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APPENDIXES

Chapter 1 Principles of Medical Oncology and Cancer Biology

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Principles of Cancer Medicine

I. Epidemiology and etiology

A. **Cancer epidemiology.** Epidemiology is the study and comparison of the incidence of cancer in various populations or over time. Differences or changes in incidence are used to define groups at increased or decreased risk and to examine risk factors that might be responsible for these differences or changes.
  1. **Incidence and mortality rates**
     a. **Incidence** refers to the overall number of people developing cancer in a particular time frame, usually 1 year.
     b. **Incidence rate** is the number of people developing cancer per 100,000 population per year. Incidence rates provide an estimate that a particular individual will develop cancer in a given time frame.
     c. **Mortality rate** refers to the number of people dying from cancer per 100,000 population per year.
     d. **Case fatality rate** is the percentage of people with a particular cancer who die from that cancer.
     e. **Prevalence** is the number of cases of cancer in a population at a specific point in time.
  2. **Overall incidence rate of cancer** in the United States increased rapidly from 1930 to 1990 and appears to have leveled off subsequently. In 1999, about 1,220,000 Americans developed cancer, and 560,000 died from cancer. See Table 1.1 for the relative frequencies and mortality rates of cancers in the United States according to gender. The incidence of certain types of cancer is changing.

Table 1.1 Relative frequency and mortality rates of various cancers in the United States in 1999

     a. **Lung cancer incidence rates** have leveled off in American men but continue to increase in American women.
     b. **Colorectal cancer rates** are declining in American women but have remained level in American men.
     c. **The incidence rates of all cancers** in American men are highest in blacks, compared with whites and Hawaiians; in American women, the highest rates for all cancers occur in Hawaiians. Native Americans have the lowest rates of cancer. The incidence of melanoma in American white women is rapidly increasing.
     d. **Stomach and endometrial cancers** have steadily declined among all Americans, but Hispanic American women continue to have high rates of uterine cervical cancer.
  3. **Survival.** Palliative treatment is essential to cancer care, but treatment in an epidemiologic context is important only as it relates to survival.
     a. **Lethality.** More than half of cancer deaths are caused by lung, colorectal, breast, and prostate malignancies.
     b. **The overall 5-year survival rate** for all cancers has improved from about 10% in 1960 to about 50% in 1990. Most of the treatment-related improvement in survival has occurred as the result of early detection of common cancers; it is not yet clear whether some of these early cancers have the same lethal biologic potential as cancers discovered in a more advanced state. New and effective treatments for uncommon cancers, such as childhood leukemia and testicular cancers, have slightly improved overall survival rates. With the exception of small cell lung cancer and breast cancer, improvement in 5-year survival rates has been negligible in the advanced stages of most malignancies.
        1. **Early detection** and diagnosis of cancers that appear histologically identical but are biologically less lethal can yield misleading survival figures.
        2. **Lead-time bias.** Patients appear to live longer from the time of diagnosis only because the cancer was detected earlier rather than because of treatment.
B. **Etiology.** At least 80% of cancers in Americans are caused by living habits (smoking, alcohol consumption, and diet) and environmental carcinogens.

Of the natural catastrophes that befall us, the most distressing are those caused by our own behavior.
      BL

  1. **Tobacco.** Smoking and other tobacco use cause about 30% of all cancer deaths in the United States. The risk for lung cancer is 10 to 20 times higher in smokers than it is in nonsmokers.
     a. At least 90% of lung cancer deaths are due to smoking. Smoking also causes cancers of the upper respiratory tract, genitourinary tract, gastrointestinal tract, and pancreas. Chewing tobacco and snuff causes cancers in the upper respiratory passages.
     b. Passive smoke (smoke produced by smokers and inhaled by nonsmokers) doubles the risk for lung cancer and appears to account for about 6,000 cancer deaths in the United States annually.
  2. **Alcohol,** although not a carcinogen, can cause cancers in the upper respiratory passages and esophagus, apparently by increasing the permeability of the mucosa to active carcinogens, especially in smokers. Alcoholic cirrhosis predisposes patients to hepatocellular cancer. Drinking beer, Eaux de Vie, and home-made apple brandy is associated with esophageal cancer in France.
  3. **Ionizing radiation** was well established as an etiologic factor in the development of leukemia in populations exposed to the atomic bomb, in patients who were treated with radiotherapy for ankylosing spondylitis, and in radiologists before the advent of safety measures. The cancer risk appears higher if the same radiation dose is accumulated over a short period of time rather than over long periods.
     a. Premenopausal Japanese women exposed to radiation from the atomic bomb blasts have had an increased risk for breast cancer. The risk for leukemia, particularly in children, is higher for those living near nuclear plants or exposed to diagnostic and therapeutic radiation.
     b. Ambient radon gas is produced as the result of naturally occurring nuclear fission deep within the earth. The gas finds its way to the surface in various geographic locations, where the risk for lung cancer and other malignancies is increased. In areas where radon is detectable, people living closest to the ground floor appear to be at a higher risk for cancer. A report of an increased risk for lung cancer (especially small cell type) in nonsmoking uranium miners in Colorado suggests that some of the 10% of lung cancer patients who never smoked may have acquired the disease from radiation, possibly arising from ambient radon gas.
  4. **Environmental exposure**
     a. **Asbestos-related cancers** of the lung, pleura, and abdominal peritoneum cause several thousand deaths every year. This substance remains a hazard in older buildings, where people can come in contact with asbestos insulation during inhabitation and during the process of removing or isolating the substance.

b. **Solar ultraviolet radiation** (UV-B) dramatically increases the risk for melanomas and squamous or basal cell carcinomas of the skin. The carcinogenic effects are the result of direct DNA damage in skin cells. Melanomas appear to be the result of genetic and environmental factors in addition to ultraviolet light.

c. **Electromagnetic fields** have an unclear relationship to malignancy. Workers on high-voltage electric lines may be at increased risk for gliomas. Clusters of leukemia have been reported in children living or going to school under high-power lines. To date, no excess cancer risk has been reported in association with magnetic resonance imaging.

5. **Dietary habits, body habitus, and cancer risk**
   a. **Dietary substances** are associated with cancers in the following sites:
      1. Fat: breast and colon
      2. High total caloric intake: breast, endometrium, prostate, colon, and gall bladder
      3. Animal protein, particularly as red meats: breast, endometrium, and colon
      4. Alcohol, particularly in smokers: mouth, pharynx, larynx, esophagus, and liver
      5. Salt-cured, smoked, or charred foods: esophagus and stomach
      6. Nitrate and nitrite additives: intestine
   b. **Dietary elements and other products that appear to reduce the risk of cancer**
      1. High-fiber foods
      2. High content of vegetables, fruits, and whole-grain cereal
      3. Indole-containing vegetables (e.g., cabbage, cauliflower, broccoli), so-called cruciferous vegetables. These decrease the risk for large bowel cancer but may increase the risk for stomach cancer.
      4. Beans (especially soybeans and lima beans)
      5. Daily use of small amounts of aspirin appears to reduce the risk for large bowel cancer.
   c. **Body habitus and exercise.** Obesity is associated with an increased risk for breast cancer in women older than 40 years of age. Thin habitus (10% or more below average body weight) is possibly associated with an increased risk for breast cancer in young women. Regular exercise may decrease the risk for colon cancer.

6. **Chemical and microbial agents and genetic risk factors** are discussed with the specific cancers.
7. **Oncogenes and viruses.** See *Cancer Biology and Oncogenes: A Primer*, later in this chapter.

II. Survival, responses to treatment, and medical statistics

A. **Importance of natural history.** The natural history of a malignancy is the course that a particular tumor usually takes without treatment and the effect of that course on the function of the host. Knowledge of the natural history of a specific cancer facilitates making patient management decisions, including using cost-effective technologies to monitor metastatic sites, selecting treatment modalities that improve the survival or comfort of patients, discriminating treatable benign conditions unrelated to a coexisting cancer, and optimizing palliative care.

B. **Application of medical statistics to practice.** Statistics is often a foreboding word for physicians, but this branch of mathematics actually helps patients. Statistics is ultimately not about numbers but about designing studies that give us a good representative sample of what universal reality looks like.
   1. **The single most important statistical concept** for the clinician is not how to "crunch numbers" but rather to determine the reliability and interpretability of published data. Many studies that show initial promise ultimately prove the ineffectiveness of such therapy; most exciting state-of-the-art therapies provide no improvement. It is essential that the clinician avoid "one-article quotes," early data, and data reported only in abstract form as a basis for making clinical decisions.
   2. **Sufficient duration of a clinical study** is essential to determine the effectiveness of treatment. Inadequate duration of a study may result in an effective therapy being considered ineffective. Studies of a treatment for most of the common cancers require at least 5 to 10 years for any meaningful interpretation. Earlier data are characteristically misleading, unless they show a measurably higher rate of mortality in the untreated patients or a large short-term survival improvement in treated patients.
      a. In rapidly lethal cancers or in widespread malignancies for which survival expectancy is short, it is usually easy to determine whether a treatment is effective in a relatively short period of time.
      b. Tumors that are likely to be associated with a long survival without treatment require long periods of study to determine whether a treatment is beneficial. An example is prostate cancer, in which most untreated patients survive 15 or more years from the time of diagnosis. Prostate cancer studies are also confounded by the fact that the disease affects older men, who often succumb to unrelated illnesses before reaching the terminal stage of their cancer.
   3. **Matched populations.** Treated and untreated patients must be closely matched for particular characteristics. For example, no information can be drawn about the effectiveness of a sarcoma therapy if the treated group consists of otherwise healthy young Asian women with low-grade localized sarcomas and the untreated group consists of elderly diabetic white men with high-grade metastatic sarcomas.
   4. **Number of patients** used to compare treated and untreated groups strongly affects the statistical power and needed duration of a study to determine effectiveness. Inadequate numbers of patients may make it impossible to find a subgroup of treated patients with readily identifiable prognostic factors who significantly benefit from a treatment.
   5. **Risks and benefits of a treatment** are an essential part of statistical study design. For example, a study that conclusively demonstrates that a treatment results in 1% improvement in 5-month survival, but increases time in the hospital for therapy of treatment-related complications in half of patients and causes death in 15%, should probably not be recommended.

C. **Statistical terms used in describing the design of a study**
   1. **Sample space** is the number of patients, tests, treatments, or other data points used to represent the entire "universe" of all such patients, tests, and so forth.
   2. **Stratification** of patients according to known prognostic factors (such as age, ethnicity, sex, performance status, and extent of disease) is essential if a clinical study is to be useful for the clinician making treatment decisions. Randomizing patients between a treated group and untreated group is a technique used to deal with unknown factors that affect prognosis. Proper stratification helps the clinician to determine whether a particular patient is represented in the population of a published study and whether that therapy has a reasonable chance of being effective.
   3. **Randomization** is the assignment of a patient to a particular treatment by random chance. Randomization is done when a treatment is being compared with another treatment or with no treatment. Each of the treatments or nontreatments is called an *arm* of the study.
   4. **Blinded studies** are ones in which patients do not know to what treatment arm of the study they have been assigned. In a double-blinded study, neither the patients nor the investigators know what arm of the study any patient is on. The data are codified; the study is stopped ("broken") if one arm is significantly providing better or worse results than another study arm.
   5. **Drug development trials**
      a. **Phase I trials** determine the optimal dose, schedule, and side effects of a new therapy.
      b. **Phase II trials** determine what kinds of cancer respond to a particular treatment.
      c. **Phase III trials** compare a treatment shown to have some effectiveness in a phase II trial with no treatment or with a treatment that has also shown effectiveness.
      d. **Meta-analysis** is a retrospective study in which data from multiple randomized trials are pooled and analyzed. All patients, including those included but not entered into each study, must be accounted for. Meta-analysis is most useful for evaluating many small, randomized trials to look for an effect not evident in a single small study and for identifying subsets (by prognostic strata) of patients who benefit from treatment.

D. **Statistical measurements used to assess clinical research results**
   1. **Confidence intervals, ratio tests, and statistical significance.** Confidence intervals are used for assessing response rate in single-arm trials and for comparing and assessing the magnitude of differences between treatments in phase III studies. For single-treatment studies, the confidence interval is the **range of values** around a measured result that would be 95% certain to contain that measured result if the entire universe of patients were tested. The more patients included in a trial, the more likely the measured value will be closer to the "true" value; the higher the number of measured responses, the higher the likelihood that the "true" response rate will be higher.
   2. **Proportion tests** compare the ratio of positive treatment outcome to the sample size in each study arm.
      a. **Confidence interval comparison of two proportions** gives the range of numbers that will contain the actual numeric difference between the ratios with 95% certainty. The confidence interval comparison is a statistical assessment of the probable magnitude of the difference between the two treatments being compared. These statistical tests are used in both one- and two-tailed clinical trials.
      b. **Statistical significance comparison of two proportions** evaluates whether there is less than a 5% false-positive result rate in studies showing a difference in the ratios. It does not provide a range for the probable magnitude of the difference. The c^2 (chi square) test, or the more politically correct Fisher's exact test, are used to determine statistically significant differences that can be correlated with the *p* value (see next paragraph) for significant differences.
   3. ***p* Value (the false-positive value)** is the probability that a measured difference between results of two arms of a study, or a confidence interval difference, would disappear if the entire universe of identical patients could be tested. When the *p* value is less than 0.05, the probability that measured differences

occurred by chance is less than 5%. The choice of a 5% false-positive error is somewhat arbitrary and is used to give a value that is two standard deviations from the average value that test results are "the true value." The p value has no significance in studies of small numbers of patients evaluated over a short time. Interval p values showing a difference in treatment arms reported before the planned number of patients are entered are usually false-positive results and should be ignored, unless the "power" of the study is also reported and has a high value (see section II.D.6).

4. **b Error (the false-negative value)** is the probability that two treatments that appear to have identical results would be different if the entire universe of patients were tested. This error is not usually reported in clinical research reports because it is a part of study design and is used in advance to determine the number of patients who must be entered into the study to meaningfully interpret a p value.

5. **One- and two-tailed (-sided) tests.** A one-tailed test gives the p value for the hypothesis that the experimental treatment arm of a randomized study is better than the control arm; it provides no statistical information regarding whether the treatment arm is the same or worse than the control arm. A two-tailed test is the same as a one-tailed test but also evaluates whether the experimental treatment is actually worse than the control arm.

6. **Power of a statistical test.** The power of a test is calculated as "1 − b." Reported studies done with small numbers of patients typically have p values of less than 0.05 and appear to be positive. The p value tends to increase both as the duration of the study becomes longer and as more patients are accrued into the study. For the p value to be interpretable and have clinical applicability, statisticians require that a predetermined number of patients have been entered into the study and are evaluated for a predetermined amount of time. The power of a statistical test takes into account the number of patients enrolled; higher powers give increasing confidence that any observed differences between arms are less likely to be by chance, no matter how many patients are enrolled.

E. **Statistical terms used in survival analysis**
1. **Cure** is a statistical term that applies to groups of cancer patients rather than to individual patients; it describes those patients who are rendered clinically free of detectable cancer and who have the same survival expectancy as a healthy age-matched control group. A cure does not guarantee that the particular patient meeting these criteria will not eventually die from the original cancer.
2. **Actuarial survival** (or life-table survival) is the life expectancy from a specified age of a group of patients with a particular cancer. These data are used to determine the chance that an individual patient will survive for a specified time. This parameter is useful in determining both the natural history of the cancer and the effectiveness of treatment by comparing patient survival with actuarial survival tables of a matched healthy population.
3. **Observed survival rate** is the percentage of patients alive at the end of a specified interval of observation from the time of diagnosis.
4. **Relative survival rate** corrects the survival rate for the "normal mortality expectation" in a matched population.
5. **Adjusted survival rate** corrects the survival rate by discounting deaths from causes other than cancer or cancer treatment in those patients who are free of cancer at the time of death.
6. **Median survival** is the time when 50% of patients are dead and 50% are still alive. Average or mean survival rates are meaningless because survival of patients with similar tumors may range from a few weeks to years. Median survival may be a useful index for comparison of clinical trials but can be misleading. In "mature studies," a significant group of patients may survive for many months or years after the time that 50% of the patients have died.
7. **Disease-free interval** is the time from when the patient is rendered free of clinically detectable cancer until recurrent cancer is diagnosed.
8. **Censored data**. Data about patients who are still living and discontinue the trial therapy or whose fate is unknown are frequently excluded (censored) from statistical analysis. Censoring data can severely skew results and make a study uninterpretable. The larger the number of censored data in relationship to the overall study, the more likely it is that the study is not interpretable. Good reporting carefully defines the reasons for censoring data, what the data would look like if censored data were included, and the percentage of data points that were censored.

F. **Terminology used to describe response to treatment**
1. **Complete remission (CR)**. No clinically detectable cancer is found after treatment.
2. **Partial remission (PR)**. Measurable tumor mass decreases by 50% after treatment, no new areas of tumor develop, and no area of tumor shows progression. The approximation of the mass of an individual area of tumor is usually given as the product of two diameters of the lesion; the measurable tumor mass is the sum of the masses of all measurable lesions.
3. **Minimal remission (MR)** is the same as partial remission, but the response does not meet the criteria of 50% reduction.
4. **Progression.** The mass (product of diameters) of one or more sites of tumor increases more than 25%, new lesions appear, or the patient dies as a result of the tumor.
5. **Stable disease.** Measurable tumor does not meet the criteria for CR, PR, MR, or progression.

G. **Recommendations for the clinical application of the literature to patient care decisions**

There is no evidence that "evidence-based" care is more effective than the best judgment of a skilled and experienced physician.
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The status of ongoing clinical trials must be reported before the data is "mature" to allow coordination of trials among different institutions and investigators. Thus, critical evaluation of research reports is essential for clinicians who are deciding whether to recommend a new treatment for a patient. No trial result, however, is a substitute for sound clinical judgment or for individualization of treatment for patients not enrolled in a study. The clinician should ask the following questions when reading the literature:

1. Are patients who benefited from the study treatment substantially like your patient with regard to age, sex, and stage of disease, performance status, and other prognostic factors?
2. Does the study exclude certain patients? If so, what were the reasons for exclusion?
3. Did the study treatment produce toxicity that is unacceptable in view of the potential benefits? On the other hand, was improvement in survival so superior that the risk for toxicity and drug-related death is warranted?
4. Did the study stratify and randomize patients in a manner that allows clear interpretation of the data?
5. Was the study large enough to provide sufficient confidence that observed differences were not by random chance? Optimally, the most useful studies are two-tailed tests with p values of less than 0.05 and a power of 80 or greater.

III. Principles of cancer diagnosis using laboratory tests

Use technology to confirm your diagnostic impression, not to rule it out.
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A. **Histopathology**
1. **Biopsy.** Histologic proof of malignancy is the cornerstone of diagnosis and treatment. Neoplasms can masquerade as benign or inflammatory conditions, and vice versa. The site that is least risky and most likely to provide the necessary information is tested. Specimens should not be routinely placed in formalin; suspected lymphomas or metastases from unknown primary tumors should be placed in a fixative, such as B5, that does not interfere with immunologic and histochemical analyses.
2. **Microscopic clues of tumor origin,** including histochemistry and electron microscopy, are presented in Appendix C-1. Immunohistochemical tumor markers are shown in Appendix C-2. Expected immunophenotypes on biopsy specimens for specific malignant cell types are shown in Appendix C-3.
3. **Shortcomings of pathologic diagnosis.** Establishing the type of tumor and determining whether it is benign or malignant is not an exact science. Errors may occur in sampling, processing, and interpreting specimens. Intraepithelial dysplasia and malignancy form a continuous spectrum. Many tumors undergo changes in clinical behavior with time. Some appear histologically benign but have a clinical course typical of malignancies (or vice versa). The clinician must view the histologic data in terms of the overall clinical syndrome, based on history, physical examination, other laboratory data, and judgment.
4. **Recommendations**
   a. Never confuse your ability to name a tumor with your ability to predict its behavior.
   b. Never accept a histologic diagnosis as unequivocal.
   c. Never act on verbal reports from anyone.
   d. Review important clinical data about the patient with the pathologist.
   e. Be sure that the pathologist is provided with a sufficient tissue sample, both for routine histopathology and for special studies.
   f. When the histologic diagnosis does not correlate with the clinical course, take the following steps:
      1. Make sure that the tissue came from your patient.
      2. Re-review the slides with the pathologist.
      3. If the data are still equivocal, obtain an opinion from another institution or obtain another biopsy specimen.
B. **Tumor markers** are cellular products that are helpful in the detection and diagnosis of certain cancers (see Table 1.2).

Table 1.2 Helpful serum tumor markers

1. **Types of tumor markers**
   a. **Cell surface markers** have become essential to the diagnosis and typing of certain malignancies. An important example are the *clusters of differentiation* (CD) antigens on cells, which are useful in diagnosing and typing hematopoietic malignancies (see Appendix C4 and Appendix C5).
   b. **Genetic markers** are useful for diagnosis and prognosis of a variety of cancers, particularly hematologic malignancies. They may also be useful for selected patients with family histories strongly suggestive of a hereditary cancer syndrome in which identification provides substantial prevention and survival benefits with early detection. An example of this is evaluation for the retinoblastoma gene in a patient with a first-degree relative with that disease. Another example is evaluation for *BRCA-1* in a young woman who has at least one first-degree relative with premenopausal breast cancer and another first-degree relative with ovarian cancer. Diagnostic tools range from gross histologic evaluation of chromosome abnormalities (such as the Philadelphia chromosome) to nucleic acid probes using the Southern blot test, which detects genetic defects.
   c. **Tumor markers found in the blood or other body fluids** are usually normal cell components that are abnormally elaborated and released by malignant cells. Serum markers can be useful in monitoring the response of some cancers to treatment, in detecting recurrence or progressions of cancers, in prognosis, and in helping to make an early diagnosis of a few tumors. Such markers are often present in small to moderate quantities in the blood of healthy people and are sometimes significantly increased either in nonmalignant disorders or as a genetic variant. Consequently, the determination of what constitutes an abnormal blood level is somewhat arbitrary. Although many tumor markers have been described, only those that are in common clinical use are discussed here.
2. **Statistical considerations** aid the clinician in interpreting blood levels of any substance, including tumor markers.
   a. **Sensitivity** is the percentage of patients with cancer who have an abnormal test.
   b. **Specificity** is the percentage of people without cancer whose test is negative.
   c. **Positive predictive value** is the probability that patients with an abnormal test actually have cancer.
   d. **Negative predictive value** is the probability that a negative test will predict that a person will not have cancer.
   e. **Prevalence.** The probability that a positive test is truly the result of cancer can be greatly improved if the test is performed in a population in which the prevalence of the cancer is high. For example, prevalence can be achieved by performing the test only in patients with known cancer, with risk factors for cancer, or with imaging studies that suggest the presence of cancer.
3. **Oncofetal proteins** are substances found normally in larger amounts during fetal development. Cancers derived from the fetal counterpart of adult tissues often elaborate these proteins in increased quantities.
   a. **a-Fetoprotein** (a-FP) in fetuses is biochemically related to albumin in adults. It is found in fetal liver, yolk sac, and the gastrointestinal tract. Consequently, a-FP is correspondingly increased in about 80% of patients with hepatomas, 60% of patients with nonseminoma germ cell cancers, and occasionally in patients with other cancers. a-FP is further discussed in Chapter 12, section III.C.2.
   b. **Carcinoembryonic antigen** (CEA) is a fetal glycoprotein found on cell surfaces. It is chemically related to immunoglobulins. CEA is produced in the fetal gastrointestinal tract, pancreas, and liver. It is present in small quantities in the blood and in cells of many normal adult tissues.
      1. CEA is a useful marker for monitoring breast, colon, and small cell lung cancers. CEA is increased in patients with a variety of other endothelial malignancies, in which case its usefulness is generally limited.
      2. Elevations of CEA blood levels (usually less than 10 ng/mL) are found in smokers and in patients with chronic obstructive lung disease, inflammatory or peptic bowel disease, liver inflammation or cirrhosis of any cause, renal failure, and fibrocystic breast disease.
4. **Hormones**
   a. **Human chorionic gonadotropin** (b-HCG) is a glycoprotein produced by placental syncytiotrophoblasts that is found in a normal blood product in women during pregnancy. *It is never found in normal males*; with rare exceptions, high levels are almost always pathognomonic of a germ cell neoplasm in this setting (see Chapter 12, section III.C.1).
   b. **Thyrocalcitonin** is produced by thyroid C cells and medullary thyroid cancer. It is an effective way to screen patients with first-degree relatives affected by medullary thyroid cancer and multiple endocrine neoplasia type 2 (MEN 2). These syndromes are dominantly inherited and have a high degree of penetration. Elevated levels are found in other tumors and benign conditions.
   c. **Hormones** are often produced by cancers of endocrine glands and in various paraneoplastic syndromes. These are discussed in Chapter 15 and with the individual tumors.
5. **Enzymes**
   a. **Prostate-specific antigen** (PSA) is a serine protease, which is produced by prostatic alveolar and ductal epithelial cells and correlates closely with tumor bulk and response to therapy for men with prostate cancer (see Chapter 13, section III.C.2).
   b. **Prostatic acid phosphatase** is currently seldom used (see Chapter 13, section III.C.3).
   c. **Lactic dehydrogenase** (LDH) blood level is elevated in association with many types of malignancy. This marker is useful in nonseminoma germ cell tumors and high-grade lymphomas, for which blood levels correlate closely with disease activity and response to therapy.
   d. **Neuron-specific enolase** (NSE) is a glycolytic enzyme found in association with several neuroendocrine tumors. It is clinically useful as a prognostic factor in neuroblastoma.
6. **Cancer antigens** (CAs) are mucin glycoproteins that have been detected by monoclonal mouse antibodies to normal epithelial antigens. A large number have been associated with various malignancies. Of the many that have been described, none is useful for cancer screening.
   a. **CA 125** is detected by monoclonal antibodies against cystadenocarcinoma cell lines. It is useful for monitoring patients with known ovarian cancer when blood levels correlate closely with extent of disease, response to therapy, and recurrence. CA 125 is useless as a general screening test for ovarian cancer. Less than 1% of healthy women have blood levels of more than 35 U/mL. Although a blood level higher than 65 U/mL carries a specificity of 98% for the diagnosis of ovarian cancer, the sensitivity using this blood level is reduced to 70% and the positive predictive value to only 2% in the general population. Furthermore, women with a variety of other epithelial cancers have a significant prevalence of elevated CA 125 blood levels. Elevated blood levels of CA 125 are also found in lymphomas, liver disease, a variety of inflammatory conditions, benign tumors, and pregnancy.
   b. **CA 15-3** is detected by immunoabsorption and may be elevated in patients with breast, ovarian, prostate, and lung cancer. For breast cancer, CA 15-3 has a 75% correlation with measurable disease and is useful for monitoring disease that cannot be measured after treatment.
   c. **CA 19-9** is a Lewis blood group antigen that is found in increased levels in gastrointestinal cancers. It is helpful in the diagnosis and monitoring of pancreatic cancer, in which it has a 70% specificity and a 90% sensitivity.
7. **Miscellaneous markers**
   a. **b$_2$-Microglobulin** correlates with tumor burden, prognosis, and response to therapy in plasma cell myeloma and with disease activity and prognosis in lymphomas. b$_2$-Microglobulin levels are significantly increased with poor renal function.
   b. **Paraproteins,** determined by serum protein electrophoresis and immunoelectrophoresis, were the first diagnostically and therapeutically useful tumor markers (for myeloma and lymphomas).
   c. **Serum ferritin** levels correlate with extent of disease in hepatoma.
   d. **Thyroglobulin** is a glycoprotein produced by thyroid follicular cells and is increased in all thyroid disorders, including thyroid carcinoma. Thyroglobulin can also be increased in patients with breast or lung cancer. Thyroglobulin levels are useful for following patients with well-differentiated thyroid cancer if residual thyroid tissue is ablated and antithyroid antibodies are determined simultaneously. Antithyroid antibodies, thyroxine, and triiodothyronine can interfere with the test for thyroglobulin. Thyroglobulin is also useful in following nonfunctioning metastases.

IV. Staging

Part of the art of medicine is the ability to make decisions in the face of insufficient data. Obtaining sufficient information is likely to alter the host to the point that a different diagnosis and treatment are required.

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A. **Principles of cancer staging**
1. **Determining the extent of disease** and the organs involved is essential to the proper management of patients with cancer. In research studies, extensive staging studies are often necessary for comparing results of cancer research trials and facilitating the exchange of information. Many staging procedures, however, are expensive and not useful for patient management decisions. Outside of a research context, clinicians should only recommend those studies that will affect patient management decisions and with the knowledge of the natural history of the specific tumor type.
2. **Staging should describe both the tumor and the host,** including the following factors:
   a. Organ of tumor origin
   b. Histologic type and grade of tumor
   c. Extent of primary tumor (size; invasion of adjacent tissues; involvement of nerves, blood vessels, or lymphatic system)

    d. Sites of metastases
    e. Functional status of the patient (see inside back cover)
B. **Staging systems.** Many tumors are associated with several staging systems, which are in continuous evolution. Readers should consult an up-to-date staging manual because of the frequent revisions.

V. Prevention and early detection

A. **Prevention**
1. **Cigarette smoking** caused the same annual number of cancer deaths in 1998 as the number of people who would have been killed if the 1995 earthquake in Kobe, Japan occurred every 11 days for a year. It would take one Boeing 747 crashing and killing all 400 passengers on board every day to match the cancer death rate from cigarettes.

   Essentially all smokers in the United States are fully aware of the dangers. Tobacco is a highly addictive drug, and tobacco smoking meets the medical (DSM IV) definitions of addiction. Smokers have little choice or control over their habit. Smoking cessation is associated with withdrawal syndromes (usually agitated depression) and has a high probability of relapse.

   Just advising the addicted smoker to quit is insufficient. A wide variety of methodologies and 12-step programs may be necessary and helpful. Because smoking causes a cumulative risk for cancer, reduction of smoking lowers the risk and is a reasonable agenda for most smokers who are unable to quit.

