADOC '03).

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. 100 push-ups, 100 sit-ups and three mile run in less than 28:00 minutes is the goal. Clients often start out doing push-ups on their knees and work up to 40 to 50 regular push-ups without stopping to rest. 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 **Marine Corp Physical Fitness 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.

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 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 (Mahler '95:169). 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.

One of the reasons for a **running routine** is the belief that running gives some immunity to the atherosclerotic process, protection against heart attacks and increased life expectancy due to a better all around prognosis due to self-diagnosis of minor arthritic conditions and speedy elimination of toxic buildups. Running also makes one feel good. Runner's high is a phenomenon which seems to be enjoyed by most long-distance runners, but not every run. It has been described as a feeling of gliding or as if the mind is separated from the running body as in a state of euphoria. The onset of the runner's high most often begins after running for 20 to 30 minutes. For long term health benefits, such as the elimination of tumors or atherosclerosis, a great deal of dedication and achievement are necessary. Significant elevation of the plasma HDL-cholesterol levels was confined either to those joggers who had been running for at least four years or to those who were running at least 56 km (36 miles) per week. It may be necessary to run at least 70 km (43 miles) per week in order to significantly raise the level of the plasma HDL-cholesterol. Elite runners and endurance swimmers have very high levels of succinate dehydrogenase (SDH). The SDH enzyme levels are used to indicated the level of oxidative capacity of the muscles, and when SDH levels are high, highly active mitochondrial oxidative capacity is generally indicated (Taylor '82: 89, 86, 87, 19, 20, 87, 88).

Many top **marathon runners** train in excess of 150 miles per week, but the most common mileage base is probably 100 to 120 miles per week. The term "long distance runner" is sometimes used to describe the runner who trains between 50 and 70 miles per week at a pace of between five to seven minutes per mile. The term "elite runner" is reserved for the runner who trains much more than 70 miles per week at paces equal to or faster than the long-distance runner. Some runners feel that the minimum weekly mileage baseline is 40 miles per week, while others feel that a runner can only "gut-out" three times his average daily mileage. Another guideline runner feel is important to avoid injuries is that a runner should not increase his weekly running mileage by more than 10% per week. Most world class runner train daily. Their daily routine may include two-a-day runs of 10 miles each, or their daily routine may include running shorter distances three or four times daily, but they will need to run at least one 20 + mile once a week. Hill training seems to be associated with an increase in training injuries, especially Achilles tendinitis. The practice of heat acclimatization over a course of 14 days is useful to prevent injury. Altitude also requires 14 days acclimatization. Injury factors. Pre-race factors: improper physical conditioning including too few 20+ mile practice runs, inadequate heat or altitude acclimatization, sickness just prior to marathon, injuries sustained, improper dietary techniques and other training errors. Race factors: initial pace too swift, overall pace too swift, inadequate assessment or adjustment to race conditions, insufficient or inadequate fluid intake, viral prodrome during race or frank illness, hilly course ,environmental factors such as wind, elevated ambient temperature and humidity high solar heat gain and inappropriate racing attire. Performance factors. Pre:race factors: adequate number of 20+ miles runs, proper heat or

altitude acclimatization, carbohydrate loading, caffeine ingestion, selection of proper racing attire. Race factors: proper initial pace, proper overall pace for weather and course conditions, caffeine ingestion, lightly sugared fluids ingested (Taylor '82: 42-47, 50, 85, 86).

It has been estimated that of the over 20 million runners in the United States in 1982 more than 30% have competed a marathon. During a war between Athens and Persia in 490 B.C., a messenger, believed to be named Pheidippides, ran almost 22 miles across the plain of Marathon carrying a message to the Athenian agora. Upon reaching his destination and delivering the message, this runner collapsed and died. In 1896, the idea that the marathon should be an Olympic event was suggested. In 1908, the distance of the marathon, as we know it today, was established, as the distance between the royal residence at Windsor Castle and the royal box at the White City Stadium, or a distance of 42.2 km (26.2 miles). Since 1908, the popularity of marathon running has increased steadily, with a marathon boom occurring during the past decade. From 1968 to 1978 the number of marathons in the United States increased from approximately 40 to 320 with the total number of entrants in 1978 being nearly 60,000. Average running velocities of the winners of the Boston Marathon from 1897 to 1981 increased steadily. Many of the women marathon winners over the past few years are faster at covering the 26.2 miles than the men winners of some prominent marathons only 15 to 20 years ago (Taylor '82: 49, 2).