2. **Diet** is closely associated with the development of cancers of the gastrointestinal tract and of cancers that are affected by hormones (breast, endometrial, ovary, and prostate). A well-rounded diet, low in saturated fats and high in fresh fruits, vegetables, and fiber, starting as early in life as possible, may have some impact on reducing certain cancers. Unfortunately, diet is also so behaviorally "programmed" that most people are unable to change long-term dietary habits.
3. **Regular** exercise reduces the risk for colon cancer. Regular walking and swimming are best because they are the least traumatic to joints and are associated with the lowest risks for other injuries.

B. **Early detection**
1. **Self-examination**
   a. All women older than 20 years of age should examine their breasts 5 days after each menstrual period. Postmenopausal women or those with irregular menses should examine their breasts on the same day each month.
   b. Patients exposed to sunlight, especially light-complexioned patients, should search for new moles, changes in old moles, and scaly patches on the skin.
   c. Other signs of cancer must be reported to the physician without delay, including blood in the urine or stools, sores in the mouth or skin that do not heal, unexplained weight loss, or tissue masses.
2. **Screening.** Unless the patient reports a specific symptom, most screening procedures are fruitless. Certain procedures have been found adequate to detect potentially curable cancers in asymptomatic people in a cost-effective manner.
   a. **Breast cancer.** Although the National Cancer Institute stopped recommending screening mammograms in 1993, the American Cancer Society has continued its recommendations based on updates of national data showing significantly increased survival in large selected subgroups of women. We recommend breast examination by a physician or qualified nurse every 3 years in women between 20 and 40 years of age and annual examination in women older than 40 years of age. Mammography is performed as a single baseline for those from 35 to 39 years of age, every 1 to 2 years for those from 40 to 49 years of age, and every year for women 50 years of age and older.
   b. **Uterine cervical cancer.** Three consecutive annual smears of the uterine cervix are recommended for sexually active girls younger than 18 years of age and for all women 18 years of age and older, followed by Papanicolaou's smear every 3 years thereafter. Smears must include cervical aspiration specimens.
   c. **Colorectal cancer.** Digital rectal examination should be performed with routine physical examinations until 50 years of age. After 50 years of age, annual rectal examination and stool for occult blood should be performed, and biannual proctosigmoidoscopy should be performed in patients with a history of adenomatous polyps.
   d. **Prostate cancer.** Men older than 50 years of age should have an annual digital rectal examination and PSA blood level determination.
   e. **General screening.** Yearly complete blood count is recommended to search for tumor-related iron deficiency anemia and other hematologic problems in older patients.

VI. Management

Hearing is the physician's most important diagnostic tool. Listening is his or her most important skill.
  BL

A. **Applied philosophy in oncology**

The withholding of technology requires as much skill and judgment as its employment. Do not use chemicals when time and words are indicated.
  BL

1. Oncology is a unique subspecialty because most patients are referred to the oncologist by family physicians who often have a long-standing relationship with the patient, want to be involved with their care, and can provide psychological support for patient and family. On the other hand, oncologists generally have more experience with differential diagnosis in cancer patients and are in a better position to diagnose treatable nononcologic diseases and to provide optimal palliative care for patients when cancer treatment is no longer effective. The coordination of oncologists with referring physicians must be individualized in the best interests of the patient.
2. Most cancers can involve multiple organ systems. It is essential that the oncologist has a thorough knowledge of the patient by taking a thorough baseline history and physical examination. This process initiates a trusting relationship between the oncologist and the patient, which will be important in implementing future recommendations.
3. Listen carefully to the patient and family, who usually provide more useful diagnostic and even therapeutic information than any laboratory test.
4. Recommendations must be individualized, taking into account the clinical data, but also providing patients with enough information and options so that they can make an informed treatment decision. The physician has the training and experience, but the patient is the "boss." If the patient chooses a course that the physician feels would cause harm, however, the physician should say so frankly and directly.
5. The physician should never threaten or desert a patient because he or she does not accept the best therapeutic recommendation.
6. Efficiency can be the worst enemy of meaningful medical care. A hands-on visit communicates caring and engenders confidence. If pressed for time, the physician can take the chart into the patient's room and interact with the patient while writing.
7. Most advanced cancers cannot be cured. Because they have the most extensive knowledge of and experience with the behavior of advanced cancer and the use of complex medication regimens, oncologists should be able to provide optimal palliative care. The trend toward separating oncologists into those who treat and those who care is destructive to the fundamental philosophy and art of medical practice.

B. **Oncologic emergencies**
1. Seizures, cerebral edema (see Chapter 14, , , and)
2. Spinal cord compression (see Chapter 32,)
3. Brain metastases (see Chapter 32,)
4. Pericardial effusion with tamponade (see Chapter 29,)
5. Hypercalcemia (see Chapter 27,)
6. Hyponatremia (see Chapter 27,)
7. Hypoglycemia (see Chapter 27,)
8. Hyperviscosity states (see Chapter 22,)
9. Infection, especially in leukopenic patients (see)
10. Superior vena cava obstruction (see Chapter 29,)
11. Lymphangitic pulmonary metastases (see Chapter 29,)
12. Pain (see)
13. Psychosocial problems (see)

Cancer Biology and Oncogenes: A Primer

I. Cancer biology: an overview

A. **Some aspects of normal cell reproduction.** In normal tissues, the number of cells that are reproduced is a function of the needs of the organism. Decreasing the birth rate of cells or increasing the death rate prevents any excess.

1. **The cell cycle** is depicted in Fig. 1.1. Cell replication proceeds through a number of phases that are biochemically initiated by external stimuli and modulated by both external and internal growth controls. Certain oncogenes and cell cycle–specific proteins are activated and deactivated synchronously as the cell progresses through the phases of the cell cycle.

Figure 1.1 Phases of cell growth.

   a. In the G_0 **phase** (gap 0 or resting phase), cells are generally programmed to perform specialized functions.
   b. In the G_1 **phase** (gap 1 or interphase), proteins and RNA are synthesized for specialized cell functions. In late G_1, a burst of RNA synthesis occurs, and many of the enzymes necessary for DNA synthesis are manufactured.
   c. In the **S phase** (DNA synthesis), the cellular content of DNA doubles.
   d. In the G_2 **phase** (gap 2), DNA synthesis ceases, protein and RNA synthesis continues, and the microtubular precursors of the mitotic spindle are produced.
   e. In the **M phase** (mitosis), the rates of protein and RNA synthesis diminish abruptly while the genetic material is segregated into daughter cells. After completion of mitosis, the new cells enter either the G_0 or G_1 phase.

2. **Cyclins** are special proteins that activate the various phases of the cell cycle. Most normal cells capable of reproduction proliferate in response to external stimuli, such as growth factors, certain hormones, and antigen–histocompatibility complexes, which affect cell-surface receptors. These receptors then transduce the signal that results in cell division. Tyrosine kinases are an essential part of the cascade of proliferative signals, from extracellular growth factors to the nucleus. Cyclins combine with, activate, and direct the action of special tyrosine kinases, called *cyclin-dependent kinases.* Cyclins specific for various phases of the cell cycle rise and fall in synchrony with the progression of the cell through the cycle.

3. **Cell cycle "checkpoints."** Cells that are capable of reproducing are normally stopped at specific phases of the cell cycle. The most important of these are immediately preceding the initiation of DNA synthesis and immediately preceding the act of mitosis. These histologically quiescent periods are probably mediated by decreased activity of cyclin-associated kinases and tumor-suppressor proteins. In fact, the cells in these phases are biochemically active because they prepare proteins to enter the next phase of the cell cycle, "inspect their handiwork" to that point, and correct any genetic defects before going on to reproduce. Thus, while venturing through the cell cycle, the cell must stop for two inspections, called *checkpoints.*

   a. **Normal cells have mechanisms that detect abnormalities in DNA sequences.** When DNA is damaged, a number of repair mechanisms replace damaged nucleotides with normal molecules. These mechanisms are most important during cellular reproduction to ensure that new genetic material in daughter cells is an exact copy of the parent cell.
   b. **The first checkpoint** occurs in the late G_1 phase, just before cells enter the S phase. Even if the proper extracellular signals are received and all of the machinery is in place for DNA synthesis, the DNA must be in an acceptable state, with no lesions, before the cell can leave G_1. If lesions are detected, they either are repaired or the cell is made to undergo apoptosis. This stopping point is one of the actions of p53 protein (see section II.C.2).
   c. **The second checkpoint** occurs just before the cell enters M phase; the cell cycle inhibitors stop the cell until it is determined whether the new progeny are worthy successors with accurate genetic copies of the parent. A cell that has not completely and accurately replicated all of its DNA or that does not have the full complement of proteins, spindle materials, and other substances to complete mitosis is arrested at this checkpoint until everything is in order and before M phase can begin.

4. **Normal populations of cells have a small component of "immortal cells,"** which, when called on by signals from other parts of the organism, can replenish themselves and also supply daughter cells that mature and differentiate into specialized tissue cells necessary for the function of the whole organism. Although a few types of tissue can dedifferentiate, most cell types lose their vitality as they differentiate, enter old age and senescence, and eventually die. The following four populations of normal cells can be identified in eukaryotes:

   a. **Germ cells,** which are capable of reproducing themselves indefinitely, possibly as a result of going through meiosis. Unlike cancer cells, these cells must undergo a meiotic "event" to produce an immortal cell line.
   b. **Stem cells,** whose only two functions are to reproduce and to produce cells destined to differentiate and perform specialized functions for the host. Unlike cancer cells, these cells have a limited biologic number of reproductive cycles.
   c. **Partially differentiated cells,** which have limited capability to reproduce and whose progeny eventually become fully differentiated, nonreproducing cells
   d. **Fully mature specialized cells,** which cannot reproduce further generations

5. **Differentiation is inversely related to immortality.** Unlike cancer cell lines that are immortal by definition, differentiated normal cells have a biologic "clock" that counts the number of times the cell can divide, after which no further division is possible. For example, a human fibroblast in culture can divide about 50 times, no matter what it is fed or the conditions of its culture, it and its progeny can divide no further (see section I.B.2, later).

B. **Characteristics of cancer cells.** Cancer can be defined as a cellular disorder characterized by progressive accumulation of a mass of cells, as a result of excessive reproduction of cells not compensated by appropriate cell loss; these cells progressively invade and damage the tissues and organs of the host. Although cancer cells are abnormal and die at a faster rate than their normal counterparts, the death rate is not able to keep up with the formation of new cells. This imbalance is the result both of genetic abnormalities in cancer cells and of the inability of the host to detect and destroy such cells. Some of the unique characteristics of cancer cells are the following:

1. **Clonal origin.** Most cancer cells appear to originate from a single abnormal cell. Some cancers arise from multiple malignant clones either as a result of a *field defect,* in which multiple cells of a tissue are exposed to a carcinogen, or as a result of inherited defects in certain genes.

2. **Immortality.** Most normal cells have limits on the number of reproductive cycles that a cell can have as it matures. Cancer cells, on the other hand, can proliferate indefinitely, providing an inexhaustible pool of precursor cells. One mechanism for immortality involves telomeres, the ends of chromosomes. Telomeres of most types of normal cells progressively shorten as the cells differentiate. In contrast, the telomeres of cancer cells and stem cells are replenished by the enzyme telomerase. This enzyme normally progressively decreases in a programmed manner as cells differentiate; the fully differentiated cell becomes senescent and eventually dies as it loses its ability to reproduce. In contrast, telomerase production is preserved or activated in many types of cancer cells; consequently, the length of the telomeres remains intact, and the cell remains "immortal."

3. **Genetic instability** due to defects in DNA repair and in detection of DNA mismatches leads to heterogeneity of cancer cells. The cancer cells produce clones that become progressively less responsive to control mechanisms of proliferation and have an increased capacity to survive in "foreign environments" as metastases.

4. **Loss of contact inhibition and anchorage-dependent growth.** Normal cells grown in tissue culture do not divide unless they become anchored to a solid substratum to which they can adhere. Normal cells also stop dividing when they attain a confluent monolayer, even if the culture medium contains all the growth factors and nutrients necessary for further division. Cancer cells can grow independently in a semisolid medium without the requirement for substrate adherence; they continue to proliferate beyond a confluent monolayer in cell culture.

5. **Progressive independence of proliferation from growth factors and nutrients** is noted in cancer cell cultures. Cancer cells can actually self-destruct by continuing to divide even after they have consumed the nutritional factors in the culture media necessary for their survival. It is of interest that many animal species demonstrate analogous behavior.

6. **Metastasis** is a feature of cancer that is not found in normal tissues or benign tumors. The ability to metastasize results from the loss of or abnormalities of cellular proteins responsible for adhesion to the extracellular matrix, abnormalities in the interaction between cells, abnormal attachment to basement membrane, abnormal production of basement membrane, and destruction of basement membrane by enzymes such as the metalloproteases (collagenases). Progress made in identification of the responsible proteins and their mechanisms of action has increased understanding of the metastatic process.

II. Causes of overproduction of cancer cells

A. **Failure of abnormal cells to undergo apoptosis.** Apoptosis is "programmed cell death."

1. **Apoptosis eliminates cells with abnormal DNA** caused by either irreparable DNA damage or by inaccurate, incomplete, or redundant transcription of DNA. This is a major mechanism for maintaining chromosome number in cells of a particular species and in preventing aneuploidy. The process ensures that only cells that have fully and accurately replicated all of their DNA can enter mitosis.

2. **Apoptosis occurs in normal tissue reabsorption;** the classic example is the disappearance of tadpoles' tails. Apoptosis also results in the disappearance during embryogenesis of webs between fingers of primates, allowing the formation of individual digits. Apoptosis results in the elimination of normal senescent cells when they become old and useless. Apoptosis results in the elimination of thymic T cells that recognize "self" and thereby prevent immune attack by these cells on the host.

3. **Apoptotic cells can be recognized microscopically.** Apoptotic cells show clumps of intracellular organelles in the absence of necrosis. The nuclei are condensed and fragmented; intracellular structures are degenerated and compartmentalized. As the cell falls apart, phagocytes take up the fragments. Unlike the process of cell necrosis, apoptosis does not cause an inflammatory response. Apoptosis requires synthesis of specific proteins that have been highly conserved throughout evolution.

4. **Cancer cells** and some immunologic cells produce substances that promote inappropriate apoptosis in normal tissues (and may contribute to the cachexia of malignancy). Apoptosis is genetically regulated and may be perturbed in malignant cells. For example, the *p53* tumor-suppressor oncogene stimulates apoptosis. The *BCL-2* oncogene inhibits apoptosis, decreases normal cell death, and increases cell populations. Apoptosis may be the major mechanism by which tumor cell populations are decreased by hormones, cytotoxic chemotherapy, and radiation therapy. Apoptosis is further discussed under mechanisms of chemotherapy in Chapter 4, section II.A.

B. **Genetic abnormalities that inappropriately stimulate cell proliferation,** independent of normal proliferation signals, occur through a variety of mechanisms. Mutations or overproduction of receptors or transducing proteins can cause the cell to become independent of growth factor or other triggers and to initiate cell division independently. These gene abnormalities are usually dominant (i.e., normal cells hybridized with abnormal cells become phenotypically malignant).

C. **Abnormalities of tumor-suppressor genes** (genes that are responsible for suppressing cell division) probably result in cancer through failure of the host to destroy genetically abnormal cells. These genes are recessive; malignant cells hybridized with normal cells become normal.

1. **Hereditary tumors.** Retinoblastoma gene *(RB1)* was the first of these abnormal genes to be discovered. Subsequently, a number of other suppressor gene abnormalities have been found, particularly in uncommon or rare hereditary diseases. Examples include Wilms' tumor *(WT1),* familial polyposis *(APC),* familial melanoma *(CDKN20),* and familial breast and ovarian cancers *(BRCA-1 and BRCA-2).*

2. *p53* **Suppressor gene.** The most important example of these genes is the *p53* suppressor gene. The p53 protein is a gene product that suppresses the cell cycle with multiple complex activities. It can detect DNA lesions, such as nucleotide mismatches and DNA strand breaks, including those caused by radiation and chemotherapy.

   a. When DNA lesions are detected, the p53 protein arrests cells in the G_1 phase of the cell cycle, preventing cells from entering the S phase of the cell cycle. The p53 protein can then induce repair mechanism proteins or trigger proteins, which cause apoptosis.

   b. *In vitro* studies have shown that chemotherapy and radiation kill cancer cells through DNA damage, which triggers p53 protein–induced apoptosis. In contrast, p53 protein–deficient mouse thymocytes and resting lymphocytes remain viable after irradiation.

   c. Many human cancers are found to have mutant *p53* suppressor genes. Mutant *p53* is characteristic of Li-Fraumeni syndrome, a hereditary autosomal dominant syndrome of both soft tissue and epithelial cancers at multiple sites starting at an early age.

D. **Tumor angiogenesis.** Cancer colonies are not larger than about 1 mm in diameter unless they have a blood supply. Colonies without adequate blood supply are not resting (not in the G_0 cell cycle phase); they typically have a high rate of proliferation but have a fully compensating cellular death rate. After the blood supply is established, the cellular death rate decreases, and the tumor grows rapidly.

1. **Several substances are required to promote formation of new blood vessels** (angiogenesis) in normal tissues. Almost all measurable cancers, however, are limited to the production of only one of these factors, called *vascular endothelial growth factor* (VEGF), which induces blood vessel formation. VEGF has a number of interesting properties that may be useful for cancer treatment, including the following:

   a. VEGF induces receptors for itself on mature and nonproliferating blood vessel endothelial cells. These normal, resting endothelial cells do not have the receptor until they are exposed to VEGF.

   b. VEGF induces the production and activity of multiple other growth factors that contribute to blood vessel formation.

   c. VEGF can be induced by *c-ras,* and by other oncogenes and growth factors, which then induce further production of VEGF.

   d. Unlike normal blood vessels that require other factors for normal development, blood vessels induced by VEGF are "leaky." VEGF-induced plasma proteins, such as fibrinogen, can leak out of the new vessels, forming a spongy gel around the tumor. This gel contains VEGF, which induces further angiogenesis.

   e. VEGF appears to prevent apoptosis in induced endothelial cells.

2. **Tumors also elaborate angiogenesis inhibitors**, which can decrease growth of tumor at distant sites. One form of murine lung cancer gives rise to metastases that elaborate such inhibitors and suppress the growth of the primary site. This mechanism may account for the difficulty in locating primary tumors that present with metastases and for the absence of a detectable primary tumor (metastases of unknown origin).

III. Glossaries of basic jargon

Jargon is the use of pseudo-words (like the word "pseudo-words") plucked from a "word salad" and used to make the simple appear arcane, to disguise one's ignorance of a subject, or to have secret codes that can be used to gain entry into a club.
BL

A. **Molecular biology terminology**

Amplification: the production of many copies of a gene. This process can occur normally in certain phases of development but is also seen when a gene, such as *c-myc,* loses its transcriptional controls.

Antisense nucleotides: a DNA or RNA sequence that is complementary to the protein-coding sequence of a gene or mRNA. Antisense nucleotides can adhere to a specific coding sequence of DNA or RNA and potentially block transcription or translation. Antisense sequences are also used as molecular probes.

Breakpoint cluster regions (BCRs): regions in the genome where chromosome translocations are likely to occur and which are often situated close to a protooncogene. In chronic myelogenous leukemia (CML), a part of a BCR on chromosome 22 near the *sis* oncogene is exchanged with a portion of chromosome 9, which contains the *abl* gene, to form the Philadelphia chromosome. The normal c-abl protein is a membrane tyrosine kinase. Infection with retroviruses containing the new *abl-bcr* fusion gene from chromosome 22 can cause CML in mice.

CDs: "clusters of differentiation" antigens, which appear on leukocyte-surface membranes and change as various leukocyte lines differentiate. The type of leukocyte and the stage of differentiation can be determined using monoclonal antibody assays of these CDs. CDs on malignant leukocytes are useful for diagnosis and prognosis of hematopoietic malignancies (see Appendix C-5).

Codon: an ordered set of three nucleotides that code for an amino acid or termination code during RNA translation.

Complementary RNA and DNA: RNA or DNA sequences whose codon sequences are mirror images of each other. Complementary sequences adhere to each other. A known RNA or DNA can be used as a molecular probe to look for its complement. The degree of adherence is a measure of how closely the complementary nucleotides mirror each other.

Chromosome rearrangements (see Appendix D for nomenclature): various inversions, translocations, and additions that can alter the environment of growth-controlling genes and lead to malignancy. A number of these rearrangements are specific for a given type of malignancy.

Cyclins: proteins that trigger the entry of cells into the cell cycle by activating the transcription of *c-myc* and *c-mos* oncogene proteins, which stimulate DNA synthesis.

Double minutes (DMs): small extrachromosomal globs of DNA without a centromere that are seen under the microscope. They often indicate abnormal gene amplification in transformed cells.

DNA: deoxyribonucleic acid

DNA polymerases: a group of enzymes that joins deoxynucleotides aligned along a complementary DNA sequence. Some of these polymerases are used for DNA replication and others for repair.

Exons: Sequences in a gene that code for polypeptides

Gene: a DNA sequence that codes for a single type of polypeptide. Normal cell genes contain sub-sequences (*introns*) scattered through the main sequence that are not used for making polypeptides (see entry for introns, below).

Heterogeneous nuclear RNA sequences: a mixture of nuclear RNA sequences of different sizes. Most of this RNA consists of primary RNA transcripts in the process of rapidly losing their introns to form mRNA.

Homologous sequences: segments of different RNA or DNA nucleotides with the same or complementary nucleotide sequences

Hybridoma: a hybrid cell that makes a specific monoclonal antibody. The hybrid cells are made from normal mouse lymphocytes that produce antibodies and immortalized mouse plasmacytoma cells that do not make antibodies. The lymphocytes are taken from the spleen of mice exposed to foreign antigens, such as human leukocytes. Each splenic lymphocyte makes an antibody to one foreign antigen. These lymphocytes do not replicate but can survive in a toxic medium (HAT medium). In contrast, the plasmacytoma cells can reproduce but cannot survive in HAT medium. The hybrid cells produce specific antibodies, can reproduce, and can survive in HAT medium, which destroys unhybridized plasmacytoma cells. After the hybrid cells are separated, they are allowed to reproduce several times. This procedure allows the isolation and expansion of clones of cells that produce antibodies to a specific antigen.

Insertional mutagenesis: transformation of a cell by a sequence of viral or cellular DNA, which is inserted into the normal host genome. Inserted sequences that cause transformation may be promoters that deregulate normal genes or may be cellular protooncogenes or viral pro-oncogenes that produce growth control substances. The inserted DNA can also disrupt or combine with normal gene sequences, which then produce abnormal polypeptides. Long-term repeats (LTRs; see retrovirus terminology, later) are powerful promoters and can cause abnormal activation of nearby genes that control normal growth.

Introns: noncoding gene sequences. After a gene is transcribed into RNA, the corresponding RNA intron folds back on itself to form loops, or "lariats," that are removed, degraded, and not used for translation of mRNA into protein. Introns appear to regulate transcription and to shuffle nucleotide sequences to produce new proteins and genetic diversity. Introns are present in normal cells but are absent in oncogenic retroviruses.

Kinases: enzymes that regulate a variety of proteins and nucleotides by phosphorylation

Messenger RNA (mRNA): RNA with all introns removed and ready to be translated into protein (see entry for introns, earlier)

Missense sequences: DNA sequences with sections of abnormal codons, whose protein products function abnormally or not at all

Monoclonal antibody: an antibody made by hybridoma cell cultures that is highly specific for a specific cell surface antigen

Nucleosides: a purine or pyrimidine base combined with a sugar (i.e., ribose or deoxyribose for RNA or DNA, respectively)

Nucleotides: a nucleoside joined with a phosphate group

Oncogene: a gene that can cause cells to manifest a malignant phenotype

Polymerase chain reaction (PCR): a technique for expanding the amount of very small sequences of DNA

Promoter: a sequence of DNA near a particular gene that initiates the transcription of that gene

Proto-oncogenes: normal cell genes that are homologous to viral oncogenes (*v-onc*) or cellular oncogenes (*c-onc*) and that typically code for proteins that are essential for control of proliferation and differentiation. Their names are written in italics and begin with a " *c-*" plus a three letter symbol for the particular gene (e.g., *c*-mos).

RNA: ribonucleic acid

Signal transduction: the mechanism by which extracellular molecules affects intracellular chemistry and biology. Signal transduction is essential for growth and differentiation in multicellular organisms.

Transcription: the production of a complementary (mirror-image) RNA sequence from a DNA template

Transcription factors: specific proteins that bind to control elements of genes. Families of transcription factors include helix-loop-helix proteins, helix-turn-helix proteins, and leucine zipper proteins.

Transfection: the introduction of DNA sequences from one cell into the genome of another. Several cellular oncogenes (*c-onc*) were discovered by transfecting normal cells with DNA taken from cancer cells. After several generations of transformed daughter cells, all of the transfected DNA is lost, except for the *c-onc*.

Translation: the production of proteins by ribosomes from mRNA in the cell cytoplasm

B. **Retrovirus terminology**

Capsid: proteins that form the protein core of the virus and are coded by the viral *gag* gene

Envelope: the outer lipid and protein bilayer of the virus that is formed from the cell membrane of the previously infected cell plus the proteins coded by the viral *env* gene. For a specific type of cell to be infected, it must have a specific membrane receptor that "recognizes" the envelope of a particular retrovirus. For example, CD4 (helper T4) cells have specific receptor sites for human immunodeficiency virus (HIV) capsid antigens.

Long-terminal repeats (LTRs): DNA transcripts of the ends of a provirus that help the virus to become incorporated into cell chromosome DNA. LTRs signal the start and stop points for transcription of proviral RNA.

Provirus: the double-stranded DNA copy of a retroviral RNA

Replication-competent retroviruses: retroviruses with the full complement of sequences necessary for reproduction

Replication-deficient viruses: retroviruses that have lost some of the normal coding for proteins necessary for viral replication. These retroviruses typically have a *v-onc* and rapidly transform cells in animal tissues and in culture into malignant phenotypes.

Reverse transcriptase: a DNA polymerase that is part of the retroviral core and uses the viral RNA template to make a double strand of complementary DNA. The viral *poi* gene encodes this enzyme.

Short-terminal repeats: located at both ends of the entire viral RNA sequence. These are reverse-transcribed after viral infection into DNA LTR.

Viral oncogenes (*v-onc*): transforming genes with close homology to normal cell genes

Viral RNA: two identical strands are present in each virus and consist of several coding sequences. The special sequences *pol, gag,* and *env* are unique to certain retroviruses that regulate viral gene expression and reproduction. Examples of unique genes include the *TAX* gene of human T-cell lymphotropic virus type I (HTLV-I) and the *TAT* gene of HIV.

IV. Carcinogenic viruses

Several different types of virus cause cancer to develop in animals and transform cells in tissue culture. Viral infection contributes to the development of a few human tumors, but cell gene mutations, host immune deficiency or stimulation, and other viral infections are required before cells actually become malignant.

A. **RNA retroviruses** cause cancers in animals and cause malignant transformation of human and animal cells in culture. As a rule, retroviruses do not kill the host cell but rather allow it to survive. Studies of these viruses have been essential in understanding growth control in normal and malignant human cells.
   1. **Molecular biology of retroviral infections**
      a. After infecting the cell, all retroviruses are reverse-transcribed into provirus DNA, which is incorporated randomly into the host genome (DNA).
      b. Replication-competent provirus DNA is transcribed into RNA, which is subsequently translated into viral protein. The RNA and some viral proteins form new retroviruses that leave the cell, take some of the membrane along as their envelope, and then infect other cells.
      c. Some retroviruses, such as HTLV-I, transform cells by their insertion next to normal cellular oncogenes. These *c-onc* genes become abnormally activated. Such retroviruses do not have oncogenes themselves, and malignant transformation is a slow process.
      d. Viral DNA can also combine with DNA of a normal cell gene and make new retroviruses that contain RNA copies of a normal host gene. If the normal host gene is a cellular oncogene (protooncogene or *c-onc*), the new virus can insert the oncogene into ectopic locations in the cell genome of newly infected cells and cause malignant transformation. Some of these viruses lose their own genes when they combine with host DNA and become replication deficient.
   2. **Nomenclature of retroviral oncogenes** is usually based on the name of the animal tumor from which the retrovirus is extracted. Examples include *src*--Rous *sarc*oma virus of chickens (the first oncovirus discovered); *sis*--*si*mian sarcoma virus; *erb*--*er*ythroblastosis virus of chickens; *H-ras*--*H*arvey *ra*t sarcoma virus; *K-ras*--*K*irsten *ra*t sarcoma virus; *myc*--*my*elocytoma; *ras*--*ra*t sarcoma.
   3. **Retroviruses and human cancer**
      a. **HTLV-I** causes lymphoblastic leukemia in southern Japan and other countries. *It is the only virus that has been clearly shown to cause a human cancer.* HTLV-I is a replication-competent virus that does not possess an oncogene. Part of its transforming activity occurs by insertional mutagenesis. It also codes for the *TAX* protein, which induces infected lymphocytes to produce interleukin-2 (IL-2) receptor proteins. IL-2 attaches to these receptors and stimulates infected cells to proliferate. Other unclear events are necessary, however, for leukemia to develop, and only a small percentage of infected people develop leukemia.
      b. **HTLV-II** may cause a small percentage of hairy cell leukemias and a variety of T-cell lymphoproliferative disorders.
      c. **HTLV-III** (HIV) is associated with high-grade B-lymphocyte malignancies in patients with acquired immunodeficiency syndrome (AIDS). It also produces the *TAT* protein, which stimulates proliferation of Kaposi's sarcoma cells. The virus does not infect these cells.
B. **DNA viruses** may become incorporated into the cell genome, but this step is not always necessary. Oncogenic DNA viral genes code for proteins that affect growth-regulating substances in the cell.
   1. **Mechanisms of DNA oncogenesis** include the following:
      a. Interference with cellular inhibitors of growth, resulting in uncontrolled cell replication (e.g., the retinoblastoma gene product)
      b. Activation of cellular DNA and RNA synthesis by viral protein products
      c. Insertional mutagenesis; viral DNA is inserted into the host genome and disrupts normal growth control.
      d. Gene translocation and rearrangement
   2. **DNA viruses shown to have an oncogenic role in human malignancies** include the following:
      a. **Human papilloma virus** (HPV) DNA sequences are found in more than 80% of human uterine cervical cancer cells. HPV appears to be necessary but not sufficient for the development of most cervical cancers.
      b. **Epstein-Barr virus** (EBV) infects more than 90% of patients during the first two decades of life but generally causes no illness. EBV infects B lymphocytes and nasopharyngeal epithelium, both of which have a specific surface receptor for the virus. When EBV-infected cells are exposed to other proliferative stimuli, such as malaria, malignancy can result. EBV is a cofactor for the development of nasopharyngeal carcinoma in Asia, epidemic Burkitt lymphoma, B-cell lymphomas in immunocompromised patients, cutaneous T-cell lymphoma (with HTLV-I), and gastric carcinoma.
      c. **Hepatitis B** viral DNA sequences are found in the genomes of essentially all hepatocellular carcinomas. These sequences are translated into proteins that stimulate transcription. They also may cause cell transformation by insertional mutagenesis, which disrupts growth-regulating genes.
      d. **Adenoviruses and polyoma viruses** cause transformation of cells in cell culture but have not yet been shown to cause or contribute to human malignancy.
      e. **Human parvovirus** oncosuppressive activity is discussed in Chapter 35, section IV.E.1.

V. Malignant transformation

Oncogenes are genes that cause malignant transformation of normal cells. They are consistently associated with malignancy and may be of either cellular or retroviral origin. In general, more than one oncogene is abnormally active in cancer. The multiple interactions among oncogenes that are necessary for cell division typically result in activation of many otherwise normal oncogenes. A one-to-one correspondence between most cancers and a single oncogene abnormality generally cannot be determined.

A. **Definitions and description**
   1. **Retroviral oncogenes** (*v-onc*) were first discovered in rapidly transforming retroviruses extracted from animal tumors. About 20 oncogenes of this type have been described.
   2. **Cellular oncogenes** were discovered by extracting DNA from cancer cells and inserting it into normal cells, which then become malignant (DNA transfection). More than 20 oncogenes of this type have been described.
   3. **Inhibitory genes** produce proteins that inhibit cell proliferation. Abnormalities in these genes can lead to abnormal proliferation of cells. About 12 such genes have been described.
   4. **Proto-oncogenes** (*c-onc* or normal cell genes) control proliferation and differentiation in normal cells and appear to be the source of all oncogenes. RNA from transforming retroviruses is homologous with various protooncogenes, which is evidence for this conclusion.
      a. Proto-oncogenes are highly conserved through evolution. Many of the same oncogenes are found in life forms as diverse as humans and yeast. They appear to be essential to life.
      b. Each proto-oncogene makes protein products that are differentially expressed during the cell cycle or at specific stages of development of a particular tissue.
   5. **Differences between *c-onc* and proviral *v-onc*.** Cellular oncogenes have both introns and exons, and viral oncogenes have only exons. Proviral DNA possesses LTRs, which are powerful promoter genes not found in *c-onc.* When LTRs are inserted near a *c-onc,* they can deregulate it and transform the cell into a malignant phenotype.
B. **Steps of signal transduction:** A model for understanding oncogene biology

Step 1. Growth factors of both proto-oncogene and nonproto-oncogene origin combine with specific growth factor receptors (GFRs) on target cells, activating tyrosine kinase activity on the GFR (see step 2). The growth factor–GFR complex is taken up by the cell and deactivated. Some growth factors and their associated proto-oncogenes are fibroblast growth factors (*Int-2* and others) and platelet-derived growth factors (*sis*).

Example: *sis* oncogene.

   a. **Normal function.** The *sis* oncogene codes for one of the chains of platelet-derived growth factor (PDGF). PDGF is manufactured in megakaryocytes and packaged in platelets. When platelets become activated, they release PDGF, which stimulates its surface receptor to produce tyrosine kinase activity and which stimulates the proliferation of fibroblasts.
   b. **Abnormalities in cancer cells** involve unregulated production as a result of the ectopic location of gene, possible amplification, and truncated protein.
   c. **Associated human cancers** include some squamous cell cancers, glioblastomas, acute myelogenous leukemia (AML), and osteosarcomas. The *sis* oncogene is possibly activated by HTLV-I.
   d. **Effects of abnormalities on prognosis.** None are known.

Step 2. GFRs and some hormone receptors are protooncogene proteins that traverse the cell membrane. The cell-surface part of the protein has sites for specific extracellular growth factors. When GFRs are activated by their growth factors, their cytoplasmic sites become active tyrosine kinases. Some GFRs and their protooncogenes are colony-stimulating factor receptor type 1 (*fms*) and epidermal growth factor receptor (*erb-B*).

The activated tyrosine kinases transduce the extracellular signal to cytoplasmic proteins and to the nucleus by a variety of mechanisms. For example, they activate cytoplasmic protooncogene proteins. They also increase the levels of diacylglycerol, which then activate protein kinase C (PKC); PKC activates a number of proteins that stimulate DNA synthesis. They also phosphorylate guanosine 5'-diphosphate (GDP) to make guanosine triphosphate (GTP), which activates p21 (a *c-ras* protein); the GTP–p21 complex stimulates DNA transcription in the nucleus.

Example: *erb-B* oncogene (others: *fms, ros, sea*).

    a. **Normal function.** The proto-oncogene counterpart of *erb-B* produces cell-surface receptors for EGF and has tyrosine kinase activity when activated by EGF.
    b. **Abnormalities in cancer cells.** The *erb-B* gene product produces a truncated product with unregulated protein kinase activity. It delivers a constant proliferative signal to the cell.
    c. **Associated human cancers** are squamous cancers and glioblastomas.
    d. **Effects of abnormalities on prognosis.** Survival is poor with increased expression of *erb-B* for patients with breast cancer, upper respiratory tumors, and uterine cervix cancer.

Step 3. Cytoplasmic kinases that modulate the activity of key cellular enzymes are activated by membrane receptor kinases. These proteins typically have serine or threonine kinase phosphorylating activity, and some have GTPase activity. These kinases have an extensive variety of effects in activating nuclear proteins and in direct activation of DNA promoter regions. For example, the cell division cycle kinase (*cdc*) is found in all eukaryotic cells and is essential to the transition of cells from the G_2 phase to M phase. Cyclin proteins and phosphorylation regulate its activity and appear to act by destabilizing the cytoskeleton in preparation for mitosis.

Example: *ras* oncogene (others: *raf, mos, src, yes, fps, abl, crk, cdc*).

    a. **Normal function.** Proto-oncogene precursors of *c-ras* proteins transduce signals from the cell surface to the nucleus. The proteins combine with GDP and GTP. The protein–GTP complex (e.g., p21– GTP) is the chemically active form, which then activates a variety of nuclear promoter proteins. The protein has GTPase activity that is enhanced by a cytoplasmic protein called GAP. The GTPase converts its own bound GTP to GDP, inactivating the complex; this phenomenon is thought to be a self-regulatory activity of the protein. The ras protein also increases levels of diacetylglycerol, which activates PKC, an important initiator of DNA transcription (see step 4).
    b. **Abnormality in cancer cells.** The *ras* oncogenes are a group of five related oncogenes with most of the activities of their normal proto-oncogene counterparts. Several defects, including defective GTPase, have been found. This abnormality leads to a constant presence of the GTP form of the molecule, which continuously activates nuclear proteins and DNA transcription.
    c. **Associated human cancers.** These include AML, some melanomas, neuroblastomas, breast cancers, bladder cancers, and lung cancers.
    d. **Effects of abnormalities on prognosis.** The prognosis is poor for patients with AML.

Step 4. Proteins directly controlling gene expression ("transcription factors") are involved in the final step of signal transduction. Some of these factors are short-lived and never leave the nucleus. For example, *c-jun* and *c-fos* proteins are among the first proteins transcribed at the G_0–S interface and appear to initiate the cell cycle. Cyclins appear to trigger the cell's entry into the cell cycle and into mitosis by activating the transcription of *c-myc* and *c-mos*. Proteins from *c-myc* and *c-mos* also reside in the nucleus and form complexes that stimulate DNA synthesis. Other factors enter from the cytoplasm (e.g., *ras, myc*); these are transcribed and activated by cytoplasmic kinases (see step 3). Several normal products of protooncogene kinases in the cytoplasm also activate gene transcription, particularly PKC, which acts directly as a DNA promoter and stimulates the production of *c-jun* and *c-fos* proteins; this *jun-fos* complex binds to specific promoter regions of DNA and stimulates DNA transcription.

Example: *c-myc* oncogene (others: *jun, fos, erb-A, rel, ski, myb*).

    a. **Normal function.** The *c-myc* oncogenes are a family of proteins with direct nuclear regulatory activity. The presence of active *myc* appears necessary for cell division. Dimethylsulfoxide inhibits *myc* transcription, stops cell division, and can cause differentiation of leukemic blast cells in culture. High levels of *c-myc* are found in immature blood cells and gastrointestinal cells. Both *c-myc* and the *c-jun/c-fos* protein products form dimers connected at a leucine-rich region called the *leucine zipper* near the site of attachment to promoter genes.
    b. **Abnormalities in cancer cells.** Amplification of the *myc* gene can be so prolific that the multiple copies sometimes cannot remain on a chromosome. Extrachromosomal DMs often microscopically give visible evidence of such amplification, with high quantities of active gene product being formed.
    c. **Associated human cancers** include Burkitt lymphoma, B-cell lymphomas, promyelocytic leukemia, neuroblastoma, small cell lung cancer, and colon cancer.
    d. **Effects of abnormalities on prognosis.** In neuroblastoma, the prognosis is poorer in direct proportion to levels of *N-myc* (*N* = neuroblastoma) for this member of the *myc* gene family.

Step 5. Growth-inhibitor genes produce substances, typically phosphatases, that normally inactivate growth-promoting oncogene products and inhibit cell proliferation. Mutations that make these genes nonfunctional lead to uncontrolled cell proliferation and malignancy. Examples of these mutations and their associated tumors include *RB1* (retinoblastoma and some osteosarcomas), *WT1* (Wilms' tumor), *NF1* (neurofibromatosis), *MEN1* (multiple endocrine neoplasia), and *FAP1* (familial adenomatous polyposis of the colon).

Chapter 2 Nuclear Medicine

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I. Definitions

A. **Nuclear medicine** is the use of radioactive tracers in the form of unsealed sources for the diagnosis, therapy, and laboratory testing of human diseases. The common radiopharmaceuticals include 25 forms for diagnostic imaging applications and 5 forms for therapy (Table 2.1).

   Table 2.1 Some diagnostic and therapeutic radiopharmaceuticals

B. **Radioactivity, radioisotopes, and radionuclides.** The nucleus contains a variety of subatomic particles, such as protons and neutrons, which are held together by incredibly strong short-range forces. The **atomic number** (Z) of an atom is the number of protons in the nucleus and is characteristic of a particular element. The **mass number** of an atom is the sum of the protons and the neutrons (A); it is this number that we refer to in this section unless otherwise specified. For most of the common elements in the earth, the nucleus is completely stable and unchanging. Radioactive elements occur when the balance of subatomic particles in the nucleus is inherently unstable. Each radionuclide has specific radioactive decay characteristics in terms of half-life and radioactive emissions.
   1. **The half-life** ($t_{1/2}$) is the time required for one half of the atoms to undergo radioactive decay.
      a. The half-life of most of the radioisotopes is short, and they therefore do not exist in nature. Some naturally occurring elements are radioactive; for example, ^{40}K accounts for 0.1% of the potassium found within the human body and has a half-life of 1.26×10^9 years. Other naturally occurring radioactive elements include radium, thorium, lead, and carbon. All elements with atomic weights greater than ^{209}Bi are radioactive. The transuranium elements may also have half-lives of 10,000 years or more.
      b. Most of the radioactivity used in nuclear medicine is artificially produced in a reactor or cyclotron (see later). ^{131}I, for example, has a half-life of 8 days and emits a gamma ray of 364 keV, along with several beta particles, including one with an average energy of 0.616 MeV. These radioactive emissions can be detected externally and permit ^{131}I to be useful as a tracer for the study of thyroid physiology.
   2. **Forms of radioactive emissions**
      a. **Gamma rays,** which are photoelectric energy that is capable of penetrating a meter or more through human tissue
      b. **Beta rays,** which are particulate emissions with the mass of an electron and a negative charge that are capable of penetrating from a few millimeters to about a centimeter in tissue
      c. **Positrons,** which are particulate emissions with the mass of an electron and a positive charge that travel for a few millimeters in tissue and then interact with an electron, forming annihilation radiation
      d. **Annihilation radiation,** which is two gamma photons of 511-keV energy traveling at 180 degrees from each other that develops when a beta ray and a positron combine (see e and f)
      e. **Alpha particles,** which are two neutrons and two protons (a helium nucleus) that are capable of traveling for about 10 to 20 cell diameters in tissues
      f. **X-rays,** which result from rearrangement of electrons in orbitals around the nucleus
      g. **Auger electrons,** which are low-energy electrons that are emitted from the orbitals around the nucleus and are capable of traveling only a few microns in tissue
      h. **Applications.** Gamma rays and annihilation radiation in particular are useful for various diagnostic imaging applications. The shorter-range particles, such as beta rays and even the auger electrons, are used for therapeutic applications.
   3. **Quantity of radioactivity**
      a. **Becquerel** (Bq). One disintegration per second (dps) is defined as 1 Bq of radioactivity, in honor of the discoverer of radioactivity. Typical doses used for imaging are often 37 megabecquerels (MBq).
      b. **Curies** (CI). The curie unit was based on the amount of radioactivity in 1 g of radium or 3.7×10^{10} dps. Typical diagnostic doses range from 1 millicurie (mCi or 37 MBq) to 30 mCi (1110 MBq).
   4. **Quantity of absorbed radiation**
      a. **Rads.** When radioactive emissions interact with matter, a fraction of the total energy is absorbed. The rad is equivalent to one erg of energy absorbed per gram of tissue.
      b. **Grays** (Gy) is the newer unit replacing the rad. One gray is 100 rad; 1 centigray (cGy) is 1 rad.
      c. **Rem** (R), or roentgen equivalents man, was introduced as a unit because not all radiation emitted has equivalent potency for the biologic effects that it exerts for a given amount of radiation dose absorbed. For gamma photons and x-rays, the rad dose and the rem dose are the same. For larger particles (e.g., the alpha particle), the rem is the rad dose times a "quality factor." For alpha particles, the quality factor is 20, so that for a given rad dose, the rem for alpha-particle exposure is 20 times that for gamma exposure.
      d. **Sieverts** (Sv). One Sv is 100 rem.

C	Carbon (^{11}C)	**O**	Oxygen (^{15}O)
F	Fluorine (^{18}F)	**P**	Phosphorus (^{32}P)
Ga	Gallium (^{67}Ga)	**S**	Sulfur (^{35}S)
I	Iodine (^{123}I, ^{125}I, ^{131}I)	**Sr**	Strontium (^{89}Sr)
In	Indium (^{111}In)	**Tc**	Technetium (^{99m}Tc); "m" means "metastable"
Kr	Krypton (^{81}Kr)	**Tl**	Thallium (^{201}Tl)
Mo	Molybdenum (^{99}Mo)	**U**	Uranium (^{235}U, ^{238}U)
N	Nitrogen (^{13}N)	**Xe**	Xenon (^{127}Xe, ^{133}Xe)

C. **How much radiation exposure is safe?** The answer is the ALARA principle, which means "as low as reasonably achievable."
   1. **In the workplace,** a maximum of 5,000 millirem (mR) per year is permitted; 25% of this dose (1250 mR) is targeted. Several decades of exposure of large populations of workers to the 5,000 mR/year limit has demonstrated no adverse effects. The U.S. Food and Drug Administration (FDA) has used this definition for what could be considered "safe" levels of total-body radiation exposure. Directives for pregnant workers permit 500 mR per 9-month gestational period.
   2. **The general public** in the United States receives an average of 290 mR/year from naturally occurring radiation. Up to 10 times this exposure may occur at high altitudes, again with no discernible adverse effects. The mandated level for the general public is now set at 100 mR/year.
   3. **Diagnostic exposure** for the purpose of patient management has no limits because the doses involved are relatively low, and it is generally believed that the benefits outweigh the risks associated with indicated studies.
   4. **Therapeutic radioisotopes** commonly require admission to the hospital with isolation procedures until the radiation levels fall to 5 mR/h at 1 meter from the treated subject. After that point, the patient is not subjected to special precautions.

D. **Instrumentation**
   1. **Well counters.** A radiation-sensitive crystal (usually sodium iodide) is fashioned so that a small test tube containing a body fluid can be placed in a well. For each decay, the energy from the emitted radiation is deposited in the crystal, and the crystal is induced to emit a pulse of light. This light pulse is converted

to a weak electrical signal by a photoelectric tube. Further amplification results in a signal that can be read as an individual "count." Typical samples have 10,000 to 20,000 counts per minute (cpm). The amount of the radiotracer present is proportional to the total amount (cpm) detected. By reference to standards of known activity, the absolute amount of tracer can be detected.

2. **Gamma camera devices** are the most commonly used imaging device for the widely available radiopharmaceuticals, such as ^{99m}Tc, ^{111}In, and ^{131}I. The gamma camera is designed as a circular sheet of sodium iodide crystal, encased in a lead shield and directly coupled to 90 or more photoelectric tubes. A collimator device in front of the crystal serves to focus the radiation; it is a 1-inch thick lead shield with holes punched in the lead. Every disintegration in the patient that results in a gamma ray travels to the collimator and passes through the holes in the lead to strike the radiation-sensitive crystal. A light pulse is created in the crystal and is detected by several photomultiplier tubes simultaneously. A computer calculates where the photon hit the crystal, with the strongest signal being nearest the site where the photon struck the detector. Resolution is about 1 cm or so for most planar gamma cameras.

3. **Single photon emission computerized tomography (SPECT).** In this form of imaging, radioactivity within the patient is collected at 360 degrees around the patient, and the data are reconstructed into a three-dimensional representation. The data are collected by rotating a specialized gamma camera around a patient who has received an injection of radioactivity that is stable in distribution for the 45- to 60-minute collection times typically required. SPECT is commonly used for the imaging of ^{67}Ga citrate in the mediastinum of patients with lymphoma, ^{201}Tl in myocardial perfusion studies, hemangiomas within the liver, and radiolabeled antitumor antibodies. The typical in-depth resolution is 16 mm, somewhat more coarse than for planar imaging. Planar gamma camera imaging provides better contrast resolution, whereas SPECT provides better images of small, deep lesions.

4. **Positron emission tomography** (PET) has the highest resolution and is the most sensitive imaging device available for nuclear medicine. For reasons related to the physics of positron emission decay, the image can be converted into an accurate, quantitative three-dimensional distribution of radioactivity with a resolution of about 3 to 5 mm in depth within the body. The radiotracers used with PET are ^{18}F, ^{15}O, ^{13}N, and ^{11}C; these elements are readily incorporated into biologic molecules. Most of these radiotracers have half-lives that are too short for shipping. Thus, they must be produced in a hospital-based cyclotron. Nonetheless, clinical applications are emerging, especially using ^{18}F-labeled tracers. For example, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) imaging of glycolysis of tumors is used to demonstrate tumor viability after treatment with radiation or drugs.

5. **Cyclotron.** The cyclotron accelerates subatomic particles (e.g., protons, deuterons, helium nuclei, alpha particles) to speeds approaching the speed of light. The particle strikes a "target" atom and produces radioactivity. For example, by accelerating protons to about 11 MeV and striking a target that contains an enriched isotope of oxygen (^{18}O), ^{18}F in the form of fluoride ion is produced. These *accelerator systems* produce a large variety of the radiotracers useful in nuclear medicine, including ^{11}C, ^{15}O, ^{13}N, ^{67}Ga, ^{111}In, ^{123}I, and ^{18}F.

6. **Reactors.** The reactor is fueled by heavy elements, such as ^{238}U and ^{235}U, which undergo spontaneous fission. Neutrons are emitted from the nucleus and, when present in sufficient quantities, "split" the uranium atoms, with the consequent release of large amounts of energy. An entire cascade of radioactive elements is produced in this process; these elements, called *fission products,* include ^{99}Mo (from which ^{99m}Tc is derived), ^{131}I, ^{125}I, ^{32}P, and ^{35}S. In some cases, a target element is bombarded with neutrons to produce the radioactive element used in medicine (e.g., ^{89}Sr). In other cases, separation of fission products may produce the radioisotope as a byproduct of reactor operation (^{131}I, ^{125}I).

II. Tumor imaging studies

A. **Bone scanning**
1. **Indications** for bone scanning are to determine the presence and extent of primary and metastatic tumor involving bone and to provide a baseline in early malignancy if the patient has a cancer that notoriously metastasizes to bone (e.g., prostate cancer, stage II or III breast cancer) or has significant bony abnormalities of a benign nature.
2. **Radiopharmaceutical.** A pyrophosphate or other phosphonate derivative is labeled with ^{99m}Tc.
3. **Principle.** Primary or metastatic tumor provokes a reaction in the adjacent bone that causes the bone crystal to remodel and in the process take up the ^{99m}Tc bone agent. Even small tumors can evoke a considerable response. (See Chapter 33, section I.D.3.)
4. **Procedural notes.** Whole-body scans are ordinarily obtained using gamma cameras with large fields of view. SPECT imaging is performed on suspect regions and is particularly helpful in the spine.
5. **Interpretation.** Against a background of bone turnover, a metastatic site stands out as avid uptake. Bone scans are more sensitive than computed tomography (CT) and magnetic resonance imaging (MRI) for detection of metastases in cortical bone. MRI may detect metastases in the bone marrow before cortical bone is affected.

B. **CEAScan**
1. **Indications.** In patients with suspected or known recurrent colorectal cancer that expresses carcinoembryonic antigen (CEA), CEAScan is possibly helpful in the following circumstances:
   a. For differentiating hepatic lesions seen on CT
   b. For determining resectability of hepatic lesions in patients with metastatic colorectal cancer
   c. For detecting extrahepatic abdominopelvic disease in patients with suspected recurrent colorectal cancer
2. **Radiopharmaceutical:** ^{99m}Tc conjugated to a murine anti-CEA Fab' antibody fragment
3. **Principle.** Most colorectal cancers express CEA. The antibody's Fab' fragment recognizes CEA present on tumor cells, which are specifically targeted. The small size of the Fab' fragment results in rapid clearance and permits diagnostic images to be obtained within the short half-life of ^{99m}Tc (6 hours).
4. **Procedural notes.** Spot images of the thorax, abdomen, and pelvis are obtained using a low-energy, general-purpose collimator. SPECT of the liver and infrahepatic abdomen and pelvis is then carried out. Equivocal images must be repeated, typically the next day; the short half-life of ^{99m}Tc usually precludes next-day SPECT.
5. **Interpretation.** Areas of increased uptake in the liver corresponding to abnormalities seen on CT, or (for larger liver lesions) areas of decreased uptake surrounded by rims of increased uptake, are consistent with liver metastases. It is important to assess the abdomen closely, especially in nodal areas and at sites of possible recurrence. Antibody targeting to disease does not clear with time, whereas antibody in normal tissue does. Renal excretion precludes detection of disease around the kidneys; perirenal disease may require special SPECT reconstruction techniques for optimal results.

C. ^{18}**FDG imaging with PET**
1. **Indications**
   a. To distinguish radiation necrosis from recurrent glioblastoma
   b. To evaluate degeneration of brain tumor from low-grade to high-grade
   c. To evaluate the potential for recurrence of meningioma
   d. To assess tumor viability and monitor treatment response
   e. To differentiate benign from malignant pulmonary nodules
2. **Radiopharmaceutical:** [^{18}F]-2-fluoro-2-deoxy-*d*-glucose (or FDG) is an analogue of glucose.
3. **Principle.** Tumors have markedly accelerated glycolysis in comparison to the tissues from which they arise. FDG enters the tumor cell through the glucose transporter and is phosphorylated to FDG-6-phosphate (FDG-6P). FDG-6P, however, is not a suitable substrate for other glycolytic enzymes, is "metabolically trapped," and accumulates in the tumor tissue in proportion to the rate of phosphorylation of FDG. Although FDG-6P can be dephosphorylated by glucose-6-phosphatase, this enzyme is not expressed in actively proliferating tumors. Most normal tissues, with the exception of brain and heart, do have glucose-6-phosphatase and rapidly clear the FDG. Thus, a gradient develops between tumor and background over time and can be readily detected by a PET scanner.
4. **Procedural notes.** ^{18}FDG is injected into a fasting patient 45 to 60 minutes before PET scanning.
5. **Interpretation.** ^{18}FDG PET imaging is likely to be of great use in the scanning of many malignancies.
   a. **For primary brain tumors,** a comparison is made to the "contralateral" white matter; a hyperactive tumor has a ratio of 1.4 times the concentration of FDG. Increased uptake is characteristic of high-grade primary and metastatic neoplasms. The more active the uptake, the more rapid the growth pattern. Areas of decreased uptake are seen with low-grade tumors and radiation necrosis.
   b. **Solitary pulmonary nodules** are commonly managed with thoracotomy because of uncertainty about the benign or malignant nature of this finding. If the ratio of ^{18}FDG PET uptake between a nodule and a normal control region is 2.5 or greater, the lesion is almost certainly malignant.

D. ^{67}**Ga imaging**
1. **Indications**
   a. To evaluate response to treatment of patients with Hodgkin lymphoma and intermediate- or high-grade (but not low-grade) non-Hodgkin lymphoma. A baseline assessment is performed before therapy and repeated at the time of restaging procedures.
   b. To evaluate viability selectively in other tumors (e.g., hepatoma, sarcoma, melanoma). These patients are studied as far from the completion of treatment as possible.
2. **Radiopharmaceutical:** ^{67}Ga citrate
3. **Principle.** ^{67}Ga is a transition element that shares a variety of properties with iron, including rapid binding to transferrin (TF) after intravenous injection. Thereafter, the ^{67}Ga-TF is taken up by tumor cells through binding to the TF receptor on the membrane of tumor cells. The expression of the TF receptor is

proportional to growth; the more rapidly proliferating the tumor, the more avid is the uptake.

4. **Procedural notes.** The patient is imaged 48 to 72 hours after injection. A purgative is administered the night before imaging. SPECT is significantly more sensitive than planar imaging for detecting active tumor sites. Anatomic correlation with CT or MRI helps greatly in interpretation. Where available, images from two different imaging modalities can be coregistered ("fused") in the computer. The anatomic image is used as a template on which the ^{67}Ga image is laid to identify the tumor-avid sites.

5. **Interpretation**
   a. ^{67}Ga citrate imaging is not normally used for staging purposes, but a baseline scan is helpful for later comparisons to help determine tumor response, particularly in patients with lymphomatous mediastinal involvement. Tumor sites may take up ^{67}Ga with strong avidity, which is greatly reduced when the tumor has responded to treatment. Persistence of ^{67}Ga is a sign of poor prognosis.
   b. ^{67}Ga imaging is nonspecific; the isotope is avidly taken up in inflammatory lesions (e.g., diffusely in the lungs with *Pneumocystis carini* and other pneumonitides). ^{201}Tl has been found to be useful when the cause of uptake on a ^{67}Ga scan is questioned. ^{201}Tl is normally concentrated in viable tumor and is rarely positive in lymphatic inflammation.

E. **Lymphoscintigraphy**
1. **Indications:** To determine the direction of lymph node drainage from truncal skin lesions (e.g., for melanoma) or the status of lymph ducts in regions of lymphedema
2. **Radiopharmaceutical:** ^{99m}Tc-labeled albumin
3. **Procedural notes.** Typically, injections are made into the webbing between the toes or fingers to assess the lower limbs or arms, respectively. Gamma camera imaging is performed to assess the direction of drainage as a guide to determining what lymph node–bearing region should undergo surgical exploration.
4. **Interpretation.** Careful attention to detailed imaging in the early images may show the sites of interruption of draining lymphatic ducts, which in some patients can be used as a basis for correcting the problem.

F. **Lymphoscintigraphy: sentinel node detection**
1. **Indication.** Detection of the sentinel lymph node in patients scheduled to undergo surgical resection of primary breast carcinoma or melanoma.
2. **Radiopharmaceutical:** ^{99m}Tc sulfur colloid passed through a 0.22-µ filter. When filtered radiopharmaceutical is used, lymphatic channels are seen more frequently, and sentinel nodes are seen earlier.
3. **Procedural notes.** After perilesional intradermal injection of the colloid, serial gamma camera imaging (anterior and lateral views) is carried out to determine the lymphatic drainage and identify the first node that concentrates tracer. This is usually supplemented by intraoperative detection of nodal radioactivity using a gamma probe.
4. **Interpretation.** Serial images permit detection of the first node to concentrate radioactivity. It has been proposed that disease status of this node is representative of overall nodal status.

G. **Metaiodobenzylguanidine (MIBG) imaging for catecholamines**
1. **Indication.** To identify metastatic and primary tumor sites for pheochromocytoma and neuroblastoma.
2. **Radiopharmaceutical:** Iobenguane sulfate ^{131}I (MIBG sulfate)
3. **Principle.** MIBG is normally concentrated by adrenergic tissues in cytoplasmic storage granules that also contain other catecholamines. Anything that blocks uptake or promotes release of these storage granules can potentially lead to false-negative results (see section II.G.6).
4. **Procedural notes**
   a. The patient is imaged with the whole-body camera at 24 and 48 hours, with special attention to the retroperitoneum and adrenal region. Patient preparation consists of administering saturated solution of potassium iodide beginning 24 hours before starting the study and for one week after administering the dose.
   b. **Warning.** Hypertensive crises have occurred after injection of MIBG, especially in patients with pheochromocytoma. Pregnancy is not an absolute contraindication, but the potential risk to the fetus should be carefully assessed.
5. **Interpretation.** MIBG is cleared by glomerular filtration from the plasma and is rapidly taken up in catecholamine storage granules in tissue sites containing sympathetic nerves or adrenergic storage sites. Thus, uptake occurs in the heart, kidneys, liver, and adrenals at most imaging times. Tumors show up as areas of increased uptake.
6. **Drug interactions.** The following drugs have the potential to interfere with the uptake of MIBG by neuroblastoma and pheochromocytoma and should be stopped a few days to weeks before beginning the imaging, depending on the pharmacology of the drug.
   a. Antihypertensives: labetalol, reserpine, calcium-channel blockers
   b. Amytriptyline, imipramine, and derivatives
   c. Doxepin
   d. Sympathetic amines (pseudoephedrine, ephedrine, phenylpropanolamine, phenylephrine)
   e. Cocaine

H. **Oncoscint imaging**
1. **Indication.** To determine the extent and location of extrahepatic abdominal disease in patients with known colorectal or ovarian cancer.
2. **Radiopharmaceutical.** Oncoscint CR/OV (satumomab pendetide) is a conjugate produced from a murine monoclonal antibody (MoAb). The MoAb is an IgG-k directed to the nonspecific cancer antigen TAG-72. It contains the site-specific linker chelator that is conjugated to ^{111}In.
3. **Principle.** The injected, radiolabeled MoAb binds to antigen sites (most commonly tumor). Over time, sufficient concentration of radioactivity builds up at tumor sites to permit detection by a gamma camera.
4. **Procedural notes.** The patient is imaged with a planar gamma camera or SPECT camera between 48 and 72 hours after injection. Later imaging and the use of cathartics may help to define a region of abdominal uptake in relationship to bowel or bladder activity.
5. **Interpretation.** The abnormal focus of uptake in tumor is seen as a hot spot. Comparison to other imaging modalities, such as CT or MRI scans, may be helpful in determining the anatomic location of the uptake.
   a. Compared with CT scanning in patients with colorectal cancer, Oncoscint detected a greater proportion of lesions in the lower abdomen and pelvis. CT scanning was better for liver lesions. When the two tests were used in combination, the aggregate sensitivity was 88%.
   b. In ovarian cancer, there is improved sensitivity, as compared with CT, for detecting peritoneal or pelvic spread and disease (about 55% versus 35%).