One method of studying the training in an athlete is to measure the **maximum oxygen consumption**,  $VO_2$  max. Physical training results in an increase in  $VO_2$  max. Normally active young men age 20 have values ranging from 60 to 80 ml/kg/min. The basic hematologic changes which enhance the maximum oxygen consumption are increased plasma volume, increased red blood cell mass and increased total hemoglobin concentration. Enhancement in the cardiovascular system is seen by resting bradycardia and left ventricular dilation and hypertrophy. The basic skeletal muscle changes to enhance the maximum oxygen consumption are an increase in mitochondria and myoglobin content of the muscles, increased number of capillaries supplying the muscle fibers, and possible changes in the type of specific muscle fibers. According to the Fick Principle, the oxygen utilization is equal to the product of the flow rate of blood and the volume of oxygen extracted from arterial blood. In general, athletes tend to have large hearts. Resting bradycardia is a universal parameter in trained athletes. Those trained for endurance running have the slowest resting heart rates, and resting heart rates below 40 beats per minute are not uncommon. This resting sinus bradycardia can give rise to first-degree atrioventricular heart block, a wandering pacemaker, a second-degree atrioventricular heart block of the Wenckebach type or a junctional rhythm (Taylor '82: 6, 7, 15, 16).

Three types of **muscle fibers** have been identified by staining muscle fiber biopsies. The Type I fiber tends to be a slow twitch (ST) fiber, while the Type II fibers are of the fast twitch (FT) variety, subdivided in Type IIa ( $FT_a$ ) and Type IIb ( $FT_b$ ) having the fastest contraction time. A typical muscle biopsy contains 200 to 400 muscle fibers. In men  $FT_a > ST > FT_b$  and in women  $ST > FT_a > FT_b$ . Endurance athletes have a high percentage of  $FT_a$  fibers and relatively few, if any  $FT_b$  fibers in the muscle groups involved in the endurance training. Weight lifters on the other hand, were found to have a decrease in  $FT_a$  number and a hypertrophy of the remaining  $FT_a$  fibers and the  $FT_b$  fibers. The runners had a much higher percentage of ST and  $FT_a$  fibers with relatively few  $FT_b$  fibers. Power lifters tired faster in all exercise regimes tested. Currently, long distance running and weight lifting are felt to be detrimental to the ultimate performance of either activity alone, but many serious runners include weight training as part of their overall training. Training may alter a runner's muscle performance to a certain degree, but genetics may

be the ultimate limitation. Maximum oxygen capacity may be limited by the conditioning of the skeletal muscles, as well as the percentage of muscle fiber type (Taylor '82: 19, 23, 25).

**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<sup>2</sup>/hour have been observed. Thus 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 delays 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).

Salts of sodium, potassium and chloride added to athletic drinks are designed to replace electrolyte loss during heavy perspiration. However, relatively small amounts of electrolytes are lost, even during prolonged exercise, and the need for immediate replacement remains controversial. As glycogen is stored, large amounts of water and potassium are stored intracellularly. As glycogen is used as an energy source, potassium and water are liberated and

the immediate need for exogenous potassium is probably insignificant in most cases. The fluid which the body has lost and needs the most of, is water. Cold water in sufficient quantities throughout the race to slightly distend the stomach without evoking pain or cramps seems to be the most effective. Even moderate quantities of carbohydrates ingested within an hour or two prior to running a marathon can result in a poor performance due to elevated insulin levels. The ingestion of 250 mg caffeine approximately one hour prior to an at intervals during endurance cycling significantly increases performance, work production (7.4%) and maximum oxygen capacity (7.3%) as compared to control groups. Coffee is a good source of caffeine. One gram of ascorbic acid, vitamin C, on a daily basis for two weeks significantly improves performance. Prerace fluids should have at least some of the following characteristics: they should contain little or no carbohydrates, they should contain caffeine, they should be of 500 ml to 750 ml in volume, and they should be ingested at least 10 to 15 minutes prior to race time. Fluids should be ingested early and often (Taylor '82: 33, 34).