I. **Pentetreotide imaging**
1. **Indication.** For diagnostic workup of neuroendocrine tumors that bear somatostatin receptors.
2. **Radiopharmaceutical.** Pentetreotide is a diethylenetriaminepentaacetic acid (DPTA) conjugate of octreotide, which is a long-acting analogue of human somatostatin. ^{111}In is bound to the agent.
3. **Principle.** ^{111}In pentetreotide binds to somatostatin receptors throughout the body. Neuroendocrine tumors highly express these receptors and thus concentrate sufficient amounts of the radioactive agent to be seen by scintigraphy.
4. **Procedural notes.** The patient undergoes daily planar and SPECT imaging until it is determined whether the agent is helpful. Typical imaging times are 4, 24, and 48 hours after injection. Because the agent is excreted into the bowel, the patient should be given a mild laxative the evening before the 24- and 48-hour imaging times.
   a. **False-negative results** may occur in patients who are concurrently taking octreotide acetate for control of symptoms related to neuroendocrine tumors. If possible, patients should stop taking this medication 2 weeks before the scan. Also, corticosteroids by prescription and adrenocorticotropic hormone–producing tumors can reduce the expression of somatostatin receptors and should also be stopped before scanning.
   b. **Warnings and adverse reactions.** Transient symptoms are occasionally seen, including dizziness, hypotension, and headache. Patients with known or suspected insulinomas should have an intravenous line running with 5% dextrose in normal saline before and during administration to avoid possible hypoglycemia.
5. **Interpretation.** The normal pituitary gland, thyroid gland, and liver are seen. To a lesser extent, the gall bladder, kidney, and bladder are also visible. Uptake in tumors bearing somatostatin receptors is apparent beginning at 4 hours, with the 24- and 48-hour images showing the greatest tissue contrast. The sensitivity for detecting tumor types depends on the frequency of somatostatin receptor. Those patients with strongly positive scans may be most likely to benefit from treatment with octreotide.
   a. **New lesions that were previously occult,** despite extensive workup, were identified in nearly 30% of patients studied with ^{111}In pentetreotide. Carcinoid tumors, neuroblastomas, pheochromocytoma, paragangliomas, small cell lung cancer, and meningiomas were detected in about 90% of cases. Lymphomas, pituitary tumors, and medullary tumors were detected in high but more variable percentages.
   b. **Granulomatous lesions** and other types of inflammatory lesions were also strongly positive, including tuberculosis, sarcoidosis, rheumatoid arthritis, and Graves' disease ophthalmopathy.

J. **Prostascint for prostate tumor imaging**
1. **Indications.** Detection of prostate cancer outside the prostatic bed or recurrent prostate cancer in the prostatic bed.
2. **Radiopharmaceutical:** ^{111}In capromab pendetide (Prostascint) consists of a monoclonal antibody against the prostate-specific membrane antigen (PSMA) to which ^{111}In is attached by a chelate.
3. **Principle.** The antibody reacts with an antigen specifically found in prostate cancer cells. After intravenous administration, the antibody is gradually cleared

from the circulation while localizing in tumor tissue.

4. **Procedural notes.** Anterior and posterior whole-body images are obtained starting about 30 minutes after injection, followed by SPECT of the infrahepatic abdomen and pelvis. Comparable images are obtained typically 4 days after injection. Because the radioactivity may be concentrated in the liver and is usually excreted through the bowel, it is important to prepare the bowel with an oral laxative the night before and an enema on the day of imaging.

5. **Interpretation.** The whole-body images are searched for areas of increased uptake in the region of the aortic and iliac nodal groups. The SPECT images are important for the region of the prostate bed and the obturator nodes. Because the antibody remains in circulation and because the increased uptake in diseased areas is sometimes difficult to distinguish from normal vascular activity, it is important to compare the early and delayed image sets to ensure that the area of uptake seen in the delayed imaging is not in a vascular region. It is also important to ensure that the patient voids urine as completely as possible before imaging and to image comparable areas of the body.

K. **Tumor viability imaging:** ^{201}Tl chloride and ^{99m}Tc sestaMIBI
1. **Indications**
   a. Differential diagnosis of breast masses
   b. Viability assessment of primary bone tumors after chemotherapy
   c. Monitoring viability of well-differentiated thyroid cancer
   d. Imaging of parathyroid adenomas
   e. Imaging of brain tumors (SPECT)
2. **Radiopharmaceutical**
   a. **^{99m}Tc methoxyisobutyl isonitrile** (MIBI) is a monovalent cationic form of ^{99m}Tc that is highly lipid soluble. The agent is formed as a central ^{99m}Tc atom surrounded by six isobutyl nitrile molecules; for this reason, it is sometimes referred to as *sestaMIBI*.
   b. **^{201}Tl (thallous) chloride** is a radioisotope of thallium, which is in the actinide series of elements and behaves *in vivc* as an analog of potassium.
3. **Principle.** ^{201}Tl chloride is a widely used cardiac perfusion agent that is taken up by most viable cells as a potassium analog and transported by the Na$^+$, K$^+$ pump. **^{99m}Tc sestaMIBI** is also used to monitor cardiac perfusion. In addition, when taken up into the cell by a different mechanism, it can be used as a marker for cellular viability. After introduction into the bloodstream, both of these agents are rapidly cleared from the circulation in proportion to cardiac output.
4. **Procedural notes.** The tracer is injected intravenously, and imaging is begun over the region of interest within 20 minutes of injection, frequently at an early and a late time after injection (e.g., 5 minutes and 60 minutes after injection). For breast imaging, a special breast apparatus permits planar lateral views of the breast in the prone position. This appears to be a technical advance. For brain and other imaging, SPECT scanning is performed.
5. **Interpretation**
   a. **Breast masses.** About 25% of patients who are subjected to screening mammography have "dense" breasts that obfuscate interpretation. If these patients also have palpable breast masses, there may be a clinical dilemma in regard to biopsy of these lesions. It has been reported that uptake of ^{201}Tl is negative in fibrocystic disease and positive in 96% of breast cancer nodules. Similar results have been observed in patients with breast masses imaged with MIBI. The negative predictive value for breast cancer with these studies is likely to improve the specificity of breast mammography and is applicable to both dense breasts and normal breasts.
   b. **Primary bone tumors** are frequently treated with chemotherapy before surgery. ^{201}Tl and ^{99m}Tc sestaMIBI are both taken up with high sensitivity into primary bone tumors and extremity sarcomas. Chondrosarcoma is an exception. MIBI uptake is lost in tumors responding to chemotherapy and has also been shown to correlate well with response to therapy.
   c. **Brain tumors.** ^{201}Tl chloride appears to be the agent of choice for evaluating supratentorial primary brain tumors when FDG-PET is not available. SPECT imaging is accurate for assessing the viability of brain tumors. In our experience, ^{201}Tl is preferred over ^{99m}Tc sestaMIBI because uptake in the choroid plexus is not as marked.
   d. **Thyroid cancer imaging.** ^{201}Tl whole-body imaging is a good way to monitor the activity of well-differentiated thyroid cancer during the interval when the patient is fully suppressed on thyroid hormone. The total uptake, as a percentage of the total-body uptake, is a monitor of the cellular viability of the tumor and can be used to assess the effectiveness of primary cancer treatment.
   e. **Parathyroid imaging.** With careful comparisons of ^{201}Tl or ^{99m}Tc sestaMIBI imaging, it is sometimes possible to detect parathyroid adenomas in the neck or upper mediastinum when other modalities are negative. Still, the sensitivity of these techniques is disappointingly low (about 50%).

III. Other imaging studies used in oncology

A. **Cardiac functional studies.** Equilibrium (gated) blood pool imaging is used to evaluate possible cardiac failure and to monitor changes after treatment with cardiotoxic drugs.
1. **Radiopharmaceutical.** Red blood cells (RBCs) may be labeled *in vivo.* Stannous pyrophosphate (1 mg) is administered 20 minutes before injecting ^{99m}Tc pertechnetate. The stannous pyrophosphate enters and is trapped in the RBCs. The ^{99m}Tc pertechnetate diffuses into the RBCs and is bound to the b chain of hemoglobin. About 75% of the dose is labeled to the RBCs. An electrocardiogram R-wave signal serves as a physiologic "gate" for collection of timed "frames" (often called *gated blood pool imaging*).
2. **Interpretation.** Images obtained during rest are interpreted qualitatively to determine areas of abnormal wall motion, size of cardiac chambers, presence of intrinsic or extrinsic compression of the cardiac contour, and size and shape of the outflow tracts. Images are interpreted quantitatively for a physiologic assessment of the quantity of blood ejected from the left ventricle with each beat (the left ventricular ejection fraction [LVEF]). A normal LVEF is usually greater than 50%. LVEFs less than 30% are usually but not always associated with clinical congestive heart failure. A decrease of more than 10% in LVEF is highly significant. Cardiotoxic chemotherapeutic agents should be stopped when ejection fractions fall to below normal (see Chapter 29, section VI.D).
B. **Vascular flow and bleeding** studies can be used to detect the patency of venous access in the upper extremities (e.g., postsubclavian catheter-placement swelling, superior vena cava syndrome), to assess for the presence of hemangioma as a space-occupying lesion, or to determine a site for bleeding. ^{99m}Tc pertechnetate or ^{99m}Tc sulfur colloid can be used as transient labels of the vasculature. *In vivc* labeling of RBCs with ^{99m}Tc may be used as more long-term vascular labels (see section III.A.1).
C. **^{99m}Tc-macroaggregated albumin for lung perfusion** can be used to evaluate patients suspected of having pulmonary embolism and to determine the lung function capacity before pulmonary resection. ^{99m}Tc-labeled to macroaggregates of albumin (30 to 60 μm in diameter) are injected intravenously and are cleared in the first pass through the pulmonary circulation. The distribution of radioactivity is proportional to blood flow to the lungs.
D. **Studies of pulmonary ventilation** can be used to determine whether a ventilation-perfusion "mismatch" exists as an aid in the differential diagnosis of pulmonary embolism and to assess the ventilatory capacity of the human lung. ^{133}Xe gas, ^{127}Xe gas, ^{81m}Kr, and ^{99m}Tc-DPTA aerosol are used to label the inspiratory air. As the patient breathes, a gamma camera obtains an image of the distribution of radioactivity. Several minutes of breathing is required to achieve equilibrium with bullae and fistulous tracts.
E. **Infection imaging**
1. **^{67}Ga citrate appears to be taken up by the cells near the region of the infection.** ^{67}Ga imaging requires several days to complete, and normal physiologic uptake (especially in the abdomen) interferes with interpretation. ^{67}Ga citrate imaging is sensitive for making the diagnosis of *P. carini* pneumonia at a relatively early stage. It is somewhat less sensitive than ^{111}In-labeled white blood cells (WBCs) in the postsurgical setting; the normal excretion of ^{67}Ga into the bowel is a drawback. Nevertheless, by using imaging methods that increase contrast, such as SPECT, satisfactory imaging can be obtained in most cases.
2. **Radiolabeled (^{111}In or ^{99m}Tc) WBCs** progressively accumulate at the site of infection. The labeled WBC method requires external manipulation and labeling of the patient's blood. WBC imaging with ^{111}In shows uptake in the liver, spleen, and bone marrow, but not in other sites within the abdomen. Sensitivity for acute infection approaches 90%.
3. **New directions for inflammation imaging.** Radiolabeled monoclonal antibodies that label WBC *in vivo,* a variety of leukotropic peptides (that also label WBC *in vivc*), and a radiolabeled nonspecific immunoglobulin (with accuracy rates of close to 90%) are in various stages of development and approval.

IV. Therapeutic radioisotopes

A. **^{131}I for well-differentiated thyroid cancer**
1. **Radiopharmaceutical:** sodium iodide (^{131}I), oral solution
2. **Patient selection** (see Chapter 15, section III). Patients are selected for study after surgery has established the diagnosis of thyroid cancer. Patients are considered for radioactive ^{131}I who are at high risk for recurrence of well-differentiated thyroid cancer, either papillary, follicular, or one of the well-known variants to these tumors. Patients are considered at "high risk" if the primary tumor is large (more than 2 cm), locally invasive, or multicentric in the neck or if there is metastatic tumor in the neck.
3. **Procedural notes.** There is considerable variation in the study and treatment protocol for thyroid carcinoma. Some experts simply treat all high-risk patients after surgery with more than 100 mCi of ^{131}I. A thyroid remnant, if present, is ablated with administered doses sufficient to deliver at least 300 Gy (30,000

cGy) to the normal thyroid.

In most situations, some form of testing is performed for the ability of the tumor to concentrate radioactive iodine, and patients are treated if there is residual ^{131}I-concentrating tissue in the neck. At the time of testing, patients are expected to be hypothyroid (thyroid-stimulating hormone level higher than 30 IU/mL) and to have a low serum iodine concentration (less than 5 μg/dL). Patients are prepared by being off thyroid hormone (thyroxine for 6 weeks and triiodothyronine for 3 weeks) and on a low iodide diet (for 3 weeks before treatment).

4. **Dose selection.** Several authorities treat with standard doses after uptake in thyroid cancer is demonstrated. If lymph nodal metastases are demonstrated in the neck only, a dose of 150 mCi is sometimes used. For pulmonary, bone, or central nervous system metastases, a dose of 200 mCi may be used.

At Memorial Sloan Kettering Cancer Center (MSKCC), a higher-dose protocol has been developed, which depends on more careful dosimetry and is called the *highest safe dose* approach. Dosimetry testing for 3 to 5 days in the well-prepared patient is used to select a dose that delivers at least 2 Gy (200 cGy) to the blood, not more than 140 mCi retained in the whole body at 48 hours, and, in patients with metastatic lung disease, less than 80 mCi retained in the lungs at 48 hours. With this set of dosing rules, several hundred patients have been treated with good treatment response and without major complications.

5. **Treatment response.** Patients respond best to treatment when the tumor is small (total tumor burden less than 200 g) and confined to local or regional areas of the body. The cure rate at MSKCC was more than 95% for patients younger than 40 years of age and 50% for those older than 40 years of age. Even when cure is not achieved, significant palliation can be obtained with ^{131}I treatment.
6. **Follow-up.** Patients are normally evaluated at yearly intervals. Consideration for retreatment requires taking the patient off thyroid hormone, allowing hypothyroidism to develop, and treating with high-dose ^{131}I until no appreciable ^{131}I tissue is present ("clean slate"). Elevation of thyroglobulin levels indicates a high likelihood of recurrence of thyroid cancer at some time in the next five years in patients with well-differentiated thyroid cancer. In patients with unusually aggressive thyroid cancers, retreatment at a shorter interval can be considered (usually at about 6 months). We usually require tumor doses of at least 2,000 rad. Ablation of known metastases has occurred with doses as low as 3,500 rad, but 10,000 rad is usually required for lymph nodes containing tumor.
7. **Treatment complications.** The most common complication of high-dose ^{131}I treatment is sialadenitis, which occurs in about 20% of patients at doses above 200 mCi; a few patients develop chronic sialadenitis.

With any exposure to whole-body irradiation, there is always the concern that an increase in malignancies may occur, particularly leukemias. However, no increase in leukemia was seen in a large group of Swedish patients treated with an average dose of 160 mCi. At higher average doses in more than 500 patients at MSKCC, no leukemias have occurred in the treatment group. These data suggest that ^{131}I does not significantly increase the risk for leukemia.

B. **Bone pain palliation with radioisotopes**
   1. **Radiopharmaceuticals:** ^{89}Sr chloride (Metastron), 4 mCi; or ^{153}Sm-EDTMP (Lexidronam), 1 mCi/Kg. ^{153}Sa emits gamma rays and thus can be evaluated for radioactivity distribution.
   2. **Principle.** Various human tumors produce a strong osteoblastic reaction that results in the deposition of bone-seeking radionuclides in the hydroxyapatite crystal in the region of the tumor. When given in sufficient quantity, the radionuclide radiates the active bony regions near the metastases sufficiently to relieve pain. It is unclear whether the benefits of treatment are due to the irradiation of the bone or of the tumor itself. The usual dose is thought to be about 700 to 1000 rad.
   3. **Procedural notes.** Patients should have platelet counts above 60,000/μL and WBC counts above 2400/μL, and an osteoblastic response on bone scan demonstrated within three weeks of the treatment. Patients should not be treated with ^{89}Sr unless their life expectancy is at least three months.
      a. Complete blood counts should be repeated every 2 weeks for 4 months. Platelet and WBC counts are typically decreased by about 30%, and the nadir counts occur 12 to 16 weeks after injection.
      b. Because the radioactivity is primarily excreted in the urine, the patient should be continent or catheterized to minimize contamination of clothing and the patient's home environment.
   4. **Treatment response.** Patients with cancers of the prostate, breast, and lung have been treated with these radiopharmaceuticals, but in principle, any tumor with an osteoblastic component on bone scan could be treated. The usual onset of pain relief occurs within 7 to 21 days after administration (earlier for Lexidronam). Patients should be counseled about the possibility of a "flare response," in which pain is increased for a period of days to weeks after the treatment. A significant proportion of patients (75% to 80%) do get significant pain relief, and the typical duration of response is 3 to 4 months.
   5. **Contraindications and precautions.** Pregnancy is an absolute contraindication, and women of childbearing age should have a pregnancy test the day before administration of a radiopharmaceutical. Patients should be counseled about the possibility of a "flare response" in which pain is increased for a period of days to weeks following the treatment. Patients may be considered for retreatment, usually after 90 days, if they have responded well to initial therapy and provided that hematopoietic toxicity was not excessively severe. Most patients tolerate multiple injections without major side effects.
C. **^{32}P for polycythemia vera** (PV)
   1. **Radiopharmaceutical:** buffered sodium ^{32}P-phosphate solution
   2. **Dosage.** Intravenous doses of 2.3 mCi/m^2 (dose not to exceed 5.0 mCi) are administered at 3-month intervals to induce remission or to control excessive cellular proliferation. The dose may be repeated twice if a remission is not achieved and is increased by 25% each dose (not to exceed 7 mCi as a single dose).
   3. **Treatment response.** About 80% of patients with PV achieve remission after one injection of ^{32}P. In comparison with phlebotomy alone, patients treated with ^{32}P survive longer and have fewer thrombotic complications but have a significantly increased incidence of acute myelogenous leukemia.
   4. **Contraindications.** Pregnancy is an absolute contraindication because of the possibility of teratogenic effects. In PV, the drug should not be administered when the WBC count is less than 5000/μL or platelets are less than 150,000/μL.
D. **Colloidal ^{32}P for malignant effusions**
   1. **Radiopharmaceutical:** chromic ^{32}P-phosphate colloidal suspension
   2. **Dosage.** In a 70-kg patient, 6 to 12 mCi is used for intrapleural administration and 10 to 20 mCi for intraperitoneal administration. Great care should be taken to ensure that all radioactivity is deposited in the intended body cavity. Large tumor masses or loculation of fluid is a relative contraindication to treatment.
   3. **Treatment response.** Most patients receive some benefit from treatment in terms of control of effusions. There is a growing interest in the use of ^{32}P in the treatment of low-volume ovarian cancer.

Chapter 3 Radiation Oncology

Robert G. Parker

I. Radiation oncology

A. **Definitions.** Radiation oncology is a clinically related medical specialty in which ionizing radiations are used to treat patients with cancer or other diseases. The radiation oncologist is a physician trained in the biology of cancer and the management of patients with cancer. These efforts are supported by medical physicists, dosimetrists, radiation therapists, nurses, and other support personnel.

B. **Objectives.** The most common objective of radiation oncology is the locoregional eradication of cancer with preservation of the structure and function of normal tissues. Such treatment is potentially curative for about half of patients and palliative for the others.

II. Biophysical basis of action

A. **Induction of damage to cells and tissues.** Radiations in the energy range used clinically are absorbed through the physical processes of ionization and excitation of atoms and molecules. This process, which occurs in about 10^{-12} seconds, is similar for all types of "ionizing" radiations. Differences in observed effects of equal physical doses are related to differences in spatial or temporal distribution. Short-lived free radicals cause molecular damage and biochemical changes.

1. **Radiations** may be electromagnetic (x-rays, gamma rays) or corpuscular (electrons, protons, heavy ions, neutrons, alpha particles). Regardless of their origin (e.g., x-rays from linear accelerators, gamma rays from ^{60}Co or ^{137}Cs, neutrons from a cyclotron), the basic biophysical mechanisms of action of all types of ionizing radiations are similar.

2. **Cell death.** Nearly all radiation-induced cell death results from disruption of the replication process (reproductive death). The direct killing of cells, unrelated to the replication process (interphase death), is infrequent, and at clinical dose levels, it occurs only in highly sensitive cells, such as lymphocytes and oocytes. Apoptosis (programmed cell death) after irradiation also appears to be important.

3. **Repair** of nonlethal and potentially lethal cellular damage occurs within a few hours and probably is never complete. Although all mammalian cells have a narrow range of radiosensitivity ($D_0 = 110 - 240$ cGy), the more efficient repair and recovery processes of normal cells, compared with tumor cells, enables clinical exploitation through the application of multiple increments separated by more than 4 to 6 hours.

B. **Radiosensitivity and radiocurability**

1. **Radiosensitivity** is a measure of the susceptibility of cells to injury by ionizing (and exciting) radiations. The conventional measurement is the dose required to reduce a population of replicating cells to 37% of the initial value on the exponential portion of the cell survival curve. With photons, cellular radiosensitivity varies throughout the replication cycle, with maximal response during the late G_2 and early M phases (see Chapter 1, Principles, section I). With other radiations, such as neutrons, pions, and heavy ions, which provoke a high intensity of ionization events per unit path (high linear energy transfer), these variations in radiosensitivity throughout the replication cycle are reduced.

2. **Radioresistance** is the reciprocal to radiosensitivity and therefore is relative, not absolute. The terms *radiosensitivity* and *radioresistance* are frequently misused clinically because of the misconception that the rate of gross reduction of a tumor is the measure of effectiveness of treatment. Actually, gross tumor response also relates to other factors, such as the rate of clearance of dead cells, tumor cell proliferation, and the proportion of intercellular material.

3. **Molecular oxygen** must be present at the time of irradiation for maximal cell killing. The probable mechanism is "fixation" of free radicals. Hypoxia may reduce cellular radiosensitivity by a factor of up to three. This is the basis of investigation of methods that reduce the adverse effects of tumor cell hypoxia, such as irradiation while the patient is in a hyperbaric chamber in 3 atm of oxygen, administration of hypoxic cell sensitizers (e.g., nitroimidazoles), and use of high linear energy transfer radiations.

4. **Cellular responses** to ionizing radiations can also be modified by changes of the dose rate, manipulation of the process of repair of damage, synchronization of cells in the replication cycle, and heating cells, especially between 42.5° and 45°C for varying times.

5. **Radiocurability,** the issue of importance to patients and their physicians, is more closely related to site and extent of tumor, its inherent biologic behavior, and a range of host-related factors than to radiosensitivity. Actually, the most radiocurable cancers are not those that grossly disappear rapidly, except for a few, such as seminoma and dysgerminoma.

C. **Dosimetry.** For decades, the radiation dose was extrapolated from exposure doses measured in air (i.e., the roentgen). However, the absorbed dose at the anatomic point of interest has clinical relevance. A physical dose is now quantified in units of gray (Gy). One gray (one joule per kilogram of absorber) is equivalent to 100 rad in the old terminology (1 cGy equals 1 rad). The biologic effectiveness of a total physical dose is modified by dose rate, dose increment size when the total dose is given as a series of dose fractions, overall time and temporal pattern of application, anatomic part and tissue volume irradiated, and, to some extent, host factors that can influence radiosensitivity.

III. Clinical use. Like surgery and chemotherapy, radiation therapy (RT) has definite indications and contraindications for clinical application. It can be used alone or in combination with other methods, either as the major component of treatment or as an adjuvant. Nearly 50% to 60% of all patients with cancer receive RT during the course of their illness. Properly used, the intent of treatment for half of these patients should be cure. For the other half, incurable by any current method, palliation of specific symptoms and signs can improve the quality of life.

A. **Treatment planning**

1. Essential pretreatment evaluation includes establishment of the diagnosis by biopsy, determination of tumor site and extent, and assessment of the host.

2. After establishing whether the intent of treatment is curative or palliative, treatment planning includes identification of the target volume, which may consist of the primary tumor site and the high-risk sites of spread, selection of the treatment unit, design and verification of the pattern of delivery, and estimation of the dose, time, and pattern of application.

3. Treatment with curative intent is often complicated, requiring professional skills and facilities that may be distant from the patient's home. Frequently, the doses to the target volume are higher than required for palliation; consequently, the risks for unfavorable sequelae are higher. Such treatment is likely to be more prolonged and expensive.

4. In contrast, palliative irradiation should have a specific objective; should minimize cost, inconvenience, discomfort, and risk; and should be completed in the shortest reasonable time.

B. **Treatment with curative intent**

1. At this time, RT frequently may be the major agent used with curative intent for anatomically limited tumors of the retina, optic nerve, brain (craniopharyngioma, medulloblastoma, ependymoma), spinal cord (low- grade glioma), skin, oral cavity, pharynx, larynx, esophagus, uterine cervix, vagina, prostate, and reticuloendothelial system (Hodgkin lymphoma, stages I, II, and IIIA).

2. RT is combined with surgery for more extensive cancers of the head and neck; cancers of the lung, uterus, breast, ovary, urinary bladder, testis (seminoma), and rectum; and soft tissue sarcomas and primary bone tumors.

3. RT is an adjuvant to chemotherapy for some patients with lymphomas or lung cancer and in children with cancer (rhabdomyosarcoma, Wilms' tumor, neuroblastoma).

C. **Treatment with palliative intent.** Objectives of palliative irradiation include relief of pain, usually from metastases to bone; relief of headache or neurologic dysfunction from intracranial metastases; relief of obstruction, such as from tumors involving the ureter, esophagus, bronchus, lymphatic system, or blood vessels; promotion of healing of surface wounds by local tumor control; preservation of the weight-bearing skeleton by control of metastases to bone; and preservation of vision by controlling metastasis to or invasion of the eye or of the orbit.

IV. Technical modalities

A. **Methods of delivery.** Ionizing radiations may be delivered clinically in three ways:
   1. External-beam irradiation from sources at a distance (usually 80 to 100 cm) from the body. This includes ^{60}Co teletherapy units and x-ray sources, such as linear accelerators.
   2. Local irradiation from sources (^{60}Co, ^{137}Cs, ^{192}Ir, ^{125}I) within, in contact with, or near the target volume, such as with interstitial, intracavitary, or surface placement of radioactive isotopes in closed containers and direct x-ray therapy through short-distance cones.
   3. Internal or systemic irradiation from radioactive sources (i.e., ^{131}I, ^{32}P, ^{89}Sr) administered enterally, intracavitarily, or intravenously.
B. **Beam energy and penetration.** Most clinical RT is done with beams of high-energy photons from linear accelerators or ^{60}Co teletherapy units. The radiations are absorbed exponentially in the body, which means that for a single beam, the intensity decreases continually with increasing depth.
   1. **The penetration** of the radiations into the body is directly proportional to the generating energy. Penetration is characterized by the thickness of a specific material, such as aluminum, copper, or lead, which reduces the intensity of the radiation beam by 50% (*half-value layer*).
   2. **Clinically used energies** range from 85 kV, for the treatment of tumors on the body surface, to 35 million V, for the treatment of tumors within the body. Compared with low-energy photons, high-energy photons are less absorbed in bone and are less side-scattered in the body, resulting in sharper beam margins. Inasmuch as x-rays are generated by high-energy electrons striking a target, removal of the target provides beams of electrons with limited penetration that can be used for tumors on or near the body surface.
   3. **Radiations such as pi mesons or heavy ions,** currently used experimentally, deliver doses that are greater at the point of interest at a depth in the body than along the path of entry, through exploitation of the Bragg peak. Beams of high-energy **fast neutrons** produce more ionizations per unit path (high linear energy transfer) in an absorber than do high-energy photons. Such fast neutron beams have been successfully tested experimentally in several tumors poorly responsive to conventional photon beams. High-energy **protons** have some dosimetric advantages but no clinically detectable radiobiologic advantage over high-energy photons and electrons.
C. **Brachytherapy** (radiation sources in or close to the target volume) can deliver a very high dose to a restricted tissue volume containing tumor with relatively lower doses to adjacent normal tissues because of the proportional reduction of radiation intensity with increasing distance from the source. This method of application requires direct access to the target volume and so is most frequently used for cancers of the oral cavity, oropharynx, uterine cervix, and prostate. The actual placement of the radioactive sources often requires anesthesia of the patient and so generates risks not inherent in external-beam irradiation.

V. Side effects of RT. Every effective therapy may generate undesirable and even dangerous side effects. Although these side effects are inherent in the method, their frequency and severity are influenced by physician competence and philosophy, adequacy of equipment and facilities, operational quality assurance, and attitudes of the patient and his or her family.

A. **Early radiation-induced reactions** occur during or immediately after treatment and are self-limiting, although they may last for a few weeks. These sequelae may be local or constitutional and include anorexia, nausea, lassitude, esophagitis, diarrhea, skin reactions (erythema, desquamation), mucosal reactions, epilation, and hematopoietic suppression. The basic mechanism is damage of actively proliferating cells. Treatment is nearly always symptomatic, although the intensity of these temporary reactions can usually be reduced or even avoided by the use of smaller daily radiation doses or treatment of smaller volumes.
B. **Late radiation-induced reactions.** The clinically important, occasionally severe sequelae of RT become evident months or years after treatment. They are not proportional to early, acute reactions. Often, they are progressive rather than self-limiting. They are local rather than systemic and include myelopathy; necrosis of bone; bowel stenosis; fibrosis of lung; skin devascularization, occasionally with ulceration; renal damage with loss of function; and pericardial and myocardial damage. Such undesirable sequelae should be infrequent and are minimized by good treatment. Until recently, the primary mechanism was considered to include small vessel endarteritis and connective tissue proliferation. Although these may be factors, a major mechanism is the damage of slowly proliferating cells. Because late sequelae are often progressive and treatment is usually ineffective, they must be anticipated and avoided or minimized whenever possible.
C. **Influence of other treatment modalities.** The side effects of RT influence other treatment methods and vice versa. For example, acute skin and mucosal radiation reactions are accentuated by concurrent or consecutive administration of dactinomycin, halogenated pyrimidines, or doxorubicin (Adriamycin) and may be reactivated by these drugs months after gross healing. Radiation-induced acute and late bowel damage is accentuated by prior abdominal surgery, presumably because of high doses delivered to segments of the bowel fixed by adhesions. Surgery at any site can be made more difficult by the presence of late radiation-induced small vessel endarteritis and soft tissue fibrosis.
D. **Hematosuppression.** A major toxicity shared by ionizing radiations and many chemotherapy agents is suppression of bone marrow function. Although recovery is usual after chemotherapy, recovery after irradiation is inversely proportional to dose and volume treated and may never be complete. Indeed, after doses in excess of 3000 cGy, the bone marrow may be replaced by fatty and fibrous tissue. The distribution of marrow in the human skeleton is shown in Fig. 34.1 in Chapter 34. Consequently, RT and chemotherapy must be carefully integrated so that hematopoietic suppression does not interrupt the therapeutic plan.

A recently recognized concern is the development of leukemia in some patients who receive both RT and chemotherapy with alkylating agents. For example, although patients curatively irradiated for anatomically limited Hodgkin lymphoma rarely develop leukemia, 5% to 7% of those receiving both alkylating agents and RT for more extensive disease develop leukemia.

E. **Tissue tolerance to RT** varies widely. The following selected radiation doses and their associated potential organ toxicities are presented as rough guidelines and not precise limits of dosage:

Eye: 5000 cGy (blindness)
Ear: 3000 cGy (otitis media)
Mouth: 5000 cGy (permanent xerostomia)
Heart: 5000 cGy (pericardial stricture, myocardiopathy)
Lung: 3000 cGy (pulmonary fibrosis)
Liver: 2500 cGy (hepatitis)
Kidney: 2000 cGy (nephritis)
Testes: 1500 cGy (sterility)
Ovaries: 1200 cGy (permanent amenorrhea)
Spinal cord: 4500 cGy (Lhermitte's syndrome)
Spinal cord: 5500 cGy (transverse myelitis)
Brain: 5500 cGy (necrosis)
Bone: 6000 cGy (necrosis)
Fetus: 200 to 450 cGy (death)

Suggested Reading

Parker RG, Withers HR. Principles of radiation oncology. In: Haskell CM, ed. *Cancer Treatment.* 5th ed. Philadelphia: WB Saunders; 2000 (in press).

Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.

Chapter 4 Cancer Chemotherapeutic Agents

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Principles

I. The cell cycle and drug activity

A. **The cell cycle** is depicted in Fig. 1.1 and is discussed in Chapter 1, Cancer Biology and Oncogenes: A Primer, section I.A.1 . Most cells must enter the cell cycle to be killed by chemotherapy or radiation therapy. Many cytotoxic agents act at more than one phase of the cell cycle, including those classified as *phase specific.* Examples of drugs that are active in specific phases of the cell cycle are as follows:
  1. **G_0 phase:** glucocorticoids for mature lymphocytes
  2. **G_1 phase:** L-Asparaginase
  3. **S phase:** procarbazine and antimetabolites
  4. **G_2 phase:** bleomycin and plant alkaloids
  5. **M phase:** plant alkaloids

B. **Categories of drugs.** Cytotoxic agents can be roughly categorized by their activities relative to the cell generation cycle.
  1. **Phase nonspecific**
    a. **Cycle-nonspecific drugs** kill nondividing cells (e.g., steroid hormones, antitumor antibiotics except bleomycin).
    b. **Cycle-specific, phase-nonspecific drugs** are effective only if the cells proceed through the generation cycle, but they can inflict injury at any point in the cycle (e.g., alkylating agents).
    c. **Pharmacokinetics.** Cycle-nonspecific and cycle-specific, phase-nonspecific drugs generally have a linear dose–response curve: the greater the amount of drug administered, the greater the fraction of cells killed.
  2. **Phase specific**
    a. **Cycle-specific, phase-specific drugs** are effective only if present during a particular phase of the cell cycle.
    b. **Pharmacokinetics.** Cycle-specific, phase-specific drugs reach a limit in cell-killing ability, but their effect is a function of both time and concentration (Fig. 4.1). Above a certain dosage level, further increases in drug dose do not result in more cell killing. If the drug concentration is maintained over a period of time, however, more cells enter the specific lethal phase of the cycle and are killed.

Figure 4.1 The relationship of time of exposure of phase-specific drugs and cell-killing ability. T1 through T4 represent progressively increasing lengths of time that cells are exposed to the drug at a particular dosage. These curves contrast with the linear relationship of log cell number and increasing drug dosage seen with phase-nonspecific drugs.

C. **Population kinetics.** Tumor growth depends on the size of the proliferating pool of cells and the number of cells dying spontaneously. The larger the tumor mass, the greater the percentage of nondividing and dying cells and the longer it takes for the average cell to divide. Fig. 4.2 demonstrates the theoretic (gompertzian) tumor growth curve. Some features of this sigmoid-shaped curve on logarithmic coordinates are as follows:

Figure 4.2 Tumor growth.

  1. Growth rate (doubling time) is rapid during early and exponential stages of growth. When the tumor is small and growing rapidly, a relatively high proportion of cells are undergoing division; that is, the *growth fraction* (ratio of dividing to total cells) is high.
  2. The growth fraction decreases as the tumor gets larger and presumably should increase after therapies that reduce tumor volume. Growth rates eventually plateau because of restrictions of space, nutrient availability, and blood supply.
  3. 1×10^9 cells represents one gram of tissue and the smallest number of tumor cells required to be clinically detectable (equivalent to a mass of 1 cm diameter found on chest x-ray film or by breast examination). Tumors with 10^{12} and 10^{13} cells (about 2 to 20 lb of cancer) usually result in damage to vital organs and death of the patient.
  4. A 50% reduction in tumor mass represents only a one-third log decrease in tumor volume. For example, a tumor mass on x-ray film containing 8×10^{10} cells that is reduced to half its volume by chemotherapy still contains 4×10^{10} cells.

II. Biologic characteristics of cancer cells can be exploited to make them susceptible to drug therapy. Although malignant cellular proliferation occurs in the absence of normal internal and external growth controls, cancer cells depend on the same mechanisms for cell division that are found in normal cells. Damage to those mechanisms leads to cell death in both normal and malignant tissues.

A. **Exploitation of apoptosis in cancer** (see Chapter 1, Cancer Biology and Oncogenes: A Primer, section II.A). Cancer cells with intact mechanisms for apoptosis can be forced to undergo apoptosis by irreversible damage to their DNA. Radiation therapy and most cytotoxic antineoplastic agents kill cancer cells by damaging the cell and inducing apoptosis. Ideally, when cancer stem cells are destroyed, the cellular "template" for the production of the malignant phenotype is diminished or destroyed; thereby, these cells would not be replaced by more of their kind. Loss of normal tissue cells as the result of DNA damage triggers proliferation of normal tissue cells and replacement of the lost cells in a self-limited manner.

B. **Exploitation of proliferation control factors in cancer.** Biologic response modifiers have been used primarily to stimulate selected immune system cells, which then demonstrate anticancer activity. These modifiers include interferons, interleukins, and several growth factors. A number of substances and gene

products directly modify growth factor activity *in vitro.* Although these agents are not currently clinically applicable, research in delivering these substances into cells using viruses, ribosomes, and liposomes in an intact organism is developing rapidly.

   C. **Exploitation of maturation abnormalities in cancer cells**
   1. Directly acting maturation factors force incompletely differentiated cells to complete puberty and fully mature. This technique is exemplified by transretinoic acid for the treatment of acute promyelocytic leukemia. Other agents, such as vitamin D and cytosine arabinoside, can induce maturation of some types of leukemic stem cells *in vitro.*
   2. Eradication of stem cells can leave behind a population of maturing cells, which then complete their differentiation into mature, nonmalignant tissues. This phenomenon is demonstrated by the finding of residual tumor masses of benign teratoma cells after successful treatment of germ cell tumors.

   D. **Angiogenesis inhibition: exploitation of the dependence of cancer cells to induce the formation of their own blood supply to proliferate** (see Chapter 1, Cancer Biology and Oncogenes: A Primer, section II.D). Angiogenesis inhibition is being actively pursued as a tool for cancer treatment.
   1. Angiogenesis inhibition has potential in controlling tumor growth by limiting tumor blood supply, with only limited effects on normal revascularization. Active clinical investigation with a synthetic analogue of a fungal antiangiogenesis inhibitor (TNP-470) is in progress for the treatment of cancer.
   2. Counteraction of the anti-apoptosis effect of vascular endothelial growth factor may prevent accumulation of genetic defects that make cancers more aggressive with time.
   3. Many inhibitors of angiogenesis are known. Some of these agents are useful in cancer therapy, including pentostatin, interferons, glucocorticoids, and suramin. Cartilage extracts, heparin, and Vitamin D are inhibitors of tumor angiogenesis in experimental systems; none of these has been demonstrated to have clinical effectiveness.

III. Mechanisms of drug resistance

   A. **Tumor cell heterogeneity.** Spontaneous genetic mutations occur in subpopulations of cancer cells before their exposure to chemotherapy. Some of these subpopulations are drug resistant and grow to become the predominant cell type after chemotherapy has eliminated the sensitive cell lines. The *Goldie-Coldman hypothesis* indicates that the probability of a tumor population containing resistant cells is a function of the total number of cells present. This hypothesis asserts the high likelihood of the presence of drug-resistant mutants at the time of clinical presentation.

   B. **Single-drug resistance**
   1. **Catabolic enzymes.** Exposure to a drug can induce the production of catabolic enzymes that result in drug resistance. The drug is catabolized more rapidly inside the cell by gene amplification of DNA for the specific catabolic enzymes. Examples include increased dihydrofolic reductase, which metabolizes methotrexate; deaminase, which deactivates cytarabine; and glutathione (GSH), which inactivates alkylating agents.
   2. **GSH** is essential for the synthesis of DNA precursors. Increased levels of GSH enzymes have been found in various cancers and not in their surrounding normal tissues. GSH and its enzymes scavenge free radicals and appear to play some role in inactivation of alkylating agents through direct binding, increased metabolism, detoxification, or repairing DNA damage. Alkylating agents share cross-resistance related to DNA repair in some settings.
   3. **DNA topoisomerases I and II.** DNA is attached at regular intervals to the nuclear matrix at sites called *domains,* which are wound together with their paired DNA molecules. Topoisomerases bind to these domains, forming a "cleavable complex" that allows DNA to unwind in preparation for cell division. Topoisomerases later participate in the resealing of DNA molecules during cell division. Topoisomerase I causes single-strand breaks in DNA and is found in increased concentrations in cancer cells. Topoisomerase II causes double-strand DNA breaks.
      a. **Inhibition of topoisomerase** causes both inhibition of DNA replication and failure to repair strand breaks. Camptothecin derivatives, such as irinotecan and topotecan, exert their cytotoxic effect by inhibiting topoisomerase I. Epipodophyllotoxin derivatives, such as etoposide, inhibit topoisomerase II. Both of these agents cause stable and, therefore, lethal DNA strand breaks.
      b. **Resistance to topoisomerase inhibitors** may develop with decreased drug access to the enzyme, alteration of the enzyme structure or activity, and increased rate of DNA repair and as the result of the action of multidrug-resistance protein (see section C subsequently).
   4. **Transport proteins.** Exposure to a drug can induce the production of transport proteins that lead to drug resistance. As a result, smaller amounts of the drug enter the cell or larger amounts are carried out because of adaptive changes in cell membrane transport. Examples include methotrexate transport and the multidrug-resistance gene.

   C. **Multidrug resistance.** Resistance to many agents, particularly antimetabolites, may result from mutational changes unique to that agent. In other cases, however, a single mutational change after exposure to a single drug may lead to resistance to apparently unrelated chemotherapeutic agents.
   1. **P-170 and the *mdr-1* gene.** The process of multidrug resistance appears to occur as a result of induction or amplification of the *mdr-1* gene. The gene product is a 170-dalton membrane glycoprotein (P-170), which functions as a pump and rapidly exports hydrophobic chemicals out of the cell. P-170 is a normal product of cells with inherent resistance to chemotherapy, including kidney, colon, and adrenal cells.

      P-170 membrane glycoprotein can be induced by and mediates the efflux of vinca alkaloids, anthracyclines, actinomycin D, epipodophyllotoxins, and colchicine. When exposed to one of these drugs, the cells become resistant to the others but remain sensitive to drugs of other classes (e.g., alkylating agents or antimetabolites). Calcium-channel blockers (e.g., verapamil), amiodarone, quinidine, cyclosporine, phenothiazines, and other agents have been studied for their ability to reverse or block the effects of P-170.

   2. **Loss of apoptosis as a mechanism of drug resistance**
      a. All cells, including cancer cells, must have intact mechanisms for replication and repair to avoid loss of information necessary for survival. In the absence of intact apoptosis, cancer cells can continue through sequential cell divisions and accumulate nucleotide mismatches and progressive DNA mutations. Overexpression of certain genes, such as *BCL-2,* suppresses apoptosis. Other mechanisms of abnormal proliferation in cancer cells can cause genetic defects that cause mutations and loss of function of genes responsible for apoptosis.
      b. Loss of apoptosis removes a major mechanism by which antineoplastic agents kill cells. This loss is manifested by the increasing aneuploidy often seen as cancers become more aggressive and the very high frequency of mutations in the p53 suppressor gene.

IV. Clinical uses of cytotoxic agents

   A. **Indications.** Chemotherapy is used in the following circumstances:
   1. To cure certain malignancies (see section IV.C.1)
   2. To palliate symptoms in patients with disseminated cancer when the potential benefits of treatment exceed the side effects of treatment
   3. To treat asymptomatic patients in the following circumstances:
      a. When the cancer is aggressive and treatable (e.g., acute leukemia, small cell lung cancer)
      b. When treatment has been proved to decrease the rate of relapse and increase the disease-free interval or increase the absolute survival (stage C colon carcinoma, stages I or II breast carcinoma, osteogenic sarcoma)

   B. **Contraindications.** Chemotherapeutic agents are relatively or absolutely contraindicated in the following situations:
   1. When facilities are inadequate to evaluate the patient's response to therapy and to monitor and manage toxic reactions
   2. When the patient is not likely to survive longer even if tumor shrinkage could be accomplished
   3. When the patient is not likely to survive long enough to obtain benefits from the drugs (e.g., severely debilitated patients)
   4. When the patient is asymptomatic with slow-growing, incurable tumors, in which case chemotherapy should be postponed until symptoms require palliation

   C. **Responsiveness of tumors to chemotherapy**
   1. **Curable.** Tumors that are potentially curable by chemotherapy include the following:
      a. Childhood cancers (50% or more): acute lymphocytic leukemia, non-Hodgkin lymphoma, Wilms' tumor, Ewing's sarcoma, retinoblastoma, rhabdomyosarcoma
      b. Hodgkin lymphoma and certain aggressive lymphomas (50% or more)
      c. Carcinoma of the testis (75% or more)
      d. Choriocarcinoma in women (90% or more)
      e. Adult acute leukemia, ovarian carcinoma (15% to 20%)
   2. **Improved survival.** Tumors for which chemotherapy provides substantial improvement in survival but is rarely curative include the following:
      a. Neuroblastoma (in childhood)
      b. Aggressive non-Hodgkin lymphomas
      c. Small cell lung cancer
      d. Carcinoma of the breast
      e. Osteogenic sarcoma
   3. **Palliation.** Chemotherapy may substantially palliate symptoms from some tumors, even though the effects of treatment on survival are unknown or negligible. Examples include the following:

a. Non-Hodgkin lymphoma (low or intermediate grade)
   b. Chronic leukemias
   c. Multiple myeloma
   d. Carcinoma of the prostate
   e. Endocrine gland cancers
4. **Occasional responses.** Tumors for which chemotherapy occasionally produces responses and, in some cases, modest improvement in survival at the expense of moderate to severe toxicity include the following:
   a. Soft tissue sarcomas
   b. Brain cancers
   c. Non–oat cell lung carcinoma
   d. Carcinoma of the head and neck
   e. Transitional cell carcinomas (of the urinary bladder)
   f. Malignant melanoma (with skin or lymph node involvement)
5. **Ineffective.** Tumors for which chemotherapy rarely or never produces a meaningful tumor response or improved survival and that are best treated with experimental protocols or symptom management alone include the following:
   a. Malignant melanoma (with visceral involvement)
   b. Pancreatic carcinoma
   c. Hypernephroma

V. Administration and withholding of chemotherapeutic agents

A. **Adjuvant chemotherapy** is given to patients who have no evidence of residual disease but who are at high risk for relapse. The justifications for adjuvant chemotherapy are the high recurrence rate after surgery for apparently localized tumors, the inability to identify cured patients at the time of surgery, and the failure of therapy to cure these patients after recurrence of disease. The disadvantages of this therapy are the immediate patient discomfort and the short- and long-term risks associated with such treatment. To date, the only malignancies for which adjuvant chemotherapy has proved beneficial are breast cancer, colon cancer, and osteogenic sarcoma.
B. **Dose intensification** has received increasing emphasis in recent years as a strategy for overcoming resistance to chemotherapy. This principle has generated the notion that drugs in combination chemotherapy regimens should be given in the highest tolerated dose over the briefest interval, perhaps even with patient rescue maneuvers, such as the intensive use of hematopoietic growth factors, autologous marrow stem cell infusion, or allogeneic bone marrow transplantation. Although dose intensification is being tested in certain malignancies, the concept that more chemotherapy is better than regimens using "standard doses" remains to be proved.
C. **Monitoring therapy.** Administration of chemotherapeutic agents requires knowledge of the extent of disease, toxicity of the previous treatment courses, and timing of the expected drug toxicity. Flow sheets with dates, doses, responses, side effects, and pertinent laboratory values are mandatory.
D. **Administering cytotoxic agents intravenously**
   1. **Vein selection.** Large veins in the forearm are preferred. Metacarpal veins on the dorsum of the hand are the second choice. If possible, avoid the antecubital fossa and wrist because extravasation in these areas can result in loss of function. Management of patients with insufficient venous access is discussed in Chapter 5, section XI.
   2. **Administering irritants and vesicants** must be accomplished through a freely flowing intravenous line with extreme caution to avoid extravasation. The management of extravasation is discussed in Chapter 28, section IV.B.
      a. **Irritants** may produce burning or inconsequential inflammation during infusion or when extravasated, but usually without necrosis. Irritants include carmustine (BCNU), cisplatin, dacarbazine (DTIC), etoposide, plicamycin, and vinca alkaloids.
      b. **Vesicants** cause pain, edema, induration, ulceration, and eventually necrosis when extravasated. Vesicant drugs are tabulated in Appendix B-1 and particularly include anthracyclines, dactinomycin, mitomycin, and nitrogen mustard.

VI. Adverse effects of chemotherapy

A. **General effects.** The adverse effects of chemotherapeutic agents are summarized in Appendix B-1. Many patients complain of malaise and fatigue, which may last a week or longer. Fever and chills after certain drugs typically begin 6 hours after therapy and may last up to 24 hours. Alopecia usually begins 2 to 3 weeks after drugs are given.
B. **Guidelines for modifying drug dosage**
   1. **Principles.** Cytotoxic agents should not be prescribed by physicians inexperienced in their use. Cytotoxic drugs must be prescribed in full doses to be effective. Dosages are modified according to the curability of the tumor and to established guidelines for each drug or regimen. Chemotherapy is generally postponed if the patient has an infection of any type, persistent toxicity from previous treatments, or significant debility from cancer (Karnofsky's scale performance status less than 50%). Tumors that are highly aggressive but responsive and life-threatening (e.g., acute leukemia, widespread small cell lung cancer) are exceptions to withholding treatment for those problems.
      a. **Radiotherapy.** Patients previously or simultaneously treated with radiation generally should be started at about 50% of the recommended dose of myelosuppressive drugs. Subsequent doses can be escalated if acceptable toxicity results from the initial dose.
      b. *In vitro* **chemosensitivity assays** are expensive and technically problematic and have not proved clinically useful.
   2. **Myelosuppression.** Myelosuppressive drugs generally should not be administered to a patient with a solid tumor who has an absolute neutrophil count of less than 2000/μL or a platelet count of less than 120,000/μL. For such patients, increasing the interval between doses is preferable to decreasing the dosage. Depending on the goals of treatment, dosage can also be modified based on the severity of the lowest (nadir) counts.

   The length of time it takes after treatment to reach the nadir is different for the various agents. Most myelotoxic agents result in a nadir at 10 days with recovery in 3 to 4 weeks. For busulfan, melphalan, dacarbazine, and procarbazine, the nadir develops in 2 to 4 weeks, with recovery in about 6 weeks. For nitrosoureas, the nadir (often two separate nadirs) develops in 4 to 5 weeks with recovery in 6 to 8 weeks, and the time to recovery usually lengthens with each course of treatment.

   3. **Alimentary tract toxicity.** Nausea and vomiting after chemotherapy is discussed in Chapter 5, section III.A.2. Drugs that cause mucositis or diarrhea must not be given until the patient has fully recovered from these symptoms. Subsequent dose reduction is often indicated.
   4. **Abnormal renal function.** Drugs that cause renal toxicity (particularly methotrexate, cisplatin, and streptozocin) should not be administered unless the creatinine clearance is greater than 55 mL/min; the use of reduced doses with lower clearance rates is not recommended. Other drugs that are excreted in the urine may require dose reduction in the presence of renal dysfunction (see Appendix B-1).
   5. **Abnormal liver function.** In the presence of hepatic functional impairment, doses of the vinca alkaloids and anthracyclines (doxorubicin, daunorubicin) must be reduced. Other drugs that are excreted in the bile require some dose reduction or cautious administration (see Appendix B-1).

Chemotherapeutic Agents

I. Alkylating agents

A. **General pharmacology of alkylating agents.** Alkylating agents target DNA and are cytotoxic, mutagenic, and carcinogenic. All agents produce alkylation through the formation of intermediates.
   1. Alkylating agents impair cell function by transferring alkyl groups to amino, carboxyl, sulfhydryl, or phosphate groups of biologically important molecules. Most important, nucleic acids (DNA and RNA) and proteins are alkylated. The number 7 (N-7) position of guanine in DNA and RNA is the most actively alkylated site; the O-6 group of guanine is alkylated by nitrosoureas. Alkylation of guanine results in abnormal nucleotide sequences, miscoding of messenger RNA, cross-linked DNA strands that cannot replicate, breakage of DNA strands, and other damage to the transcription and translation of genetic material.
   2. The primary mode of action for most alkylating agents is by means of cross-linking of DNA strands. Cytotoxicity is probably a result of damage to the DNA templates rather than inactivation of DNA polymerase and other enzymes responsible for DNA synthesis. DNA strand breakage also appears to be a minor determinant of cytotoxicity.
   3. Alkylating agents are cell cycle-specific but not phase-specific. The drugs kill a fixed percentage of cells at a given dose.
   4. Tumor resistance to these drugs appears to be related to the capacity of cells to repair nucleic acid damage and to inactivate the drugs by conjugation with

GSH.

B. **Amsacrine** [m-AMSA, 4'- (9-acridinylamino)-methanesulfon-*m*-anisidide]
  1. **Indication.** Experimental for acute myelogenous leukemia
  2. **Pharmacology**
      a. **Mechanisms of action.** Alkylating agent; intercalates with DNA and also inhibits topoisomerase II
      b. **Metabolism.** Metabolized in the liver and excreted in the bile and urine as unchanged drug and metabolites
  3. **Toxicity**
      a. **Dose limiting.** Myelosuppression (expected)
      b. **Common.** Mild thrombocytopenia; tissue damage with infiltration; alopecia, phlebitis, stomatitis, diarrhea; orange urine, yellow skin color
      c. **Occasional.** Mucositis, vomiting, abnormal liver function tests (LFTs); cardiac arrhythmias, congestive heart failure (cardiac arrests have occurred during infusion of the drug, usually in the presence of hypokalemia)
      d. **Rare.** Urticaria, rash; headache, dizziness, neuropathy, seizures
  4. **Administration.** Ensure that serum potassium levels are normal.
      a. **Supplied** as 50 mg/mL vial
      b. **Dose modification.** Use cautiously with hepatic dysfunction
      c. **Dose:** 75 to 125 mg/m^2 IV daily for 5 days

C. **Busulfan** (Myleran)
  1. **Indications.** Chronic myelogenous leukemia, bone marrow transplantation (high doses)
  2. **Pharmacology**
      a. **Mechanism.** Alkylation (see section A)
      b. **Metabolism.** Acts directly; catabolized to inactive products that are excreted in the urine.
  3. **Toxicity**
      a. **Dose limiting.** Reversible and irreversible myelosuppression with slow recovery; blood cell counts fall for about 2 weeks after discontinuation of drug.
      b. **Common.** Gastrointestinal (GI) upset (mild), sterility
      c. **Occasional.** Skin hyperpigmentation, alopecia, rash; gynecomastia, cataracts, LFT abnormalities
      d. **Rare.** Pulmonary fibrosis ("busulfan lung"; see Chapter 29, section IV.A), retroperitoneal fibrosis, endocardial fibrosis; addisonian-like asthenia (without biochemical evidence of adrenal insufficiency); hypotension, impotence, hemorrhagic cystitis, secondary neoplasms
  4. **Administration**
      a. **Supplied** as 2-mg tablets
      b. **Dose modification.** Hematologic
      c. **Dose:** usually 2 to 8 mg/day PO; or 0.05 mg/kg/day

D. **Chlorambucil** (Leukeran)
  1. **Indications.** Chronic lymphocytic leukemia, Waldenström's macroglobulinemia, indolent lymphomas, trophoblastic neoplasms
  2. **Pharmacology**
      a. **Mechanism.** Alkylation (see section A)
      b. **Metabolism.** Acts directly; spontaneously hydrolysed to inactive and active products (e.g., phenylacetic acid mustard); some is also metabolized in the liver. The drug and metabolic products are excreted in urine.
  3. **Toxicity.** Least toxic alkylating agent
      a. **Dose limiting.** Myelosuppression
      b. **Occasional.** GI upset (minimal or absent at usual doses), mild LFT abnormalities, sterility
      c. **Rare.** Rash, alopecia, fever; cachexia, pulmonary fibrosis, neurologic or ocular toxicity, cystitis; acute leukemia
  4. **Administration**
      a. **Supplied** as 2-mg tablets
      b. **Dose modification.** Hematologic
      c. **Dose:** various dosage schedules are used. For example, 0.05 to 0.15 mg/kg/day PO for 3 to 6 weeks, then decrease dose for maintenance

E. **Cyclophosphamide** (Cytoxan)
  1. **Indications.** Used in a wide variety of conditions
  2. **Pharmacology**
      a. **Mechanism.** Alkylation (see section A); also inhibits DNA synthesis
      b. **Metabolism.** Native drug is inactive and requires activation by liver microsomal oxidase system to form an aldehyde that decomposes in plasma and peripheral tissues to yield acrolein and an alkylating metabolite (e.g., phosphoramide mustard). The liver also metabolizes metabolites to inactive compounds. Drugs that induce microsomal enzymes (e.g., barbiturates) may enhance toxicity; liver disease may decrease toxicity. Active and inactive metabolites are excreted in urine.
  3. **Toxicity**
      a. **Dose limiting**
          1. **Myelosuppression.** Leukopenia develops 8 to 14 days after administration. Thrombocytopenia occurs but is rarely significant.
          2. **Effects on urinary bladder.** Degradative products are responsible for hemorrhagic cystitis, which can be prevented by maintaining a high urine output. Hemorrhagic cystitis is more common and can be severe when massive doses are used (e.g., for bone marrow transplantation); under these circumstances, the use of mesna can be preventative. Urinary bladder fibrosis with telangiectasis of the mucosa can occur (usually after long-term oral therapy) without episodes of cystitis. Bladder carcinoma has occurred.
      b. **Side effects**
          1. **Common.** Alopecia, stomatitis, aspermia, amenorrhea; headache (fast onset, short duration). Nausea and vomiting are common after doses of 700 mg/m^2 or more.
          2. **Occasional.** Skin or fingernail hyperpigmentation; metallic taste during injection; sneezing or a cold sensation in the nose after injection; abnormal LFTs, dizziness; allergy, fever
          3. **Rare.** Transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH, especially if given with a large volume of fluid), hypothyroidism, cataracts, jaundice, pulmonary fibrosis; cardiac necrosis and acute myopericarditis (massive doses); secondary neoplasms (acute leukemia, bladder carcinoma)
  4. **Administration.** The drug should be administered with a large volume of fluid in the morning or early afternoon to avoid cystitis.
      a. **Supplied** as 25- or 50-mg tablets; vials contain 100 to 1000 mg
      b. **Dose modification.** Hematologic; may be required for hepatic functional impairment
      c. **Dose.** Cyclophosphamide is frequently employed as part of combination chemotherapy regimens. Some common doses are 0.5 to 1.5 g/m^2 IV every 3 weeks or 50 to 200 mg/m^2 PO for 14 days every 28 days.
      d. **Drug interactions.** With warfarin to prolong the prothrombin time further; with succinyl choline to increase neuromuscular blockade

F. **Ifosfamide** (isophosphamide, Ifex)
  1. **Indications.** Lymphomas, sarcomas, and relapsed testicular carcinoma
  2. **Pharmacology**
      a. **Mechanisms.** An alkylating agent (see section A); DNA cross-linking and chain breakage. Metabolites are alkylating agents that are similar to cyclophosphamide but not cross-resistant.
      b. **Metabolism.** Inactive until activated by hepatic microsomal enzymes. Like cyclosphamide, the drug undergoes hepatic activation to an aldehyde form that decomposes in plasma and peripheral tissues to yield acrolein and its alkylating metabolite. Acrolein is highly toxic to urothelial mucosa. The chloroacetaldehyde metabolite may be responsible for much of the neurotoxic effects, particularly in patients with renal dysfunction. Drug and metabolites are excreted in the urine.
  3. **Toxicity**
      a. **Dose limiting.** Myelosuppression, hemorrhagic cystitis
      b. **Common.** Alopecia, nausea and vomiting
      c. **Neurotoxicity** (especially when given in 1 day rather than for 5 days and when renal dysfunction is present or when sedatives are given); lethargy, dizziness, confusion, ataxia, coma
      d. **Occasional.** Salivation, stomatitis, diarrhea, constipation; urticaria, hyperpigmentation, nail ridging; abnormal LFTs, phlebitis, fever; hypotension, hypertension, hyponatremia, hypokalemia; renal tubular acidosis (at high doses)
  4. **Administration.** Aggressive concomitant hydration (2 to 4 L/day) and mesna are given to reduce the incidence of hemorrhagic cystitis.
      a. **Supplied** as 1- and 3-g vials; mesna is available as 400-mg vials
      b. **Dose modification.** Hematologic and renal dysfunction

c. **Dose:** 1000 to 1200 mg/m^2 IV over 30 minutes for 5 days every 3 to 4 weeks
d. **Mesna** (sodium 2-mercaptoethanesulfonate, Mesnex). The total dose of mesna is 60% of the ifosfamide dose. Twenty percent of the ifosfamide dose is given just before, 4 hours after, and 8 hours after ifosfamide. The last dose of mesna can be given orally to allow the patient to leave the hospital sooner. When given as a continuous infusion, mesna and ifosfamide can be mixed in equal dosages, preceded by a mesna loading dose of about 10% of the total ifosfamide dose.