The total caloric expenditure of runners completing a marathon is difficult, if not impossible to measure accurately. 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<sup>2</sup>/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<sup>2</sup>/hr. For thin runner 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. Solar heat gain can result in hyperthermia (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. If an elite marathon runner did not make a major increase in daily caloric intake, in a period of only a few months of training, they would not have the muscular strength to run. 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 and 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: 57, 60, 71, 72).

Considering that a runner's feet are forcefully driven to the ground over 1,000 times a mile at a force which is a few times their body weight, and that this force is conducted to the legs and back, it can be seen that any minor anatomical or bio-mechanical flaw can produce injury. Nearly one third of the reported injuries to serious runners involve **knee injury**. The runner who describes the pain as a dull ache underneath the medial aspect of the patella is giving a classic account of chondromalacia of the patella, or runner's knee. The pain may lessen while running, and it may occur at the end of a workout or later in the day. Prolonged sitting may exacerbate the pain, and attempts to "run through" the pain may worsen the condition. Acute treatment consists of ice pack, rest and anti-inflammatory medication. When the pain subsides, progressive resistive exercise for leg extension to strengthen the quadriceps muscle group, especially the vastus medialis, which is used primarily in the last 15° of extension, is indicated. Knee wraps and antirotation braces have been used by some. (If the knee injury does not get better metronidazole (Flagyl ER) is highly effective at curing the infected injury to avoid expensive but effective knee surgery, a common cruel test of the patience of medical college aspirants, to see if they are quacks or "practice metronidazole". The runner who complains of a burning pain that occurs about the Achilles tendon early in a run, becomes less painful during the run, and usually worsens after the run, probably has **Achilles tendonitis**. This is a common running injury that may be caused when a runner increases the amount of hills. A running shoe with an inadequately padded heel wedge may also predispose to his injury. The acute treatment usually consists of ice packs, non-steroidal anti-inflammatory medication, reduced hill running or reduced running in general, or correction of improperly padded heel wedge in the running shoe by inserting a heel lift, or by purchasing a new pair of running shoes with appropriate design.

**Plantar fasciitis** is a common overuse running injury that causes heel pain usually during the beginning of a run or between runs. As with many of the overuse injuries, the pain is severe during the onset of running, diminishes during the run, and returns at some time after finishing the run. The plantar fascia, which has its attachment to the tuberosity of the calcaneus, may become inflamed with overuse. Again, ice packs, rest, and anti-inflammatory medication are indicated for treatment. The use of the term **shin splints** usually describes the condition where there is pain over the distal third of the medial tibia. Bony stress fractures of the tibia occur in normal fatigued bone usually from increased or prolonged muscular force applied by the muscles which attach to the tibia. Ischemia of the muscles of the lower leg has also been proposed as a causative mechanism for the syndrome of shin splints. The soft tissues of the lower leg may also give rise to the pain associated with myositis, periostitis or fasciitis (Taylor '82: 52, 53).

Classical **heat injury** can be considered as a progressive continuum beginning with heat cramps, progressing to heat exhaustion, and if left untreated, continuing to heat stroke and possible death. Heat cramps generally occur after heavy prolonged perspiration losses are coupled with inadequate fluid replacement. Muscle twitching may be a prelude to frank muscle cramping and spasm. If, in a race, a marathon runner develops heat cramps, it will prevent the runner from continuing the race. Rest and fluid replacement are indicated as treatment. **Heat exhaustion** may take the form of headache, nausea, vomiting, confusion, or light-headedness with or without muscle cramps. Classically, the runner ceases to sweat and the skin becomes clammy. Heat exhaustion is a severe running injury, which is rarely fatal but may require intravenous fluid therapy and body cooling with cold towels in severe cases. **Heat stroke**, which is a medical emergency, usually occurs when a runner has run through the presenting signs and symptoms of heat exhaustion. Swathing has stopped and the skin is usually very warm and dry. Concomitant signs include irrational behavior, seizures, cyanosis, vomiting, diarrhea, and chorea; in some cases death ensues. Initial treatment is similar to that for heat exhaustion. A high incidence of