G. **Melphalan** (Alkeran, phenylalanine mustard, l-PAM)
1. **Indications.** Multiple myeloma, ovarian carcinoma. The injection form is used in bone marrow transplantation studies.
2. **Pharmacology**
   a. **Mechanism.** Alkylation (see section A)
   b. **Metabolism.** Acts directly. Ninety percent of the drug is bound to plasma proteins and undergoes spontaneous hydrolysis in the bloodstream to inert products. Melphalan is excreted in the urine as unchanged drug and metabolites.
3. **Toxicity**
   a. **Dose limiting.** Myelosuppression may be cumulative and recovery may be prolonged.
   b. **Occasional.** Anorexia, nausea, vomiting, mucositis, sterility
   c. **Rare.** Alopecia, pruritus, rash, hypersensitivity; secondary malignancies (acute leukemia); pulmonary fibrosis, vasculitis, cataracts
4. **Administration**
   a. **Supplied** as 2-mg tablets
   b. **Dose modification.** Hematologic; administer cautiously in patients with azotemia
   c. **Dose.** If no myelosuppression is observed after oral dosing, poor oral absorption should be suspected. For continuous therapy: 0.10 to 0.15 mg/kg PO daily for 2 to 3 weeks; no therapy for 2 to 4 weeks, then 2 to 4 mg PO daily. For pulse therapy: 0.2 mg/kg (10 mg/m^2) PO daily for 4 days every 4 to 6 weeks
   d. **Drug interaction.** Cimetidine may result in reduced serum melphalan levels.

H. **Nitrogen mustard** (mechlorethamine, Mustargen)
1. **Indication.** Hodgkin lymphoma
2. **Pharmacology**
   a. **Mechanism.** Rapid alkylation of DNA, RNA, and protein (see section A)
   b. **Metabolism.** Native drug is highly active and is rapidly deactivated within the blood by spontaneous hydrolysis; the elimination half-life is 15 minutes. Metabolites are mostly excreted in the urine.
3. **Toxicity**
   a. **Dose limiting.** Myelosuppression
   b. **Common.** Severe nausea and vomiting beginning 1 hour after administration; skin necrosis if extravasated (sodium thiosulfate may be tried); metallic taste; discoloration of the infused vein
   c. **Occasional.** Alopecia, sterility, diarrhea, thrombophlebitis
   d. **Rare.** Neurotoxicity (including hearing loss), angioedema, secondary neoplasms
4. **Administration.** Patients should always be premedicated with antiemetics. The drug should be administered through the tubing of a running intravenous line using extravasation precautions.
   a. **Supplied** as 10-mg vials
   b. **Dose modification.** Hematologic; none required for hepatic or renal impairment
   c. **Dose:** 10 mg/m^2 as a single or divided dose monthly or 6 mg/m^2 on day 1 and day 8 of the MOPP regimen

I. **Nitrosoureas.** Carmustine (BCNU, bischlorethyl nitrosourea [BiCNU]); lomustine (CCNU, cyclohexyl chlorethyl nitrosourea [CeeNU]); streptozocin, which is a nitrosourea with a different mechanism of action (see section J)
1. **Indications.** Brain cancer, lymphomas, multiple myeloma, melanoma, and some carcinomas
2. **Pharmacology**
   a. **Mechanism.** Alkylation of DNA and RNA (see section A); DNA cross-linking; inhibition of DNA polymerase, DNA repair, and RNA synthesis
   b. **Metabolism.** Highly lipid-soluble drugs that enter the brain. Rapid spontaneous decomposition to active and inert products; the drugs also are metabolized. Most of the intact drug and metabolic products are excreted in urine; some products have an enterohepatic cycle.
3. **Toxicity**
   a. **Dose limiting.** Myelosuppression is prolonged, cumulative, and substantially aggravated by concurrent radiation therapy.
   b. **Common.** Nausea and vomiting may last 8 to 24 hours. BCNU causes local pain during injection or hypotension during a too rapid or concentrated injection.
   c. **Occasional.** Stomatitis, esophagitis, diarrhea, LFT abnormalities; alopecia, facial flushing, brown discoloration of skin; lung fibrosis (with prolonged therapy and higher doses); dizziness, optic neuritis, ataxia, organic brain syndrome; renal insufficiency
   d. **Rare.** Secondary malignancies
4. **Administration**
   a. **Supplied** as 100-mg vials of BCNU; 10-, 40-, and 100-mg capsules of CCNU in a dose pack of 300 mg
   b. **Dose modification.** Hematologic and renal
   c. **Dose**
      1. **BCNU:** 150 to 200 mg/m^2 IV (as a single dose or divided over 2 days) every 6 to 8 weeks. Do not infuse over longer than 2 hours because of incompatibility of the drug with intravenous tubing. If blood and BCNU are mixed in the syringe before administration, the painfulness of injection may be decreased.
      2. **CCNU:** 100 to 130 mg/m^2 PO every 6 to 8 weeks
   d. **Drug interactions.** With cimetidine to decrease nitrosourea metabolism, resulting in increased hematosuppression

J. **Streptozocin** (streptozotocin, Zanosar)
1. **Indications.** Islet cell cancer of the pancreas (in combination with fluorouracil), carcinoid syndrome
2. **Pharmacology**
   a. **Mechanism.** Alkylating agent (see section A). Inhibits DNA synthesis and the DNA repair enzyme, guanine-O^6-methyl transferase; affects pyrimidine nucleotide metabolism and inhibits enzymes involved in gluconeogenesis
   b. **Metabolism.** Drug is a type of nitrosourea that is extensively metabolized and has a short plasma half-life. Crosses the blood– brain barrier. Excreted in urine as metabolites and unchanged drug.
3. **Toxicity**
   a. **Dose limiting.** Nephrotoxicity initially appears as proteinuria and progresses to glycosuria, aminoaciduria, proximal renal tubular acidosis, and renal failure if the drug is continued.
   b. **Common.** Nausea and vomiting (often severe), myelosuppression (mild, but may be cumulative), hypoglycemia after infusion, vein irritation during infusion
   c. **Occasional.** Diarrhea, abdominal cramps, LFT abnormalities
   d. **Rare.** Central nervous system (CNS) toxicity, fever, secondary malignancies
4. **Administration.** Urinalysis and serum creatinine levels are monitored before each dose. Patients are routinely premedicated with antiemetics. The dose is administered over 30 to 60 minutes to prevent local pain.
   a. **Supplied** as 1-g vials
   b. **Dose modification.** Proteinuria or elevated serum creatinine levels contraindicate use of the drug until the abnormalities resolve.
   c. **Dose:** 1.0 g/m^2 IV weekly, or 0.5 g/m^2 IV daily for 5 days every 3 to 4 weeks

K. **Thiotepa** (triethylenethiophosphoramide, Thioplex)
1. **Indications.** Intracavitary for malignant effusions, intravesicular for urinary bladder, severe thrombocytosis
2. **Pharmacology**
   a. **Mechanism.** Alkylation (see section A)
   b. **Metabolism.** Rapidly decomposed in plasma and excreted in urine
3. **Toxicity**
   a. **Dose limiting.** Myelosuppression, which may be cumulative
   b. **Common** (for intravesicular administration). Abdominal pain, hematuria, dysuria, frequency, urgency, ureteral obstruction
   c. **Occasional.** GI upset, abnormal LFTs, rash, hives
   d. **Rare.** Alopecia, fever, angioedema
4. **Administration.** Thiotepa has been administered intravenously, intramuscularly, intravesicularly, intrathecally, intraarterially, intrapleurally, intrapericardially, intraperitoneally, intratumorally, and as an ophthalmic instillation.

    a. **Supplied** as 15-mg vials

    b. **Dose modification.** Necessary for patients with cytopenias. Apnea can occur in patients receiving succinylcholine.

    c. **Dose:** 12 to 16 mg/m^2 IV every 1 to 4 weeks; 30 to 60 mg intravesicularly every week for 4 weeks

L. **Cisplatin** (*cis*-diaminedichloroplatinum [CDDP], Platinol)

1. **Indications.** A wide variety of malignancies

2. **Pharmacology**

    a. **Mechanism.** A heavy metal alkylator of DNA. Covalently bonds to proteins, RNA, and especially DNA, forming DNA cross-linking and intrastrand N-7 adducts. The *trans* isomer has virtually no antitumor activity. Acquired resistance to cisplatin involves alterations in transmembrane transport of drugs, intracellular levels of GSH or sulfhydryl-containing proteins, and the capacity to repair cisplatin DNA lesions.

    b. **Metabolism.** Widely distributed in the body, except for the CNS. Long half-life in plasma (up to 3 days); may remain bound in tissues for months. Native drug (30%) and metabolites excreted in urine; biliary excretion accounts for less than 10% of the total drug excretion.

3. **Toxicity**

    a. **Dose limiting**

        1. **Cumulative renal insufficiency.** The incidence of renal insufficiency is about 5% with adequate hydration measures and 25% to 45% without hydration measures. Nephrotoxicity (and perhaps ototoxicity) is increased by concurrent administration of nephrotoxic drugs, such as aminoglycoside antibiotics, or methotrexate.

        2. **Peripheral sensory neuropathy** develops after the administration of 200 mg/m^2 and can become dose limiting when the cumulative cisplatin dose exceeds 400 mg/m^2. Symptoms may progress after treatment is discontinued and include loss of proprioception and vibratory senses, hyporeflexia, and Lhermitte's sign. Symptoms may resolve slowly after many months.

        3. **Ototoxicity** with tinnitus and high-frequency hearing loss occurs in 5% of patients. Ototoxicity occurs more commonly in patients receiving doses of more than 100 mg/m^2 by rapid infusion or high cumulative doses.

    b. **Common.** Severe nausea and vomiting occur in all treated patients; preventative antiemetic regimens are required. Hypokalemia, hypomagnesemia (occasionally difficult to correct), and mild myelosuppression occur very frequently.

    c. **Occasional.** Alopecia, loss of taste, vein irritation, abnormal LFTs, SIADH, hypophosphatemia, myalgia, fever

    d. **Rare.** Altered color perception and reversible focal encephalopathy that often causes cortical blindness. Raynaud's phenomenon, bradycardia, bundle-branch block, congestive heart failure; anaphylaxis, tetany

4. **Administration**

    a. **Supplied** as 10- and 50-mg vials

    b. **Dose modification.** Renal function must return to normal before cisplatin can be given. Many physicians avoid using cisplatin when the creatinine clearance is less than 40 mL/min. Cisplatin is relatively contraindicated in patients with documented hearing impairment.

    c. **Dose**

        1. 40 to 120 mg/m^2 or more IV every 3 to 4 weeks, or

        2. 20 to 40 mg/m^2 IV daily for 3 to 5 days every 3 to 4 weeks

    d. **Method.** The principles of cisplatin administration are as follows:

        1. **Monitoring.** Serum creatinine, electrolytes, magnesium, and calcium levels should be measured daily during therapy. Audiometry is usually not necessary.

        2. **Antiemetics.** Patients should be given prophylactic antiemetics, such as ondansetron and dexamethasone.

        3. **Hydration and diuresis** are required when 40 mg/m^2 or more of cisplatin is given to maintain a urine output of 100 to 150 mL/hour before administration of the drug. Furosemide is given to prevent fluid overload. Mannitol is given if urine output is insufficient. Intravenous fluids are supplemented with KCl and MgSO$_4$.

        4. **Amifostine cytoprotection** (see section VIII.A)

    e. **Drug interactions.** Cisplatin inhibits renal elimination of bleomycin.

M. **Carboplatin** (Paraplatin)

1. **Indications.** Ovarian and other carcinomas

2. **Pharmacology**

    a. **Mechanisms.** Heavy metal alkylating-like agent with mechanisms very similar to cisplatin, but with different toxicity profile. Like cisplatin, it produces predominantly interstrand DNA cross-links rather than DNA–protein cross-links; this effect is apparently cell cycle nonspecific. Cisplatin and carboplatin exhibit substantial clinical cross-resistance.

    b. **Metabolism.** Plasma half-life of only 2 to 3 hours. Excreted in the urine as unchanged drug (70%) and metabolites

3. **Toxicity**

    a. **Dose limiting.** Median nadir hematosuppression at 21 days; increased myelosuppression in patients who have reduced creatinine clearance levels or who have received prior chemotherapy

    b. **Common.** Nausea and vomiting (less severe than with cisplatin), pain at injection site

    c. **Occasional.** Abnormal LFTs, azotemia; neurotoxicity (5%)

    d. **Rare.** Alopecia, rash, flu-like syndrome, hematuria, hyperamylasemia; hearing loss, optic neuritis

4. **Administration**

    a. **Supplied** as 50-, 150-, 450-mg vials

    b. **Dose modification.** Reduce dosage for creatinine clearance of less than or equal to 60 mL/minute. Caution is advised when concomitantly administering other myelosuppressive or nephrotoxic drugs.

    c. **Dose by creatinine clearance** (Cl_{Cr}), as follows:

Cl_{Cr} ³ 60 mL/min; dose = 360 mg/m^2

Cl_{Cr} = 41 to 59 mL/min; dose = 250 mg/m^2

Cl_{Cr} = 16 to 40 mL/min; dose = 200 mg/m^2

    d. **Dose by Calvert's formula** (AUC, area under the curve; GFR, glomerular filtration rate)

Total dose (mg [not per m^2]) = (target AUC) × (GFR + 25)
Target AUC = 4 to 6 for previously treated patients
Target AUC = 5 to 7.5 for previously untreated patients

N. **Dacarbazine** (dimethyltriazenoimidazolecarboxamide [DTIC])

1. **Indications.** Hodgkin lymphoma, malignant melanoma, sarcomas

2. **Pharmacology**

    a. **Mechanisms.** Inhibits purine, RNA, and protein synthesis. Has some alkylating activity. Causes DNA methylation and direct DNA damage

    b. **Metabolism.** Native drug inactive; requires activation by oxidative N-methylation by liver microsomal oxidases. Excreted in urine predominantly; minor hepatobiliary and pulmonary excretion

3. **Toxicity**

    a. **Dose limiting.** Myelosuppression; nadir blood counts occur 2 to 4 weeks after treatment

    b. **Common.** Nausea and vomiting (often severe); pain along the injection site, local irritant if injected subcutaneously (not a vesicant)

    c. **Occasional.** Alopecia, facial flushing, photosensitivity, abnormal LFTs. Flu-like syndrome (malaise, myalgia, chills, and fever) developing 1 week after treatment and lasting 1 to 3 weeks

    d. **Rare.** Diarrhea, stomatitis; cerebral dysfunction; hepatic vein thrombosis, hepatic necrosis; azotemia; anaphylaxis

4. **Administration.** Dacarbazine is often used in combination chemotherapy regimens. Withdrawing blood into the drug-filled syringe before injecting the mixture reduces the pain of injection.

    a. **Supplied** as 100- and 200-mg vials

    b. **Dose modification.** Necessary for patients with impaired bone marrow, hepatic, or renal function

    c. **Dose**

        1. 375 mg/m^2 every 15 days in ABVD regimen, or

        2. 50 to 250 mg/m^2 IV daily for 5 days every 21 to 28 days

O. **Procarbazine** (Matulane, Natulan, *N*-methylhydrazine)

1. **Indications.** Hodgkin and non-Hodgkin lymphomas, myeloma, brain cancer
2. **Pharmacology**
   a. **Mechanism.** DNA alkylation and depolymerization. Methylation of nucleic acids. Inhibition of DNA, RNA, and protein synthesis
   b. **Metabolism.** Metabolic activation of the drug is required. Readily enters the cerebrospinal fluid. Degraded in the liver to inactive compounds, which are excreted in urine
3. **Toxicity**
   a. **Dose limiting.** Myelosuppression, which may not begin until several weeks after starting treatment
   b. **Common.** Nausea and vomiting, which decrease with continued use; myalgia, arthralgia; sensitizes tissues to radiation
   c. **Occasional.** Dermatitis, hyperpigmentation, photosensitivity; stomatitis, dysphagia, diarrhea; hypotension, tachycardia; urinary frequency, hematuria; gynecomastia, sterility
   d. **Neurologic.** Procarbazine results in disorders of consciousness or mild peripheral neuropathies in about 10% of cases. These abnormalities are reversible and rarely serious enough to alter drug dosage. Manifestations of toxicity include sedation, depression, agitation, psychosis, decreased deep-tendon reflexes, paresthesias, myalgias, and ataxia.
   e. **Rare.** Xerostomia, retinal hemorrhage, photophobia, papilledema; allergic pneumonitis, secondary malignancy
4. **Administration**
   a. **Supplied** as 50-mg capsules
   b. **Dose modification.** Reduce dose in patients with hepatic, renal, or bone marrow dysfunction.
   c. **Dose:** 100 mg/m^2 PO daily for 10 to 14 days in combination regimens
   d. **Drug interactions.** Procarbazine is a monoamine oxidase inhibitor and thus interacts with numerous prescribed and nonprescribed agents. For the most part, these interacting agents should be avoided for about 2 weeks after stopping procarbazine. Potential reactions from procarbazine interactions with other drugs include the following:
      1. **Disulfiram** (Antabuse)-like reactions: alcohol
      2. **Severe hypertension**
         a. Sympathomimetic amines, levodopa, methyldopa; cocaine, narcotics; buspirone, methylphenidate (Ritalin); dextromethorphan (with hyperpyrexia); caffeine
         b. Foods and beverages containing amines (e.g., aged cheese, beer, and wine (with or without alcohol); smoked or pickled meats, poultry or fish; fermented sausage; any overripe fruit)
      3. **Hypotension:** Hypotension-producing medications, spinal anesthetics
      4. **CNS depression and anticholinergic effects:** antihisamines, phenothiazines, barbiturates, and other CNS depressants
      5. **Hyperpyrexia, convulsions, and death:** tricyclic antidepressants, monamine oxidase inhibitors, fluoxetine; sympathomimetic amines; meperidine and other narcotics (also possibly hypotension, respiratory depression, and coma)
      6. **Other:** Hypoglycemia with insulin or sulfonylurea; increased anticoagulant effect with coumarin derivatives; shaking, hyperventilation, confusion, and so forth with tryptophan

II. Antimetabolites

A. **General pharmacology of antimetabolites**
   1. Some antimetabolites are structural analogues of normal molecules that are essential for cell growth and replication. Other antimetabolites inhibit enzymes that are necessary for the synthesis of essential compounds. Their major effect is interfering with the building blocks of DNA synthesis (Fig. 4.3). Their activity, therefore, is greatest in the S phase of the cell cycle. In general, these agents have been most effective when cell proliferation is rapid.

Figure 4.3 Sites of action of antimetabolites. 2-Cda, 2-chlorodeoxyadenosine; 5-Aza, 5-azacytidine; 5-FU, 5-fluorouracil; 6-MP; 6-mercaptopurine; 6-TG, 6-thioguanine; Ara C, cytosine arabinoside; Dcf, deoxycoformycin; Flud, fludarabine; HU, hydroxyurea; MTX, methotrexate; reductase, dihyrofolate reductase.

   2. The pharmacokinetics of these drugs are characterized by nonlinear dose–response curves; after a certain dose, no more are killed with increasing doses (fluorouracil is an exception). Because of the entry of new cells into the cycle, the length of time that the cells are exposed to the drug is directly proportional to the killing potential (Fig. 4.1).
B. **Azacytidine** (5-azacytidine)
   1. **Indication.** Acute myelogenous leukemia (experimental)
   2. **Pharmacology**
      a. **Mechanism.** Antimetabolite (cytidine analogue). Rapidly phosphorylated and incorporated into DNA and RNA, thereby inhibiting protein synthesis; also inhibits pyrimidine synthesis and DNA methylation
      b. **Metabolism.** Activated by phosphorylation and deactivated by deamination; similar to cytarabine. Excreted in urine (20% as unchanged drug)
   3. **Toxicity**
      a. **Dose limiting.** Myelosuppression; nausea and vomiting (severe, but less common with continuous infusion)
      b. **Common.** Hepatic dysfunction, diarrhea, alopecia
      c. **Occasional.** Neurotoxicity (restlessness, confusion), azotemia (transient), hypophosphatemia with myalgia, stomatitis, phlebitis, fever
      d. **Rare.** Progressive lethargy and coma, renal tubular acidosis, rhabdomyolysis, hypotension, rash
   4. **Administration**
      a. **Supplied** as 100-mg vials
      b. **Dose modification.** Necessary for patients with impaired liver function. Use with caution in patients with altered mental status or serum albumin concentration of less than 3 g/dL.
      c. **Dose:** 150 to 300 mg/m^2 IV for 5 days by continuous infusion
C. **Cladribine** (2-chlordeoxyadenosine [2-CdA], Leustatin)
   1. **Indications.** Hairy cell leukemia, indolent lymphomas, chronic lymphocytic leukemia, Waldenström's macroglobulinemia
   2. **Pharmacology**
      a. **Mechanism.** Antimetabolite. A deoxyadenosine analogue that accumulates in cells, blocks adenosine deaminase, and inhibits RNA synthesis
      b. **Metabolism.** Rapidly distributed and eliminated
   3. **Toxicity**
      a. **Dose limiting.** Myelosuppression
      b. **Common.** Nausea, skin reactions at injection site, fever, chills
      c. **Occasional.** Headache, fatigue
      d. **Rare.** Neurotoxicity, pancreatitis
   4. **Administration**
      a. **Supplied** as 20-mg vials
      b. **Dose modification.** Hematologic
      c. **Dose:** either 0.10 mg/kg/day (4 mg/m^2/day) by continuous IV infusion for 7 days, or 0.14 mg/kg daily IV over 2 hours for 5 days
D. **Cytarabine** (cytosine arabinoside, Cytosar, ara-C)
   1. **Indications.** Acute leukemia, chronic myelogenous leukemia, lymphoma, meningeal involvement with tumor
   2. **Pharmacology**
      a. **Mechanism.** Antimetabolite. Phosphorylated derivative of the drug competitively inhibits DNA polymerase, which is involved in the conversion of cytidine to deoxycytidine; some is incorporated into DNA. Blocks DNA repair and terminates DNA chain elongation
      b. **Metabolism.** Requires activation to triphosphate by kinase; deactivated by deaminase; ara-C is rapidly and completely deaminated in liver, plasma, and peripheral tissues; ara-C antitumor activity depends on relative amounts of kinase and deaminase in cells. In patients with renal insufficiency, one metabolite (uracil arabinoside) has the ability to produce high concentrations of ara-C triphosphate, which may result in CNS toxicity. Excreted in urine as inactive metabolites.
   3. **Toxicity**
      a. **Dose limiting.** Myelosuppression

    b. **Common.** Nausea, vomiting, diarrhea (potentiated by the addition of an anthracycline); conjunctivitis (usually within the first 3 days of high-dose regimens, but reduced with prophylactic glucocorticoid eye drops); hydradenitis, arachnoiditis with intrathecal administration

    c. **Cerebellar toxicity** begins on the fourth or fifth day of infusion and resolves within 7 days. The incidence and severity of toxicity are related to the dose given (especially with total dose of more than 48 g/m^2), the rate of infusion (least incidence for continuous infusions), age (particularly older than 60 years of age), gender (especially male), and the degree of hepatic or renal dysfunction (particularly with creatinine clearance of less than 60 mL/min). In some cases, it is irreversible or fatal.

    d. **Occasional.** Alopecia, stomatitis, metallic taste, esophagitis, hepatic dysfunction (mild and reversible), pancreatitis, severe GI ulceration; thrombophlebitis; flu-like syndrome, myalgias, arthralgias, fever, headache; rash, transient skin erythema without exfoliation

    e. **Rare.** Sudden respiratory distress rapidly progressing to pulmonary edema; pericarditis, cardiomegaly, tamponade; urinary retention

  4. **Administration**

    a. **Supplied** as 100-, 500-, 1000-, and 2000-mg vials

    b. **Dose modification.** Use cautiously in patients with liver or renal disease or with risk factors for neurotoxicity.

    c. **Dose**

      1. See Chapter 21 for use in patients with lymphoma and Chapter 25 for use in patients with acute leukemia.

      2. For intrathecal administration: 50 to 100 mg in 10 mL saline for 1 to 3 days weekly

      3. Low-dose regimen: 10 mg/m^2 SC every 12 to 24 hours for 15 to 21 days

    d. **Drug interactions.** Nephrotoxic drugs may reduce the clearance of ara-C. This drug enhances activity of alkylating agents.

E. **Fludarabine** (2-fluoroadenine arabinoside-5-phosphate, Fludara)

  1. **Indications.** Chronic lymphocytic leukemia and low-grade lymphomas

  2. **Pharmacology**

    a. **Mechanism.** Antimetabolite. Its active metabolite, 2-fluoro-ara-A, appears to act by inhibiting DNA primase, DNA polymerase- a, and ribonucleotide reductase

    b. **Metabolism.** Metabolites are excreted primarily in the urine.

  3. **Toxicity**

    a. **Dose limiting.** Myelosuppression, which may be cumulative

    b. **Common.** Nausea and vomiting

    c. **Occasional.** Alopecia (mild), abnormal LFTs, tumor lysis syndrome

    d. **Rare.** Stomatitis, diarrhea; dermatitis; neurotoxicity (somnolence, transient paresthesias, demyelination); chest pain, hypotension, fever

  4. **Administration**

    a. **Supplied** as 50-mg vials

    b. **Dose modification.** Decrease dosage by 30% for patients with creatinine clearance of less than 70 mL/min.

    c. **Dose:** 25 mg/m^2 IV over 30 minutes daily for 5 consecutive days every 4 weeks

F. **Fluorouracil** (5-FU, Adrucil)

  1. **Indications.** A wide variety of carcinomas

  2. **Pharmacology**

    a. **Mechanism.** Antimetabolite. Interferes with DNA synthesis by blocking thymidylate synthetase, an enzyme involved in the conversion of deoxyuridylic acid to thymidylic acid. It is incorporated into several RNA species, which may thereby interfere with RNA function and protein synthesis. It is cell cycle S-phase specific but acts in other cell cycle phases as well and is unique in having a log linear cell-killing action.

    b. **Metabolism.** 5-FU rapidly enters all tissues, including spinal fluid and malignant effusions. The drug requires intracellular activation by a series of phosphorylating enzymes and phosphoribosyl transferase. Most of the drug degradation occurs in the liver. Responsive tumors appear to lack degradation enzymes. Metabolism eliminates 90% of 5-FU. Inactive metabolites are excreted in the urine, bile, and breath (as carbon dioxide).

  3. **Toxicity** is more common and more severe in patients with dihydropyrimidine dehydrogenase deficiency.

    a. **Dose limiting.** Myelosuppression (less common with continuous infusion); mucositis (more common with 5-day infusion); diarrhea

    b. **Common.** Nasal discharge; eye irritation and excessive lacrimation due to dacrocystitis and lacrimal duct stenosis; vein pigmentation

    c. **Reversible cerebellar dysfunction** occurs in about 1% of patients. Symptoms usually disappear 1 to 6 weeks after the drug is discontinued, but they abate after the dose is reduced or even if the same dose is maintained.

    d. **Occasional.** Nausea, vomiting, esophagitis; hand–foot syndrome with protracted infusion (paresthesia, erythema, and swelling of the palms and soles); myocardial ischemia (particularly in patients with a prior history of myocardial ischemia); thrombophlebitis

    e. **Rare.** Alopecia, dermatitis, loss of nails, dark bands on nails; photosensitivity, blurred vision, "black hairy tongue" (hypertrophy of filiform papillae), anaphylaxis, fever

  4. **Administration.** The optimal method of administration for fluorouracil is controversial. It is given by IV bolus, IV infusion over 15 minutes, continuous IV infusion, arterial infusion, intracavitarily, topically, or orally

    a. **Supplied** as 500-mg vials

    b. **Dose modification.** Fluorouracil is withheld if the patient has stomatitis, diarrhea, evidence of infection, leukopenia, or thrombocytopenia; drug is resumed when these problems have resolved. Drug should be prescribed cautiously in the presence of hepatic dysfunction.

    c. **Dose.** Fluorouracil is erratically absorbed orally. Several regimens have been used, including the following:

      1. 425 mg/m^2 IV weekly

      2. 300 to 450 mg/m^2 IV daily for 5 days every 28 days

      3. 1000 mg/m^2/day by continuous infusion for 4 to 5 days every 28 days

      4. 250 to 300 mg/m^2/day by continuous infusion indefinitely

    d. **Drug interactions.** Allopurinol inhibits activation of 5-FU and may result in decreased effectiveness. Toxicity is enhanced by leucovorin, methotrexate, and phosphonacetyl-I-aspartic acid (PAIA).

G. **Leucovorin** (citrovorum factor, folinic acid, 5-formyl tetra-hydrofolate)

  1. **Indications.** Combined with 5-FU in treatment of colorectal and other adenocarcinomas; the rescue agent for antifol toxicity (e.g., methotrexate)

  2. **Pharmacology**

    a. **Mechanism.** Leucovorin is a tetrahydrofolic acid derivative that acts as a cofactor for carbon transfer reactions in the synthesis of purines and pyrimidines. It inhibits the effects of methotrexate and other dihydrofolate reductase antagonists. Leucovorin potentiates the cytotoxic effects of fluorinated pyrimidines (i.e., 5-FU and floxuridine) by increasing the binding of folate cofactor and activated 5-FU to thymidylate synthetase within the cells.

    b. **Metabolism.** Excreted in the urine as metabolites

  3. **Toxicity.** Potentiates the toxic effects of fluoropyrimidine therapy

  4. **Administration**

    a. **Supplied** as 50-, 100-, and 350-mg vials for IV use and as a 60-mg bottle for oral use

    b. **Dose.** Depends on combination regimen

H. **Capecitabine** (Xeloda)

  1. **Indications.** Metastatic breast cancer resistant to anthracyclines and taxanes

  2. **Pharmacology.** Capecitabine is a fluoropyrimidine carbamate that is a systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR), which is converted *in vivc* to 5-FU.

    a. **Mechanisms.** See fluorouracil

    b. **Metabolism.** Hepatic

  3. **Toxicity.** Similar to 5-FU and 5-FUDR

    a. **Dose limiting.** Diarrhea

    b. **Common.** Hand–foot syndrome (palmar–plantar erythrodysesthesia or chemotherapy-induced acral erythema)

    c. **Occasional.** Nausea, vomiting, hematosuppression

  4. **Administration**

    a. **Supplied** as 150- and 500-mg tablets

    b. **Dose modification.** Use with caution with liver dysfunction and in patients taking coumarin derivatives.

    c. **Dose:** 1250 mg/m^2 PO twice daily (approximately every 12 hours) with food for 14 days every 3 weeks

I. **Gemcitabine** (Gemzar)

  1. **Indications.** Carcinoma of pancreas, bladder, lung

  2. **Pharmacology.** A nucleoside analogue

    a. **Mechanisms.** Cell-phase specific, primarily killing cells in S-phase and also blocking the progression of cells through the G_1-phase to S-phase boundary. Metabolized intracellularly to the active diphosphate and triphosphate. Inhibits ribonucleotide reductase; competes with deoxycytidine triphosphate

(dCTP) for incorporation into DNA
   b. **Metabolism.** Nearly entirely excreted in the urine as active drug and metabolites
3. **Toxicity**
   a. **Dose limiting.** Myelosuppression
   b. **Common.** Fever with flu-like symptoms (40%); nausea, vomiting, diarrhea, stomatitis; macular or maculopapular rash; transient LFT elevations; mild proteinuria and hematuria
   c. **Occasional.** Hair loss, rash, edema
   d. **Rare.** Hemolytic-uremic syndrome; pulmonary drug toxicity; allergic reactions
4. **Administration**
   a. **Supplied** as vials of 200 and 1000 mg
   b. **Dose modification.** Use with caution in patients with hepatic or renal insufficiency.
   c. **Dose:** 1000 mg/m^2 over 30 minutes weekly for 7 weeks or until toxicity, followed by 1 week rest; then for 3 of every 4 weeks

J. **Hydroxyurea** (Hydrea)
1. **Indications.** Chronic myelogenous leukemia, myeloproliferative disorders
2. **Pharmacology**
   a. **Mechanism.** Antimetabolite. Inhibits DNA synthesis by inhibiting nucleotide reductase, the enzyme that converts ribonucleosides to deoxyribonucleosides. Inhibits DNA repair and thymidine incorporation into DNA. Cell cycle S-phase specific, but acts in other phases as well.
   b. **Metabolism.** Crosses the blood–brain barrier. Half of the drug is rapidly degraded into inactive compounds. Inactive products and unchanged drug (50%) are excreted in urine.
3. **Toxicity**
   a. **Dose limiting.** Myelosuppression, which recovers rapidly when treatment is stopped (prominent megaloblastosis)
   b. **Occasional.** Nausea, vomiting, diarrhea; skin rash, facial erythema, hyperpigmentation; azotemia, proteinuria; transient LFT abnormalities; radiation recall phenomenon
   c. **Rare.** Alopecia, mucositis, diarrhea, constipation; neurologic events; pulmonary edema; flu-like syndrome; painful perimalleolar ulcers; possible acute leukemia in myeloproliferative disorders
4. **Administration**
   a. **Supplied** as 500-mg capsules
   b. **Dose modification.** The drug should be given cautiously in the presence of liver dysfunction or when combined with other antimetabolites. Dosages should be reduced for creatinine clearance levels of less than 50 mL/min and when given with concomitant radiotherapy.
   c. **Dose:** 10 to 30 mg/kg PO daily

K. **Mercaptopurine** (6-MP, Purinethol)
1. **Indication.** Acute lymphoblastic leukemia (maintenance therapy)
2. **Pharmacology**
   a. **Mechanism.** Purine antimetabolite. Undergoes extensive metabolic changes; mechanisms of cytotoxicity are complex. Inhibits *de novo* purine synthesis and purine interconversion. Competes with ribotides for enzymes responsible for conversion of inosinic acid to adenine and xanthine ribotides. Its incorporation into DNA or RNA is of uncertain significance.
   b. **Metabolism.** Mercaptopurine is slowly degraded in the liver, largely by xanthine oxidase. Allopurinol, a xanthine oxidase inhibitor, causes marked increase in its toxicity. Clearance is primarily hepatic with conventional doses.
3. **Toxicity**
   a. **Dose limiting.** Myelosuppression
   b. **Common.** Nausea, vomiting, anorexia (25%); usually reversible cholestasis (30%)
   c. **Rare.** Stomatitis, diarrhea, dermatitis, fever, hematuria, Budd-Chiari–like syndrome, hepatic necrosis
4. **Administration**
   a. **Supplied** as 50-mg tablets
   b. **Dose modification.** Dose is reduced by 50% to 75% for patients with hepatic dysfunction.
   c. **Dose:** 70 to 100 mg/m^2 PO daily until patient responds or toxic effects are seen; then adjust for maintenance therapy.
   d. **Drug interactions.** If given allopurinol, the 6-MP dose must be reduced by 75%. Dosage may also need to be modified if other hepatotoxic drugs are given. Warfarin dosages may be affected by 6-MP.

L. **Methotrexate** (amethopterin, MTX)
1. **Indications.** A wide variety of conditions
2. **Pharmacology**
   a. **Mechanism.** Antifol metabolite. MTX blocks the enzyme dihydrofolate reductase, preventing formation of reduced (tetrahydro-) folic acid; tetrahydrofolic acid is crucial to the transfer of carbon units in a variety of biochemical reactions (Fig. 4.3). MTX thus blocks formation of thymidylate from deoxyuridylate and prevents synthesis of DNA. The drug also inhibits RNA and protein synthesis and prevents cells from entering the S phase of the cell cycle.
   b. **Metabolism.** MTX is minimally metabolized by the human species. The drug is distributed to body water; patients with significant effusions eliminate the drug much more slowly. Because 50% to 70% of the drug is bound to plasma proteins, displacement by other drugs (e.g., aspirin, sulfonamides) may result in an increase in toxic effects. Excreted in urine as unchanged drug (90%). Renal dysfunction results in dangerous blood levels of MTX and possible further renal damage
3. **Toxicity.** Leucovorin can reverse the immediate cytotoxic effects of MTX; generally, 1 mg of leucovorin is given for each 1 mg of MTX.
   a. **Dose limiting.** Myelosuppression, stomatitis, renal dysfunction
   b. **High-dose regimens.** Nausea, vomiting, renal tubular necrosis, cortical blindness
   c. **Previously irradiated areas.** Skin erythema, pulmonary fibrosis, transverse myelitis, cerebritis
   d. **Chronic therapy.** Liver cirrhosis (reversible hepatic dysfunction occurs with short-term intermittent therapy); osteoporosis (in children)
   e. **Neurotoxicity.** MTX neurotoxicity depends on dose and route of administration. Within a few hours after intrathecal administration, MTX can produce an acute aseptic meningitis that is usually self-limited. A subacute encephalopathy and myelopathy can also occur after intrathecal administration.

   High-dose systemic administration can cause a reversible encephalopathy of rapid onset and resolution that lasts from minutes to hours (stroke-like episodes). Chronic intrathecal combined with high-dose systemic administration can produce a more serious and irreversible leukoencephalopathy that develops months after treatment, is more likely to occur after brain irradiation, and causes dementia, seizures, spasticity, and ataxia.

   f. **Occasional.** Nausea, vomiting, diarrhea (GI ulceration, hemorrhage, and perforation can occur if therapy is continued after the onset of diarrhea); dermatitis, photosensitivity, altered pigmentation, furunculosis; conjunctivitis, photophobia, excessive lacrimation, cataracts; fever, reversible oligospermia, flank pain (with rapid intravenous infusion)
   g. **Rare.** Alopecia, MTX pneumonitis (see Chapter 29, section IV.A)
4. **Administration**
   a. **Supplied** as 2.5-mg tablets and 20 to 1000-mg vials.
   b. **Dose modification.** The drug must not be administered to any patient with a creatinine clearance level of less than 60 mL/min (serum creatinine more than 1.5 mg/dL).
   c. **Dose.** Varies according to regimen
      1. High-dose regimens use supralethal doses of MTX followed by administration of the antidote leucovorin. This treatment is complex and requires experience on the part of the clinician and use of special monitoring techniques.
      2. Intrathecal administration: 5 to 10 mg/m^2 (maximum, 15 mg) in 7 to 15 mL of preservative-free saline (3 mL if given using an Ommaya reservoir) every 3 to 7 days
   d. **Drug interactions**
      1. Leucovorin rescues normal tissues from MTX toxicity
      2. L-Asparaginase blocks MTX toxicity and antitumor action.
      3. Aspirin, other nonsteroidal anti-inflammatory agents, penicillins, and probenecid decrease renal clearance of MTX and increase its toxicity.
      4. Sulfonamides and phenytoin displace MTX from protein-binding sites and may enhance its toxicity.
      5. Trimethoprim is also an inhibitor of dihydrofolate reductase and can enhance MTX toxicity.
      6. Parenteral acyclovir and concomitant intrathecal MTX may result in neurologic abnormalities.
      7. MTX may increase serum levels of theophylline and coumarin.

M. **Mitoguazone** (methyl-GAG, methylglyoxal-bis[guanylhydrazone])
1. **Indications.** Investigational agent for lymphomas

2. **Pharmacology**
   a. **Mechanism.** An antimetabolite that inhibits 5'-adenosylmethionine decarboxylase, which is important in the production of spermidine, which inhibits DNA and RNA synthesis
   b. **Metabolism.** Triphasic elimination pattern
3. **Toxicity**
   a. **Dose limiting.** Mucositis (severe); diarrhea (sometimes severe or bloody), nausea and vomiting (rarely severe)
   b. **Common.** Flushing during infusion, myelosuppression
   c. **Other.** Polyneuropathy and myopathy; vasculitis, hypoglycemia
4. **Administration**
   a. **Supplied** as 1-g vials
   b. **Dose:** 500 mg/m^2/week by IV infusion over at least 45 minutes

N. **Pentostatin** (2'-deoxycoformycin [dCF], Nipent)
   1. **Indications.** Hairy cell leukemia
   2. **Pharmacology**
      a. **Mechanism.** Antimetabolite. Inhibitor of adenine deaminase, an enzyme that is important for the metabolism of purine nucleosides. The mechanism of its antineoplastic effects is not established.
      b. **Metabolism.** Most dCF is excreted unchanged in the urine.
   3. **Toxicity**
      a. **Dose limiting.** Myelosuppression
      b. **Common.** Immunosuppression; mild nausea and vomiting, diarrhea, altered taste; fatigue, fever
      c. **Occasional.** Chills, myalgia, arthralgia; abnormal LFTs; keratoconjunctivitis, photophobia; renal failure
      d. **Rare.** Hepatitis; pulmonary infiltrates and insufficiency
   4. **Administration**
      a. **Supplied** as 10-mg vials
      b. **Dose modification.** Reduce doses for renal impairment.
      c. **Dose:** 4 mg/m^2 IV infusion over 20 minutes every 2 weeks

O. **Thioguanine** (6-TG, aminopurine-6-thiol-hemihydrate)
   1. **Indication.** Acute myelogenous leukemia
   2. **Pharmacology**
      a. **Mechanism.** Purine antimetabolite. After metabolic alteration into abnormal nucleotides, the drug is incorporated extensively into DNA, resulting in miscoding of transcription and DNA replication.
      b. **Metabolism.** Thioguanine is not degraded by xanthine oxidase and, unlike mercaptopurine, can be given in full doses with allopurinol. Clearance of the drug is primarily hepatic.
   3. **Toxicity**
      a. **Dose limiting.** Myelosuppression
      b. **Common.** Stomatitis, diarrhea
      c. **Occasional.** Nausea and vomiting, hepatic dysfunction, hepatic venoocclusive disease; decreased vibratory sensation, unsteady gait
   4. **Administration**
      a. **Supplied** as 40-mg tablets
      b. **Dose modification.** Dose is reduced with impaired liver function.
      c. **Dose** depends on regimen.

III. Antitumor antibiotics

A. **General pharmacology of antitumor antibiotics**
   1. Antitumor antibiotics generally are drugs derived from microorganisms. They usually are cell cycle–nonspecific agents that are especially useful in slow-growing tumors with low growth fractions.
   2. They act by a variety of mechanisms. Several of these drugs interfere with DNA through intercalation, a reaction whereby the drug inserts itself between DNA base pairs. Intercalation with DNA prevents DNA replication and messenger RNA production, or both. Other drugs have other actions.

B. **Actinomycin D** (dactinomycin, Cosmegen)
   1. **Indications.** Trophoblastic neoplasms, sarcomas, testicular carcinoma, Wilms' tumor
   2. **Pharmacology**
      a. **Mechanism.** Intercalates between DNA base pairs and prevents synthesis of messenger RNA; inhibits topoisomerase II
      b. **Metabolism.** Unknown; extensively bound to tissues, resulting in long half-life in plasma and tissue. Excreted in bile and urine as unchanged drug
   3. **Toxicity**
      a. **Dose limiting.** Myelosuppression
      b. **Common.** Nausea and vomiting (often worsening after successive daily doses and lasting several hours); alopecia, acne, erythema, desquamation, hyperpigmentation; radiation-recall reaction. Drug is a vesicant that can cause necrosis if extravasated.
      c. **Occasional.** Stomatitis, cheilitis, glossitis, proctitis, diarrhea; vitamin K antagonism
      d. **Rare.** Hepatitis, anaphylaxis, hypocalcemia, lethargy
   4. **Administration.** Premedicate patients with antiemetics. Administer through a running intravenous infusion with extravasation precautions.
      a. **Supplied** as 0.5-mg vials
      b. **Dose modification.** Reduce by 50% in the presence of renal or hepatic functional impairment.
      c. **Dose:** 0.25 to 0.60 mg/m^2 IV daily for 5 days every 3 to 4 weeks

C. **Bleomycin** (Blenoxane)
   1. **Indications.** Lymphomas, squamous cell carcinomas, testicular carcinoma, malignant effusions, and other malignancies
   2. **Pharmacology**
      a. **Mechanism.** Binds to DNA, thereby inhibiting synthesis of DNA and, to a lesser extent, of RNA and proteins. Causes DNA strand cleavage by free radicals and inhibits DNA repair by a marked inhibition of DNA ligase. Cell cycle G$_2$-phase specific; also active in late G$_1$, S, and M phases
      b. **Metabolism.** Activated by microsomal reduction; bound to tissues but not to plasma protein; extensive degradation by hydrolysis in nearly all tissues. Both free drug and metabolic products are excreted into the urine.
   3. **Toxicity**
      a. **Dose-limiting**
         1. Mild to severe shaking chills and febrile reactions are common (25% of patients), frequently occurring within 4 to 10 hours of injection. However, they decrease in incidence and severity with subsequent administrations.
         2. Bleomycin pneumonitis with dyspnea, dry cough, fine moist rales, interstitial radiographic changes, reduced diffusing capacity, hypoxia, and hypocapnia may be lethal. Pulmonary fibrosis and insufficiency occur in 1% of patients receiving cumulative doses of less than 200 U/m^2 and in 10% of patients receiving larger doses (see Chapter 29, for further details). Advanced age, underlying pulmonary disease, prior or concomitant radiotherapy to the chest, and prior exposure to bleomycin predispose patients to pulmonary toxicity.
      b. **Common**
         1. Sensitizes tumor and normal tissues to radiation
         2. Dermatologic (50% of patients): hyperpigmentation of skin stretch areas (e.g., knuckles, elbows), hyperpigmented striae; hardening, tenderness, or loss of fingernails; hyperkeratosis of palms and fingers, scleroderma-like changes; skin tenderness, pruritus, urticaria, erythroderma, desquamation, alopecia
         3. Anorexia, mucositis; a rancid smell ("like old gym socks") beginning about 10 seconds after injection
      c. **Occasional.** Nausea, vomiting, unusual tastes; mild reversible myelosuppression, Raynaud's phenomenon, phlebitis, pain at injection site
      d. **Rare**
         1. Hepatotoxicity, pleuropericarditis, arteritis
         2. Anaphylaxis-like reaction develops in 1% to 7% of patients who have lymphoma, usually after the first or second dose and particularly if the dose is 25 U/m^2 or more. This idiosyncratic reaction manifests confusion, faintness, fever, chills, and wheezing that can progress to hypotension, renal failure, and cardiovascular collapse.
   4. **Administration.** A 2-U test dose is given before the first treatment, followed by a 1- to 2-hour observation period to reduce the potential for cardiovascular collapse.

a. **Supplied** as 15-unit (mg) vials
b. **Dose modification.** The drug should not be given to patients with symptomatic chronic obstructive lung disease. It must be discontinued in patients who have erythroderma (continued treatment may lead to fatal exfoliative dermatitis). The drug must also be discontinued if there are symptoms or signs of interstitial lung disease. Routine pulmonary function tests are generally not helpful; some authorities recommend monitoring carbon monoxide– diffusing capacity. Dosage should be reduced in patients with renal failure.
c. **Dose.** Avoid cumulative dosage of greater than 400 U; some physicians limit the total dose to 300 U.
  1. 10 to 20 U/m^2 IM, IV, or SC once or twice weekly (twice-weekly doses higher than 20 U each are likely to cause serious toxic reactions of the skin), or
  2. 15 to 20 U/m^2 daily for 3 to 7 days by continuous infusion, or
  3. 60 U/m^2 dissolved in 100 mL of normal saline for intracavitary therapy

D. **Daunorubicin** (daunomycin, rubidomycin, Cerubidine)
  1. **Indication.** Acute leukemias
  2. **Pharmacology.** Anthracycline antitumor antibiotic. Essentially the same as doxorubicin. Active metabolite is daunomycinol.
  3. **Toxicity.** Same as doxorubicin. Daunorubicin may also cause precipitous fatal cardiomyopathy months after therapy has stopped; incidence becomes unacceptable after a total dose of 500 to 600 mg/m^2 has been given.
  4. **Administration.** Same as doxorubicin. Use extravasation precautions.
    a. **Supplied** as 20-mg vials
    b. **Dose modification.** Same as doxorubicin
    c. **Dose.** 45 to 60 mg/m^2 IV daily for 3 days

E. **Doxorubicin** (Adriamycin, Rubex, hydroxydaunorubicin)
  1. **Indications.** Effective in a large variety of tumors
  2. **Pharmacology**
    a. **Mechanism.** Anthracycline antitumor antibiotic. Intercalates between DNA base pairs, forms free radicals, alters cell membranes, induces topoisomerase II–dependent DNA damage, inhibits preribosomal DNA and RNA. Cell cycle–phase nonspecific.
    b. **Metabolism.** About 70% of the drug is bound to plasma proteins. Rapidly metabolized by the liver to other compounds, some of which are cytotoxic (including the active metabolite, doxorubicinol). The release rate from tissue binding sites is slow compared with the capacity of the liver for metabolism; this results in relatively prolonged plasma levels of drug and metabolites.
    c. **Excretion.** Metabolites and free drug are extensively excreted in the bile; however, known elimination accounts for only half of the drug. The rate of drug elimination and its toxicity thus is rarely limited by liver function. Some chromogens are excreted through the kidney, occasionally imparting a red tinge to the urine.
  3. **Toxicity**
    a. **Dose-limiting**
      1. Myelosuppression, particularly leukopenia
      2. Cardiomyopathy with congestive heart failure, which may become refractory (see Chapter 29, section VI.D for further details). Monitor the left ventricular ejection fraction with radionuclide angiography, before the initiation of treatment, particularly when the cumulative dose exceeds 300 mg/m^2, and periodically thereafter. Risks and benefits should be considered at total cumulative doses of 550 mg/m^2 (400 mg/m^2 with a history of mediastinal irradiation) or for electrocardiographic changes (voltage reduction, significant arrhythmias, ST-T wave changes). Dexrazoxane (see section VIII.B), a cardioprotectant, can be considered when the cumulative dose exceeds 300 mg/m^2.
    b. **Common**
      1. Alopecia (nearly 100% of patients when administered as a bolus every 3 to 4 weeks, but minimal when the dose is divided and given weekly); nausea and vomiting (mild to severe); stomatitis
      2. Doxorubicin is a vesicant; extravasation of the drug results in severe ulceration and necrosis.
      3. Previously irradiated skin sites may become erythematous and desquamate when the drug is started; this "radiation-recall reaction" can occur years after radiation was given.
    c. **Occasional.** Diarrhea; hyperpigmentation of nail beds and dermal creases, facial flush, flush along injected vein, skin rash; conjunctivitis, lacrimation; red-colored urine
    d. **Rare.** Activation of fibrinolysis, muscle weakness, fever, chills, anaphylaxis
  4. **Administration.** The drug must be slowly pushed through a running intravenous line using extravasation precautions or continuously infused through a central venous line.
    a. **Supplied** as 10-, 20-, 50-, 100-, and 150-mg vials
    b. **Dose modification.** Doxorubicin should not be given to patients with congestive heart failure from any cause. The package insert recommends reduction of dose by 50% for serum bilirubin of 1.2 to 3.0 mg/dL and by 75% for bilirubin of 3 to 5 mg/dL (but see section E.2.c).
    c. **Dose.** 50 to 75 mg/m^2 IV bolus every 3 to 4 weeks or 10 to 20 mg/m^2 IV weekly

F. **Doxorubicin, liposomal** (Doxil)
  1. **Indications.** Kaposi's sarcoma with acquired immunodeficiency syndrome (AIDS), refractory ovarian carcinoma
  2. **Pharmacology.** Doxorubicin is encapsulated in long-circulating liposomes (microscopic vesicles composed of a phospholipid bilayer). For mechanisms and metabolism, see doxorubicin. The plasma clearance is slower than standard doxorubicin.
  3. **Toxicity**
    a. **Dose-limiting.** Hematosuppression
    b. **Common.** Fatigue; diarrhea, nausea, vomiting; alopecia; "infusion reactions" (chills, facial swelling, headache, hypotension, shortness of breath), which resolve upon interruption of infusion and which do not preclude continued treatment.
    c. **Occasional.** Cardiomyopathy, pain at injection site, radiation recall reaction; palmar–plantar erythrodysesthesia (ulceration, erythema, and desquamation on the hands and feet with pain and inflammation)
    d. **Rare.** Allergic reaction, hyperglycemia, jaundice, optic neuropathy
  4. **Administration**
    a. **Supplied** as 20-mg vials
    b. **Dose modification.** Same as for doxorubicin
    c. **Dose.**
      1. Kaposi's sarcoma in AIDS: 20 mg/m^2 IV over 30 minutes every 2 or 3 weeks
      2. Ovarian carcinoma: 40 to 50 mg/m^2 IV over 1 to 2 hours every 4 weeks

G. **Epirubicin** (Ellence) is the 4'-epimer of doxorubicin and is a semi-synthetic derivative of daunorubicin. An *epimer* is one of a pair of isomers that differ only in the position of the H- and OH-attached to one asymmetric carbon atom.
  1. **Indicatons.** Breast cancer
  2. **Pharmacology.** Anthracycline antitumor antibiotic. For mechanisms and metabolism, see doxorubicin.
  3. **Toxicity.** Same as doxorubicin. The risk of developing cardiomyopathy increases substantially after a total dose of 900 mg/m^2
  4. **Administration.** Intravenously over 5 minutes using extravasation precautions
    a. **Supplied as** 50- and 200-mg vials
    b. **Dose modification.** Same as for doxorubicin. Cimetidine appears to increase plasma levels of epirubicin.
    c. **Dose.** 100 to 120 mg/m^2 IV every three weeks in combination chemotherapy regimens

H. **Idarubicin** (4-demethoxydaunorubicin, Idamycin)
  1. **Indications.** Acute leukemia
  2. **Pharmacology.** Anthracycline antitumor antibiotic. More lipophilic and better cell uptake than other anthracycline antibiotics; otherwise similar to doxorubicin. The active metabolite is 13-epirubicinol.
  3. **Toxicity.** Similar to doxorubicin. Myelosuppression is expected. Although idarubicin is less cardiotoxic than doxorubicin and daunorubicin, the same monitoring criteria apply.
  4. **Administration.** Intravenously over 15 minutes using extravasation precautions.
    a. **Supplied** as 5- and 10-mg vials
    b. **Dose modification.** Same as doxorubicin
    c. **Dose.** 12 mg/m^2 IV daily for 3 days with induction therapy

I. **Mithramycin** (plicamycin, Mithracin)
  1. **Indication.** Refractory hypercalcemia
  2. **Pharmacology**
    a. **Mechanism.** Osteoclast inhibitor, antitumor antibiotic. Cytotoxicity probably related to DNA intercalation and adlineation; inhibits DNA-dependent RNA

synthesis without affecting DNA synthesis
   b. **Metabolism.** Unknown, eliminated in the urine (40%)
3. **Toxicity.** Renal and hepatic damage are rare with dosage schedules used for hypercalcemia
   a. **Dose-limiting.** Thrombocytopenia; coagulation defects may occur in the absence of thrombocytopenia and result in a severe hemorrhagic diathesis (usually with frequent doses).
   b. **Common.** Nausea, vomiting; hypocalcemia, hypophosphatemia, hypokalemia, hypomagnesemia, rebound hypercalcemia; abnormal LFTs (including prothrombin time); azotemia; skin and soft tissue necrosis if extravasated
   c. **Occasional.** Leukopenia, anemia; stomatitis, diarrhea; hyperpigmentation, acneiform rash; headache, dizziness, drowsiness, nervousness
   d. **Rare.** Toxic epidermal necrolysis, fever, lethargy, periorbital pallor
4. **Administration.** A running intravenous line using extravasation precautions
   a. **Supplied** as 2.5-mg vials
   b. **Dose modification.** Mithramycin must be given cautiously to patients with hepatic or kidney dysfunction.
   c. **Dose for hypercalcemia:** 15 to 25 µg (0.025 mg)/kg IV every 3 to 7 days
J. **Mitomycin** (mitomycin C, Mutamycin)
1. **Indications.** A variety of carcinomas
2. **Pharmacology**
   a. **Mechanism.** Antitumor antibiotic. After intracellular activation, functions as an alkylating agent. DNA cross-linking, DNA depolymerization, and free radical formation
   b. **Metabolism.** Metabolized predominantly in the liver. Free drug (25%) and metabolites excreted in urine, but renal dysfunction does not significantly alter mitomycin elimination.
3. **Toxicity**
   a. **Dose-limiting.** Cumulative myelosuppression, which may be severe and prolonged (particularly thrombocytopenia)
   b. **Common.** Mild nausea and vomiting, anorexia; a vesicant drug that can cause necrosis if injected subcutaneously (skin erythema and ulceration can occur weeks to months after administration and may appear at a site distant from the site of injection)
   c. **Occasional.** Alopecia, stomatitis, skin rashes, photosensitivity, pain at site of injection, phlebitis; hemolytic-uremic–like syndrome (see Chapter 34, Cytopenia, section IV.C for details)
   d. **Rare.** Hepatic and renal (cumulative) dysfunction, paresthesias, blurred vision, fever; acute interstitial pneumonitis (especially when given with vinblastine)
4. **Administration.** Administer through a running intravenous infusion using extravasation precautions.
   a. **Supplied** as 5-, 20-, and 40-mg vials
   b. **Dose modification.** Reduce dose by 50% to 75% for patients who were previously treated with extensive irradiation or developed a white blood cell count of less than 2000/µL with prior doses of mitomycin
   c. **Dose**
      1. **Single agent:** 10 to 20 mg/m^2 IV every 6 to 8 weeks, or
      2. **In combination:** 5 to 10 mg/m^2 IV every 5 weeks
K. **Mitoxantrone** (Novantrone, dihydroxyanthracenedione)
1. **Indications.** Breast and prostate cancer, lymphoma, acute leukemia
2. **Pharmacology.** Mitoxantrone is in the anthracenedione class of compounds, which are analogues to the anthracyclines. Its mechanism of action and routes of metabolism are similar but not identical to doxorubicin.
   a. **Mechanism.** DNA intercalation, single- and double-strand DNA breakage, inhibition of topoisomerase II
   b. **Metabolism.** Metabolized by the liver; excreted in the bile and urine as metabolites and unchanged drug
3. **Toxicity.** Compared with the anthracyclines, mitoxantrone is associated with less cardiotoxicity, less nausea and vomiting, and decreased potential for extravasation injury
   a. **Dose-limiting.** Bone marrow suppression
   b. **Common.** Mild nausea and vomiting, mucositis; alopecia (usually mild); blue discoloration of the urine, sclerae, fingernails, and over venous site of injection that may last 48 hours
   c. **Occasional.** Cardiomyopathy (most well-defined for patients who have previously received doxorubicin; appears to be less cardiotoxic than doxorubicin. Pruritus, LFT abnormalities, allergic reactions
   d. **Rare.** Jaundice, seizures, pulmonary toxicity
4. **Administration** as a 30-minute infusion; rarely causes extravasation injury if infiltrated
   a. **Supplied** as 20-, 25-, and 30-mg vials
   b. **Dose modification.** Hematologic
   c. **Dose:** is 10 to 12 mg/m^2 IV given every 3 weeks for solid tumors