**hematuria** following the prolonged, strenuous stress of marathon running in runners free of known renal disease and with negative pre-exercise urinalysis has been reported. In fact 28% of the 50 physician marathon runners tested before and after the 1978 Doctor's Marathon portion of the Boston Marathon showed post-race hematuria. This type of hematuria seems to be frequent, self-limited and benign condition which usually returns to normal within 48 hours after the severe exertional stress. **Sudden cardiac death** (SCD) in athletes can be classified in four categories (1) unrecognized preexisting heart disease, which explains the majority of deaths; (2) excessive environmental stress with both extreme heat and cold being implicated; (3) blunt cardiac trauma; (4) the overstressed heart, which is the type of death seen in dedicated athletes during extreme exertion such as attempts to break a personal record or a world record. Over 200 cases of sudden cardiac death have been reported during marathons (Taylor '82: 54, 55).

The most common problem associated with sporting activity are fungal infections, and the most common of these is **athlete's foot**, which develops between the toe webs and may also involve the nails. Small particles of skin may be rubbed from the soles of the feet onto the floor of changing rooms, swimming pools, etc. and may be picked by the next person who walks over the area. If the skin infection is recognized and treated promptly, it can usually be cleared relatively easily. If, however the infection on the skin is not recognized or is ignored, the same fungal infection may spread to involve the nails. When this happens the nail becomes rough, crumbles and develops irregular white patches. The nail may become very thick and difficult to cut. This can lead to pain and difficulty finding comfortable shoes. Once the nails are involved with fungal infection, curing the problem is very much more difficult. It takes from 1 to 2 years for a toe-nail to grow right out, and treatment for fungal infection of the toe-nail needs to be continued for this entire period of time. Even then it is very easy to re-infect toe-nails from shoes, and many people who developed fungal infection of toe-nails when they were teenagers still have the problem 20, 30 and even 40 years later. For many years the most effective oral treatment available was friseofulvin. This was very effective in the treatment of infections of the skin, although less effective for treatment of the nails. As the present time there are some exciting new developments in the treatment of fungal infection of the skin, and newer drugs which are very effective in the treatment of fungal infection of the nail, are now becoming available. One of these is terbinafine (Lamisil), clotrimazole (athlete's foot crème) is effective. Hydrocortisone crème for fungal infections above the shin. Other skin problems associated with sporting activities include friction and chafing, sometimes even blisters, caused by ill-fitting, usually tight, footwear. Sports shoes should be comfortable for the sport being played (Mackie '92: 92, 51-53).

## 6. Diet

The best approach to preventing heart disease and cancer is the tried-and-true combination of exercise, eating a healthy diet, weight control, not smoking and undergoing appropriate cardiovascular health and cancer screenings (Mooney '07: 76). 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).

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, we 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, we 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 polycyclic hydrocarbon (Greaves '00:185-189).

A **calorie** is the heat required to raise the temperature of 1g of water 1°C. 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 legumes and nuts. 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). In cancer patients protein-caloric deficiency is often cited as a

serious complication leading the rapid weight loss characteristic of advanced cancer, however a protein free diet, is often curative.

The most important vitamins and minerals for the health of the skin are vitamin A, the B vitamins, vitamin C, vitamin E and zinc. **Vitamin A** helps maintain the structural integrity of skin cells. A deficiency disturbs the delicate balance of the skin and results in the loss of cells that produce lubricants to keep the skin soft and supple. This in turn leads to infection, irritation and sloughing off of the surface of the skin. Everyday foods contain two forms of vitamin A: retinol, which is derived from animal products, and carotenes (mostly beta-carotene), which can be found in fruit and vegetables. The best sources of retinol are liver, fish liver oils, kidneys, dairy foods, and eggs. Beta-carotene is found mainly in carrots and dark green, yellow, or orange vegetables. The darker the vegetable, the more beta-carotene it contains. The recommended daily intake (RDI) of vitamin A is 700 micrograms for a man and 600 micrograms for a woman. A glass of carrot juice or a 90 gram serving of spinach provides the daily amount; a serving of liver or liver pate exceeds it at least fourfold. **B-group vitamins** Niacin is a B vitamin, and niacin deficiency has been linked to a disease called pellagra. Symptoms include dermatitis, in which the skin becomes dark and scaly – especially when exposed to light – as well as diarrhea and dementia. Although it is rare to develop a deficiency in the U.S. an adequate amount must be secured in the diet. The U.S. RDI for niacin is 13 to 18 milligrams for adults and 9 to 13 for children. Good sources include meat, potatoes, bread and fortified breakfast cereals. Deficiency of B-group vitamins riboflavin (vitamin B<sub>2</sub>) and pyridoxine (vitamin B<sub>6</sub>) cause skin lesions or sores, especially at the corners of the mouth, eyelids, and genital areas. Deficiency is rare unless the diet is short on milk, meat, fortified cereal products and eggs. The RDIs for riboflavin and pyridoxine are 1.7 milligrams and 2 milligrams, respectively, for all adults. The B-group vitamin biotin is needed in small amounts by the body to break down fat. A rich source is egg yolk, and smaller amounts are found in milk and dairy products, cereals, fish, yeast, fruit and vegetables. Biotin deficiency is rare. It can occur if excessive amounts of raw egg white are consumed. Raw egg white contains the compound avidin, which attaches or binds itself to biotin making it unavailable to the body for absorption. In such cases, deficiency leads to a dry scaly dermatitis.

**Vitamin C** is an important antioxidant that helps maintain healthy tissues and fight wrinkles. It also plays an important role in the formation of collagen in the skin. A deficiency results in bleeding, especially from blood vessels underneath the surface of the skin and the gums. The best sources include citrus fruits, potatoes, peppers, cabbage and eggplant. The RDI is 60 milligrams for all adults. **Vitamin E** is another important antioxidant for healthy skin. It helps maintain the structural integrity of cell membranes. This vitamin is found in many foods and, because it is fat soluble, can be stored in the body, so deficiency is rare. The richest sources are vegetable oils, nuts and seeds, some cereal products, and egg yolk. The RDI is 8 to 19 milligrams per adults – cooking 1 tablespoon of sunflower oil and eating a handful of hazelnuts produces the daily requirement. **Zinc** works with vitamin C to make healthy collagen – an essential compound of connective tissues. The total amount of zinc in the adult body has been estimated to be about 1.4 to 2.3 grams, of which 20 percent is in the skin. A deficiency can lead to weeping dermatitis around the body orifices and on the extremities such as hands and feet, eczema, poor wound healing, and reduced immune system function. Zinc deficiency has also been shown to worsen preexisting acne. Oysters, pumpkin seeds, pecan nuts, red meat, whole wheat, and rye flour are all good sources. The U.S. RDI is 15 milligrams per day for adults. **Essential fatty acids** are type of polyunsaturated fat that are deemed essential because they must be derived from the diet – the body cannot make them from other polyunsaturated fats. These

EFAs are called omega-3 and omega-6 fats, and they help hydrate the skin and increase its moisture content. A deficiency of EFAs can result in a scaly rash because water loss from the skin increases. Topical application on the skin have been shown to reverse these symptoms. Good sources of EFAs include oil fish, vegetables, and red meat. There is not yet an RDI EFAs, but many doctors recommend 0.65 gram of omega-3 (no less than 0.2 gram) and 4.4 grams of omega-6 per day. Flax seeds (and flax seed oil) are also good sources of EFAs. Flax seeds can be sprinkled on salads and cooked vegetables or combined with flour to make breads and pancakes. Flaxseed oil comes in an edible form and, like olive and rapeseed oils, is high in unsaturated fats, which is heart healthy. It also contains lignans, which have anticancer properties (Davenport et al '03: 68, 69).

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). 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<sub>12</sub> 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).

### Vitamin and Mineral Deficiencies

Site	Sign or Symptom	Deficiency
Hair	Dryness Alopecia Easy pluckability Corkscrew hair Color change	Zinc Zinc Vitamins E and A Vitamin C Biotin
Nails	Dystrophic	Iron
Skin	Hyperpigmentation Erythema Scrotal dermatitis Follicular keratosis Acneiform lesions Xerosis Ecchymosis Petechiae Nasolabial seborrhea	Niacin Niacin Niacin Vitamin A Vitamin A Vitamin A, linoleic acid Vitamins C and K Vitamins C and K Vitamin B <sub>6</sub>
Eyes	Angular palpebritis Bitot's spots Conjunctival keratosis Keratomoalacia	Vitamin B <sub>2</sub> Vitamin A Vitamin A Vitamin A

Mouth	Glossitis Angular stomatitis Cheilosis Magenta tongue Scarlet, raw tongue Atrophic papillae Swollen, bleeding gums	Vitamin B <sub>12</sub> , niacin, folate Vitamin B <sub>2</sub> Vitamin B <sub>2</sub> Vitamin B <sub>2</sub> Niacin Niacin Vitamin C
Neurologic	Peripheral neuropathy Wernicke's encephalopathy Encephalopathy (Pellagra) "Burning feet" syndrome Loss of deep tendon reflexes	Thiamine, niacin, B <sub>6</sub> Thiamine Niacin Pantothenic acid Thiamine, vitamin B <sub>1</sub> & B <sub>12</sub>
Musculoskeletal	Osteomalacia  Joint pain Tender muscles	Vitamin D, calcium, phosphorus Vitamin C Thiamine
Hematologic	Hemolytic anemia Macrocytic anemia Microcytic anemia Coagulopathy Thrombocytopenia	Vitamin E Vitamin B <sub>12</sub> , folate Vitamin B <sub>6</sub> , iron, copper Vitamin K Linoleic acid
Visceral	Congestive heart failure Diarrhea Goiter Hepatosplenomegaly	Thiamine Iron, folate, zinc, niacin Iodine Zinc

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

In some individuals **food allergies** have been linked to the consumption of milk, eggs, fish, shellfish, nuts and strawberries, and if any one of these is implicated, exclusion of that food is advised. This type of allergy arises in early childhood and appears to trigger abnormal inflammatory processes in the skin that are chronic and recurrent. If the colon is not moving food efficiently or if the liver or kidneys are struggling to process waste, toxins may build up in the bloodstream. This may have an impact on the appearance of the skin. To aid the proper functioning of the digestive system, it is important to eat plenty of fiber. Many people find that drinking a cup of warm water with a squeeze of fresh lemon juice first thing in morning helps flush out toxins, and herbalists recommend milk thistle supplements to help cleanse the liver and improve skin health. The average adult should consume 2.5 quarts of water a day. This will help to avoid dehydration, which can lead to dull, lifeless, dry skin. Although rarely seen in Western countries, malnutrition can lead to a skin condition in which a sequence of changes similar to sunburn occur. The skin becomes darker, with the outer skin becoming dry and thin, and is easily split and ulcerated (Davenport et al '03: 70).

A **well balanced diet** for the general good health of the hair and nails. Iron keeps blood in good health but also has an effect on the condition of the hair. General hair loss has been linked to low iron levels. To maximize iron absorption, various dietary factors should be considered when preparing a meal. Consuming vitamin C-rich foods such as fruits, vegetables and juice with a meal will double or triple the amount of iron absorbed from nonmeat or fish sources. Protein-rich foods such as meat, fish and seafood promote the absorption of iron. Fermented products such as soy sauce enhance the absorption of iron. Tea, coffee, cocoa, spinach, and spices contain

compounds called phenols that inhibit iron absorption from legumes, cereals, and vegetables. Calcium-rich foods such as milk and cheese interfere with the absorption of iron in a meal. To optimize iron levels, include **iron-rich foods** the diet. The best sources are red meat – especially liver – egg yolks, dried fruit, fortified breakfast cereals, and green leafy vegetables. Then, to maximize iron absorption, eat these foods together with those that are high in vitamins. Try not to drink tea or coffee for at least half an hour after a meal to minimize the adverse effects of tea, coffee and milk on iron absorption. The RDI for iron in infants up to 6 months old is 6 milligrams; for those up to 1 year old and adult men, it is 10 milligrams. Women and adolescent girls need 15 milligrams per day, 30 during pregnancy. Malnutrition can have serious effects on the hair, weakening its attachment to the skin so that it falls out easily and painlessly. Remaining hair becomes thin and straight and may turn gray. Patients can go completely bald, although this is usually reversible. Iron deficiency can cause nails to become spoon shaped, brittle and thin. Two sources of iron – hem and nonhem – can be found in food. Very small amounts of the B-group vitamin biotin is needed for the formation of strong nails. This can be produced by the bacteria in the large intestine. Rich sources include egg yolk, milk and dairy products, liver and other organ meats, soy products, and yeast. Calcium is the most abundant mineral in the body, with about 99 percent of it in the bones, teeth, and nails. When bound together with phosphorous, calcium strengthens the skeleton. Few foods besides milk, yogurt, cheese, most breads, calcium-fortified soy milk, tofu, green leafy vegetables and hard water contain significant amounts of calcium. The RDI for calcium for an adult is 1100 milligrams a day, which is achieved, for example, by eating a container of yogurt, a small chunk of cheese, and a serving of young leaf spinach. Breastfeeding mothers require an additional 500 milligrams a day. To meet this, add a serving of tofu and a slice of white bread, for example, or a serving of canned sardines with bones and handful of raisins. Vitamin D is formed when UV light converts 7-dehydrocholesterol in the skin into vitamin D<sub>3</sub>. A protein in the skin then transports it to the blood and the liver for use (Davenport '03: 71, 72, 75). The juices of normal humans contain 400-500 mg of hydrochloric acid. Its pH lies between 0.97 and 0.80 (Gerson (Gerson '90: 165). This is a very powerful acid and one must be very careful of what one eats so as not to upset one's stomach.

Cancer is a chronic, degenerative disease, where almost all essential organs are involved in the more advanced cases: The entire metabolism with the intestinal tract and its adnexa, the liver and pancreas, the circulatory apparatus (the cellular exchange supporter), the kidneys and bile system (as main elimination organs), the reticulo-endothelial and lymphatic system (as defense apparatus), the central nervous system and especially the visceral nervous system for most metabolic and motoric purposes. In the nutritional field, observations for centuries have shown that people who live according to natural methods in which plants, animals and human beings are only fragments of the eternal cycle of Nature do not get cancer. On the contrary, people who accept methods of modern nutrition on an increasing scale become involved in degenerative diseases, including cancer, in a relatively short time. In later medical history the best known cancer-free people were the Hunzas, who live on the slopes of the Himalaya mountains and who use only food grown in their own country and fertilized with natural manure. Imported food is forbidden. Very similar is the story of the Ethiopians who also have natural agriculture and living habits which seems to prove that this type of agriculture keeps people free of cancer and most of the degenerative diseases. In 1954 it was reported from Central Africa that many natives, especially those who are living in larger communities, do not live now the same way as formerly – they used to live almost exclusively on fruits and vegetables, bananas, cassava, agnam, taro, sweet potatoes and other fruits. They now live on condensed milk, canned butter, meat and fish preserves and bread and the hospitals now see cancer patients. The Bantu

population of South Africa has 20 percent primary liver cancers. Their diet, of a very low standard, consists chiefly of cheap carbohydrates, maize and mealy meals. Seldom do they have fermented cow's milk. Meat is eaten only at ceremonies. When an extract of the liver of a Bantu man was painted on the back of mice, tumors developed (Gerson '90: 11, 14, 15).

Vegans live on average six to ten years longer than the rest of the population and in fact seem to be healthier on every measurement we have of assessing health outcomes. 60 to 70 percent of all cancers can be prevented by staying physically active, not smoking and most important, by choosing predominantly plant-based diets rich in a variety of vegetables, fruits, legumes and minimally processed starchy staple foods. Vegetarian diets decrease the risk of cancer. The vast majority of all cancers, cardiovascular diseases, and other forms of degenerative illness can be prevented simply by adopting a plant-based diet. Vegetarians eat more fruits and vegetables than meat-eaters. This is one of the reasons vegetarians live longer, and cancer rates for vegetarians are 25 to 50 percent less than those of the general populace, even after controlling for smoking, body mass index and socioeconomic status. A low-fat plant based diet would lower the heart attack rate about 85 percent, and cancer rate 60 percent (Robbins '01: 14, 15, 21, 22, 39, 47). The main task of the saltless diet is to eliminate the retained Na, Cl, H<sub>2</sub>O, together with toxins and poisons from the tissues all over the body. All poisons and other substances difficult to eliminate are stimulants for the sick tissues, especially liver and kidneys. Sodium chloride excretion increases in tuberculosis, cancer and other chronic diseases after two to three days on a saltless diet, and this condition stays at that higher level for several weeks corresponding to a favorable development in the course of the disease. Indications for a saltless diet are high blood pressure, edema and abnormal deposition of sodium and chloride in the subcutaneous tissue (nephropathias), cardio-renal insufficiency, K-loss and Na-retention, and detoxification (Gerson '90: 165, 158).

The adverse health impacts of excessive meat-eating stem in part from what nutritionists call the “great protein fiasco” a mistaken belief of many Westerners that they need to consume large quantities of protein. This myth has resulted in Americans and other members of industrial societies ingesting twice as much protein as they need. Among the affluent, the protein myth is dangerous because of the saturated fats that accompany protein and dairy products. Those fats are associated with most of the disease of affluence that are among the leading causes of death in industrial countries: heart disease, stroke, breast, lung and colon cancer. 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. Although much smaller than lipids, protein is by its very nature too large to be absorbed into human cells which are themselves composed of protein and must be broken down into amino acids to pass through the cell walls. Vegans recovering from cancer generally try not to mix large quantities of certain vegetables together, like rice and beans or beans and corn, to avoid making the complete proteins, most Americans eat in excess (Robbins '01: 71, 67). People who are gluten (wheat protein) intolerant, acute heart attack and acute cancer patients must scrupulously avoid all intentional consumption of protein, and often become deficient in essential vitamins and minerals in the process of recovering. Gluten is debilitatingly painful but other proteins causing only minor discomfort will sustain the allergy,

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 many 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 gluconeogenesis 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.

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. The 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).

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 Monsanto's 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 premenopausal 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).

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 took 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).

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 – chlorpyrifos, coumaphos, fonofos, phorate, permethrin 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). Chemically grown vegetables may be eaten for food, but they cannot be used as medicine (Fukuoka '77.100).

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 (Gerson '90: 139).

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 scaping 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).

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-- Ihde, Daniel C. *Small Cell Lung Cancer*. Chapter 26. Pgs. 195-200

-- Osborne, C. Kent. *Breast Cancer*. Chapter 27. Pgs. 201-211

-- Jacobs, Charlotte D. *Head and Neck Cancers*. Chapter 28 Pgs. 212-222

-- Macdonald, John S. *Gastrointestinal Cancers*. Chapter 29. Pgs. 223-241

-- Friedman, Michael A. *Cancers of the Pancreas and Hepatobiliary System*. Chapter 30. Pgs. 242-245

-- Yagoda, Alan. *Genitourinary Cancers*. Chapter 31. Pgs. 246-260

-- Bosl, George. *Germ Cell Tumors*. Chapter 32. Pgs. 261-269

-- Young, Robert C. *Gynecologic Cancers*. Chapter 33. Pgs. 270-291

-- Elias, Anthony D.; Antman, Karen H. *Soft-Tissue and Bone Sarcomas*. Chapter 34. Pgs. 292-303

-- Kelsen, David. *Tumor of APUD Cell Origin*. Chapter 36. Pgs. 316-322

-- Creagan, Edward T. *Malignant Melanoma*. Chapter 37. Pgs. 323-328

-- Wittes, Robert E.; Sober, Arthur J. *Nonmelanoma Skin Cancer*. Chapter 38. Pgs. 329-331

-- Hamilton, J. Michael. *Primary Tumors of the Central Nervous System*. Chapter 39. Pgs. 332-343

-- Fisher, Richard I. *Non-Hodgkin's Lymphoma*. Chapter 43. Pgs. 374-381

-- Payne, Richard. *Pain*. Chapter 57. Pgs. 469-489

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