IV. Mitotic spindle agents

A. **General pharmacology of mitotic spindle agents.** Mitotic spindle inhibitors are classically represented by vincristine and vinblastine. These drugs bind to microtubular proteins, thus inhibiting microtubule assembly (M phase of the cell cycle) and resulting in dissolution of the mitotic spindle structure. Taxanes (paclitaxel and docetaxel) not only bind to microtubules but also promote microtubule assembly and resistance to depolymerization, resulting in the production of nonfunctional microtubules.
B. **Paclitaxel** (Taxol)
1. **Indications.** Breast and ovarian carcinomas, AIDS-associated Kaposi's sarcoma, and other malignancies
2. **Pharmacology**
   a. **Mechanism.** Plant alkaloid (antimicrotubule agent); see section A.1.
   b. **Metabolism.** Nearly totally protein bound and distributed well to body fluids (including effusions) with a plasma half-life of about 5 hours
3. **Toxicity**
   a. **Dose-limiting**
      1. **Neutropenia,** particularly in patients who were previously heavily treated or who receive cisplatin just before paclitaxel
      2. **Hypersensitivity** (3%) is manifested by cutaneous flushing, hypotension, bronchospasm, urticaria, diaphoresis, pain, or angioedema. Reactions usually develop within 20 minutes of starting the treatment; 90% of hypersensitivity reactions develop after the first or second dose.
      3. **Peripheral neuropathy,** particularly in the higher dosage schedules and in patients with concomitant etiologies for peripheral neuropathy. Neurotoxicity occurs less frequently when infused over 24 hours (5%) than when infused over 3 hours (25%). The distribution typically is "stocking-glove" and consists of dysesthesias, paresthesias, and loss of proprioception.
   b. **Common.** Alopecia (usually total and sudden, within 3 weeks of treatment); thrombocytopenia (usually not severe); transient arthralgias and myalgias within 3 days of treatment (ameliorated by nonsteroidal antiinflammatory agents and prednisone), transient bradycardia (usually asymptomatic)
   c. **Occasional.** Nausea, vomiting, taste changes, mucositis (cumulative), diarrhea; atrioventricular conduction defects, ventricular tachycardia, cardiac angina; necrosis when extravasated; intoxication when infused over 1 hour (because of high alcohol content in the preparation)
   d. **Rare.** Paralytic ileus, generalized weakness, seizures; myocardial infarction
4. **Administration.** Paclitaxel should be given before cisplatin in combination regimens in which both are administered. Cardiac monitoring is recommended for patients with a history of cardiac disease. Administer with extravasation precautions.
   a. **Supplied** as 30-, 100-, and 300-mg vials
   b. **Dose modification.** Hematologic
   c. **Dose:** 135 to 175 mg/m^2 infused over 3 to 24 hours with the following premedications: dexamethasone, 20 mg PO or IV given 12, 6, and 0.5 hours before paclitaxel; diphenhydramine, 50 mg IV, and ranitidine, 50 mg IV, are given 30 minutes before administering paclitaxel
C. **Docetaxel** (Taxotere)
1. **Indications.** Breast cancer after ineffectiveness of anthracycline-based treatment
2. **Pharmacology.** The drug is prepared by semisynthesis beginning with a precursor extracted from the needles of yew plants.
   a. **Mechanisms.** Inhibitor of microtubular depolymerization (see section IV.A.). The binding of docetaxel to microtubules does not alter the number of protofilaments in the bound microtubules, which differs from most spindle poisons currently in clinical use.
   b. **Metabolism.** More than 75% is excreted in the feces, and a small percentage in the urine.
3. **Toxicity**
   a. **Dose-limiting.** Myelosuppression; severe fluid retention
   b. **Common.** Alopecia (80%), stomatitis, skin eruptions

c. **Occasional.** Severe hypersensitivity reactions despite premedications. Fluid retention that is cumulative in incidence and severity (especially after a cumulative dose of 705 mg/m^2) is reversible (usually within 8 months); the fluid retention usually affects the lower extremities but can also result in ascites or pleural or pericardial effusions. GI upset, severe nail reactions; hypotension; elevated liver function tests

d. **Rare.** Cardiac events

4. **Administration**

a. **Supplied** as vials to produce a 10 mg/mL solution

b. **Dose modification.** Patients with elevated serum bilirubin or significantly elevated liver enzymes should generally not receive docetaxel.

c. **Dose**

1. 60 to 100 mg/m^2 IV over 1 hour every 3 weeks; give dexamethasone, 8 mg PO b.i.d. for 5 days starting 1 day before docetaxel administration to reduce the incidence and severity of fluid retention and hypersensitivity reactions

2. 36 mg/m^2 weekly for 6 weeks of an 8-week cycle (the weekly schedule is associated with less hematologic toxicity and no hair loss; it requires a maximum of 4 mg dexamethasone on the morning and evening of dosing)

D. **Vinblastine** (Velban)

1. **Indications.** Lymphomas, testicular carcinoma

2. **Pharmacology**

a. **Mechanism.** Plant alkaloids; see section A.1. Binds to microtubular proteins. Inhibits RNA synthesis by affecting DNA-dependent RNA polymerases. Cell cycle–phase specific; it arrests cells at the G$_2$-phase and M-phase interface.

b. **Metabolism.** Highly bound to plasma proteins and to formed blood elements, especially platelets. Metabolized by the liver to active and inactive metabolites. Predominantly excreted in bile. Minimal free drug is recovered in urine.

3. **Toxicity**

a. **Dose-limiting.** Neutropenia

b. **Common.** Cramps or severe pain in jaw, pharynx, back, or limbs after injection; local vesicant if extravasated

c. **Occasional.** Thrombocytopenia, anemia

d. **Rare.** Nausea, vomiting, diarrhea, mucositis, abdominal cramps, GI hemorrhage; acute interstitial pneumonitis (especially when administered with mitomycin C); ischemic cardiotoxicity

4. **Administration.** Administered by rapid infusion through the tubing of a running intravenous line with extravasation precautions

a. **Supplied** as 10-mg vials

b. **Dose modification.** Decrease dose by 50% for patients with serum bilirubin greater than 3.0 mg/dL.

c. **Dose:** 5 mg/m^2 IV every 1 or 2 weeks.

E. **Vincristine** (Oncovin, Vincasar, leurocristine)

1. **Indications.** A wide variety of malignancies

2. **Pharmacology**

a. **Mechanism.** Same as vinblastine

b. **Metabolism.** Same as vinblastine

3. **Toxicity**

a. **A dose-dependent peripheral neuropathy** universally develops. Cranial nerves and the autonomic system may also be involved. The neuropathies usually reverse within several months. Jaw, throat, or anterior thigh pain occurring within hours of injection disappears within days and usually does not recur.

1. **Dose-limiting.** Severe paresthesias, ataxia, foot-drop (slapping gait), muscle wasting, cranial nerve palsies, paralytic ileus, obstipation, abdominal pain, optic atrophy, cortical blindness, seizures

2. **Not dose-limiting.** Mild hypoesthesia, mild paresthesias, transient jaw pain (and similar syndromes), loss of deep tendon reflexes

b. **Common.** Tissue necrosis if extravasated, alopecia (20% to 40%)

c. **Occasional.** Mild leukopenia (does not have significant effect on erythrocytes or platelets); rash, SIADH

d. **Rare.** Nausea, vomiting, pancreatitis; fever

4. **Administration.** Patients receiving vincristine should be given bulk laxatives routinely. Administered by rapid infusion using extravasation precautions

a. **Supplied** as 1 mg/mL vials

b. **Dose modification.** Hepatic dysfunction; same as for vinblastine

c. **Dose:** 1.0 to 1.4 mg/m^2 IV every 1 to 4 weeks (often limited to a one-time total dose of 2 mg in adults); continuous infusion regimens involve 0.4–0.5 mg/day for 4 days

F. **Vindesine** (Eldisine, desacetylvinblastine amide sulfate)

1. **Indications.** Experimental for lung cancer, leukemias, and others

2. **Pharmacology.** Same as vinblastine

3. **Toxicity.** Same as vinblastine, but alopecia is more common with vindesine. Neurotoxicity is same as for vincristine but is generally less severe.

4. **Administration.** Same as vinblastine

a. **Supplied** as 10-mg vials

b. **Dose modification.** Necessary for patients with hepatic dysfunction; same as for vinblastine

c. **Dose:** 3 to 4 mg/m^2 IV every 7 to 14 days

G. **Vinorelbine** (Navelbine)

1. **Indications.** Non–small cell carcinoma, lung cancer, and breast cancer

2. **Pharmacology**

a. **Mechanisms.** Disorganizes microtubules of the mitotic figure (see section IV.A).

b. **Metabolism.** Drug and metabolites are excreted in bile.

3. **Toxicity**

a. **Dose-limiting.** Neutropenia

b. **Common.** Fatigue; nausea, vomiting

c. **Occasional.** Stomatitis; allergic-type pulmonary reactions; peripheral neuropathy

d. **Rare.** Thrombocytopenia; hemorrhagic cystitis

4. **Administration.** Same as vinblastine

a. **Supplied** as 10- and 50-mg vials

b. **Dose modification.** Reduce dose for hyperbilirubinemia

c. **Dose:** 30 mg/m^2 IV weekly

d. **Drug interactions.** Acute pulmonary reactions have been reported when given with mitomycin

V. Topoisomerase inhibitors

A. **General pharmacology of topoisomerase inhibitors.** DNA is attached at regular intervals to the nuclear matrix at sites called *domains,* which are wound together with their paired DNA molecules. DNA topoisomerases are enzymes that alter DNA topology by causing and resealing DNA strand breaks. Topoisomerases bind to DNA domains, forming a "cleavable complex," which allows DNA to unwind in preparation for cell division. Topoisomerase I relaxes supercoiled DNA for a variety of crucial cellular processes. Topoisomerase II catalyzes the double-stranded breaking and resealing of DNA, thereby allowing the passage of one double helical segment of DNA through another. They relax superhelical turns, interconvert knotted rings, and intertwist complementary viral sequences into DNA. Topoisomerases are essential for such events as transcription, replication, and mitosis.

Of all the topoisomerases, groups I and II are the targets of cytotoxic agents. Camptothecin derivatives (irinotecan, topotecan) exert their cytotoxic effect by inhibiting topoisomerase I. Epipodophyllotoxin derivatives (etoposide, teniposide) inhibit topoisomerase II. Drugs from other classes (e.g., amsacrine and the anthracyclines) also inhibit topoisomerases as part of their mechanism of action. Inhibition of topoisomerase interferes with transcription and replication by causing DNA damage, inhibition of DNA replication, failure to repair strand breaks, and then, cell death.

B. **Irinotecan** (Camptosar, CPT-11)

1. **Indications.** Colorectal cancer refractory to 5-FU–based chemotherapy

2. **Pharmacology.** A water-soluble analogue of camptothecin that is a relatively inactive prodrug, which is converted to the active agent

a. **Mechanisms.** Inhibits topoisomerase I; see section V.A; cell cycle– phase specific.

b. **Metabolism.** Metabolized in the liver. Renal clearance is a major route of elimination.

3. **Toxicity**
   a. **Dose-limiting.** Profuse diarrhea (especially in patients 65 years of age and older)
   b. **Common.** Neutropenia; mild nausea, vomiting, abdominal cramps; flushing during administration; alopecia
   c. **Occasional.** LFT abnormalities, headache, fever, dyspnea
4. **Administration.** Administer as a 90-minute infusion once weekly for 4 weeks in 6-week cycles. If diarrhea, abdominal cramps, or diaphoresis (mostly cholinergic in nature) develops during the infusion of the drug, administer atropine, 0.25 to 1.0 mg IV. For the first poorly formed stool preceding delayed diarrhea, administer loperamide (Imodium), 4 mg PO, then 2 mg every 2 hours (4 mg PO every 4 hours at night) until the patient is free of diarrhea for 12 hours.
   a. **Supplied** as 100-mg vials
   b. **Dose modification.** Use with caution for hepatic insufficiency.
   c. **Dose:** start at 125 mg/m^2 IV weekly; may need to be reduced to 100 mg/m^2 because of diarrhea (but observed response rates are lower as well).
C. **Topotecan** (Hycamtin)
   1. **Indications.** Ovarian cancer after failure to respond to previous (cisplatin-based) therapies
   2. **Pharmacology**
      a. **Mechanisms.** A derivative of camptothecin, it inhibits topoisomerase I activity; see section V.A; cell cycle–phase specific. It exerts its cytotoxic effect by blocking DNA repair.
      b. **Metabolism.** Metabolized in the liver; 30% of the drug is excreted in the urine.
   3. **Toxicity**
      a. **Dose-limiting.** Myelosuppression
      b. **Common.** Nausea, vomiting, diarrhea, constipation, abdominal pain; alopecia; headache, fatigue, fever; dyspnea
      c. **Occasional.** Elevation of liver function tests; paresthesia; rash
   4. **Administration**
      a. **Supplied** as 4-mg vials
      b. **Dose modification.** None for impaired hepatic function. Reduce dosage by 50% for creatinine clearance levels of 20 to 40 mL/min.
      c. **Dose:** 1.25 to 1.50 mg/m^2 IV over 30 minutes for 5 consecutive days every 3 weeks.
D. **Etoposide** (VP-16, VePesid)
   1. **Indications.** Testicular carcinoma, lung cancer, lymphoma, and other malignancies
   2. **Pharmacology**
      a. **Mechanisms.** An epipodophyllotoxin; a topoisomerase II inhibitor (see section V.A); cell cycle–phase specific at G$_2$, late S, and M phases.
      b. **Metabolism.** Highly bound to plasma proteins; metabolized by the liver. Excreted in urine (40%) as intact and degraded drug; excretion of the remaining 60% is uncertain.
   3. **Toxicity**
      a. **Dose-limiting.** Neutropenia
      b. **Common.** Nausea and vomiting (with oral dosing, but uncommon with intravenous dosing); alopecia (usually mild); hypotension if rapidly infused
      c. **Occasional.** Anemia, thrombocytopenia, pain at injection site, phlebitis, abnormal LFTs, peripheral neuropathy
      d. **Rare.** Stomatitis, dysphagia, diarrhea, constipation, parotitis, rash, radiation-recall reaction, hyperpigmentation; anaphylaxis, transient hypertension, arrhythmias; somnolence, vertigo, transient cortical blindness
   4. **Administration.** Administer slowly over at least 30 minutes when given intravenously.
      a. **Supplied** as 50-mg capsules and 100-mg vials
      b. **Dose modification.** Administer with caution in the presence of renal dysfunction; reduce doses by 25% or 50% for creatinine clearance levels of less than 50 mL/min and less than 10 mL/min, respectively.
      c. **Dose**
         1. 50 mg/m^2 PO daily for 21 days, or
         2. 50 to 120 mg/m^2 IV daily for 3 to 5 days
      d. **Drug interactions.** Calcium-channel antagonists, such as verapamil, or methotrexate may increase cytotoxicity of etoposide.
E. **Teniposide** (VM-26, Vumon)
   1. **Indications.** Acute lymphoblastic leukemia
   2. **Pharmacology**
      a. **Mechanism.** Plant alkaloid; topoisomerase II inhibitor (see section V.A)
      b. **Metabolism.** Virtually all of the drug is bound to protein. Systemic metabolism is significant, but metabolites have not been identified. Renal excretion is only a small fraction of its clearance.
   3. **Toxicity**
      a. **Dose-limiting.** Neutropenia
      b. **Common.** Thrombocytopenia, hypotension with too rapid an infusion
      c. **Occasional.** Nausea and vomiting, alopecia, abnormal LFTs, phlebitis
      d. **Rare.** Diarrhea, stomatitis; rash, anaphylaxis; azotemia; fever; paresthesias, seizures
   4. **Administration.** The drug is administered by slow intravenous infusion over at least 30 minutes.
      a. **Supplied** as 50-mg vials
      b. **Dose:** 150 to 250 mg/m^2 once or twice weekly
      c. **Drug interactions.** Anticonvulsants increase clearance of teniposide.

VI. Miscellaneous agents

A. ʟ-Asparaginase (Elspar)
   1. **Indication.** Acute lymphoblastic leukemia
   2. **Pharmacology**
      a. **Mechanism.** This enzyme hydrolyzes asparagine into aspartic acid and, to a lesser extent, glutamine into glutamic acid. Leads to inhibition of protein synthesis. Kills cells that cannot synthesize asparagine by destroying extracellular asparagine stores. Cell cycle specific for postmitotic G$_1$ phase.
      b. **Metabolism.** Plasma half-life (8 to 30 hours) is independent of dose. Metabolism is independent of hepatic and renal function. Only trace amounts are recovered in urine.
   3. **Toxicity**
      a. **Dose-limiting.** Allergic reactions (including chills, urticaria, skin rashes, fever, laryngeal constriction, asthma, and anaphylactic shock) are the most frequent. Allergic reactions develop within 1 hour of dosing and are most likely to occur after several doses are given, particularly if the last dose was given more than 1 month previously and if the drug is administered intravenously rather than intramuscularly. Patients who respond to *Escherichia coli* asparaginase but develop allergic reactions may be treated relatively safely with another source of the enzyme.
      b. **Common**
         1. **Encephalopathy** in 25% to 50% of patients. Lethargy, somnolence, and confusion tend to occur within the first few days of therapy, reverse after completion of therapy, and are rarely a cause for discontinuing treatment. Hemorrhagic and thrombotic CNS events occur later and are associated with induced imbalances in the coagulation and fibrinolytic systems.
         2. **GI:** Nausea, anorexia, vomiting (60%)
         3. **Hepatitis** (abnormal LFTs in more than 50% of treated patients, but rarely severe); pancreatitis (10%)
         4. **Coagulation defects** associated with decreased synthesis of clotting factors, especially fibrinogen and antithrombin III (usually subclinical but may result in thrombosis or pulmonary embolism)
         5. **Prerenal azotemia** (65%); a rise in blood urea nitrogen and blood ammonia levels not evidence of toxicity
         6. **Hyperglycemia**
      c. **Rare.** Myelosuppression, diarrhea, severe renal failure, hyperthermia
   4. **Administration.** Administer a small (2-U) intradermal test dose to check for hypersensitivity. Epinephrine (1 mg, 1:1000), hydrocortisone (100 mg), and diphenhydramine (50 mg) should be readily available to treat anaphylaxis each time the drug is given.
      a. **Supplied** as 10,000-IU vials
      b. **Dose modification.** None for renal dysfunction. Use with caution for hepatic dysfunction or pancreatitis.
      c. **Dose:** usually administered in combination with vincristine and prednisone at a dose of 6000 IU/m^2 IM three times weekly for nine doses
      d. **Drug interactions.** Asparaginase blocks the action of methotrexate and thus "rescues" the patient from methotrexate toxicity.

B. **Estramustine** (Emcyt)
1. **Indications.** Progressive prostate cancer
2. **Pharmacology.** Exact mechanism of antineoplastic action is unknown. Structurally, it is a phosphorylated combination of estradiol and mustargen.
3. **Toxicity.** Similar to estrogens (see section VII.F)
4. **Administration**
   a. **Supplied** as 140-mg capsules
   b. **Dose:** 600 mg/m^2/day in three divided doses taken on an empty stomach
C. **Levamisole** (Ergamisole)
1. **Indications.** Adjuvant therapy for colon cancer in combination with 5-FU
2. **Pharmacology**
   a. **Mechanism.** An antihelminthic drug that is believed to stimulate the immune system. Its mechanism of action for antitumor activity is unknown.
   b. **Metabolism.** Extensively metabolized by the liver. Only 5% of the drug is excreted unchanged in the urine.
3. **Toxicity.** Levamisole was originally thought to be nearly nontoxic, but experience has shown otherwise.
   a. **Dose-limiting.** Intolerance of the drug
   b. **Common.** Nausea; striking dysosmia and dysgeusia with exposure to city water (including sprinklers and showers)
   c. **Occasional.** Vomiting, flu-like syndrome, arthritis, edema; CNS hyperexcitation syndromes (agitation, confusion, nightmares, jitters, silliness, hyperalertness, headache, blurred vision, dysesthesias, tremors, tardive dyskinesia, hallucination, seizure)
   d. **Rare.** Alopecia, hematosuppression, dermatitis, conjunctivitis
4. **Administration**
   a. **Supplied** as 50-mg tablets in packages of 36
   b. **Dose:** 50 mg t.i.d. PO for 3 days every 2 weeks given with 5-FU
   c. **Drug interactions.** Antabuse-like reactions with alcohol; may increase blood levels of phenytoin and warfarin
D. **Octreotide** (Sandostatin, l-cysteinamide)
1. **Indications.** Control of symptoms in patients with carcinoid syndrome, vasoactive intestinal peptide–secreting tumors, or cholera-like diarrhea caused by chemotherapeutic agents
2. **Pharmacology**
   a. **Mechanism.** A long-acting analogue of somatostatin that inhibits the secretion of serotonin, vasoactive intestinal peptide, gastrin, motilin, insulin, glucagon, secretin, and pancreatic polypeptide
   b. **Metabolism.** The elimination half-life is 1.5 hours, and the duration of action is about 12 hours. Thirty percent of the drug is excreted unchanged in the urine.
3. **Toxicity**
   a. **Dose-limiting.** Abdominal pain, vomiting, and loose stools
   b. **Dermatologic.** Injection site pain or other reactions, hair loss, rash, thinning of skin, hyperhidrosis
   c. **Occasional.** Hypoglycemia, hyperglycemia, hypertension, hypotension, thrombophlebitis, cardiac ischemia or failure; fat malabsorption, abnormal LFTs; visual disturbance, rhinorrhea, dry mouth, throat discomfort, prostatitis, chills, fever
   d. **Rare.** GI bleeding, cholelithiasis, hepatitis
4. **Administration**
   a. **Supplied** as 1-mL ampules containing 0.05, 0.1, and 0.5 mg/mL
   b. **Dose:** 0.1 to 0.6 mg SC in two to four divided doses
E. **Suramin**
1. **Indications.** Investigational agent for prostate cancer
2. **Pharmacology**
   a. **Mechanism.** Suramin is a glycosaminoglycan, an antitrypanosomal agent. Antitumor activity may be related to binding to growth factors and to other mechanisms.
   b. **Metabolism.** Totally bound to plasma proteins; nearly all is excreted in the urine with an elimination half-life of 40 to 50 days.
3. **Toxicity.** Life-threatening toxicities can usually be avoided by keeping the plasma concentrations below 300 μg/mL.
   a. **Dose-limiting.** Thrombocytopenia
   b. **Neurotoxicity.** Paresthesias, polyradiculoneuropathy (muscle weakness progressing to generalized flaccid paralysis)
   c. **Other.** Leukopenia (mild), elevated clotting times, bleeding; adrenocortical insufficiency, hypocalcemia; nausea, vomiting, abnormal LFTs, metallic taste; nephrotoxicity; keratopathy, photophobia, blurred vision; fever, transient erythematous rash, pruritus
4. **Administration**
   a. **Supplied** as 1-g vials
   b. **Dose:** 350 mg/m^2/day as a continuous IV infusion until plasma level reaches 250 to 300 μg/mL, then variable dosing schedules are used.
F. **Hexamethylmelamine** (Hexalen, altretamine)
1. **Indications.** Recurrent ovarian carcinoma
2. **Pharmacology**
   a. **Mechanism is unknown.** It structurally resembles an alkylating agent but does not have alkylating agent activity.
   b. **Metabolism.** Rapidly demethylated and hydroxylated in the liver by microsomal enzymes. Excreted in urine and hepatobiliary tract as metabolites
3. **Toxicity**
   a. **Dose-limiting.** Nausea and vomiting, which may worsen with continued therapy
   b. **Common.** Myelosuppression (mild) with nadir blood cell counts occurring 3 to 4 weeks after starting treatment
   c. **Occasional.** Neurotoxicity, including paresthesias, hypoesthesia, hyperreflexia, motor weakness, agitation, confusion, hallucinations, lethargy, depression, coma
   d. **Rare.** Alopecia, skin rashes, cystitis, secondary malignancies
4. **Administration**
   a. **Supplied** as 50-mg capsules
   b. **Dose modification.** Give cautiously to patients with hepatic dysfunction.
   c. **Dose:** 200 to 260 mg/m^2 PO daily in divided doses for 14 to 21 days, then repeated every 28 days when recovery permits
   d. **Drug interactions.** Cimetidine may inhibit metabolism. Barbiturates may enhance metabolism. Monamine oxidase inhibitors may result in severe orthostatic hypotension.
G. **Anagrelide** (Agrylin)
1. **Indications.** Thrombocytosis in myeloproliferative disorders
2. **Pharmacology**
   a. **Mechanisms.** Anagrelide reduces the platelet count by uncertain mechanisms. It does not affect the leukocyte count and does not affect DNA synthesis.
   b. **Metabolism.** The drug is extensively metabolized, and less than 1% is excreted in the urine as unaltered drug.
3. **Toxicity.** Adverse effects are treated symptomatically and usually abate upon continuation of therapy. Cardiovascular complications that occur are usually related to underlying diseases.
   a. **Dose-limiting.** Thrombocytopenia
   b. **Common.** Headache (45%), palpitations, tachycardia, fluid retention, diarrhea, bloating, abdominal pain, asthenia, dizziness
   c. **Occasional.** Nausea, vomiting, other GI disturbances; other painful sites, dyspnea, paresthesia, rash, fever
4. **Administration.** Platelet counts should be monitored every 2 to 7 days until maintenance dosage is attained.
   a. **Supplied** as 0.5 and 1 mg capsules
   b. **Dose modification.** None for renal or hepatic dysfunction
   c. **Dose:** Start at 0.5 mg q.i.d. or 1 mg b.i.d. PO; increase dosage weekly by 0.5 mg/day until the desired platelet count is achieved. Maximum recommended dosages are 10 mg/day or 2.5 mg/dose.

VII. Hormonal agents

A. **Adrenocorticosteroids**
1. **Indications.** Broad variety of oncologic problems that include the following:
   a. Component of combination chemotherapy regimens
   b. Symptomatic lymphangitic lung carcinomatosis; bronchial obstruction by tumor
   c. Symptomatic brain metastases with or without cerebral edema; spinal cord compression

d. Painful liver metastases
  e. Immune-mediated cytopenias
  f. Prevention of chemotherapy-induced vomiting
  g. Appetite stimulant and mood elevator in patients with far advanced cancer
2. **Toxicity and side effects** (usually associated with long-term therapy)
  a. Peptic ulcer disease
  b. Sodium retention (edema, heart failure, hypertension)
  c. Potassium wasting (hypokalemia, alkalosis, muscle weakness)
  d. Glucose intolerance, accumulation of fat on trunk and face, weight gain
  e. Proximal myopathy
  f. Personality changes, including euphoria and psychosis
  g. Osteoporosis, aseptic hip necrosis
  h. Thinning and fragility of the skin
  i. Suppression of the pituitary-adrenal axis
  j. Susceptibility to infection
3. **Administration.** Patients receiving high doses of corticosteroids are given prophylactic oral antacid therapy. Methylprednisolone is preferred for patients with severe hepatic dysfunction. Dexamethasone is preferred for peritumoral edema. These drugs are supplied in a wide variety of dosages, as follows:
  a. **Prednisone** (Deltasone, Orasone, and others): 1.0-, 2.5-, 5.0-, 10-, 20-, 25-, and 50-mg tablets and 1- and 5-mg/mL oral solutions
  b. **Methylprednisolone** (Medrol and others): 2-, 4-, 8-, 16-, 24-, and 32-mg tablets
  c. **Dexamethasone** (Decadron, Hexadrol, and others): 0.25-, 0.5-, 0.75-, 1.0-, 1.5-, 2.0-, 4.0-, and 6.0-mg tablets and 0.5 to 1.0 mg/mL elixir
B. **Adrenal inhibitors**
  1. **Aminoglutethimide** (Cytadren)
    a. **Indications.** Cushing's syndrome, breast cancer, prostate cancer
    b. **Pharmacology.** An aromatase enzyme inhibitor that inhibits adrenocortical conversion of cholesterol to pregnenolone and blocks peripheral conversion of androgens to estrogens
    c. **Toxicity**
      1. **Dose-limiting.** Adrenal insufficiency; postural hypotension (hypoaldosteronism)
      2. **Common.** Mild GI upset; transient maculopapular eruptions associated with fever (these remit in about 6 days without stopping the drug); transient fatigue; drowsiness (resolves about 6 weeks after starting treatment)
      3. **Occasional.** Cerebellar signs, hypercholesterolemia, virilization, myalgia, fever, leg cramps
      4. **Rare.** Myelosuppression, desquamation, oral ulcers, hypothyroidism, lupus hepatitis–like syndrome
    d. **Administration**
      1. **Supplied** as 250-mg tablets
      2. **Dose:** Start at 250 mg PO b.i.d. (with hydrocortisone, 100 mg/ day) for 2 weeks; then increase dose to 250 mg PO q.i.d., and decrease hydrocortisone to 10 mg in the morning and at 5:00 pm and 20 mg at bedtime. The hydrocortisone prevents overriding of the adrenal blockade by inhibiting pituitary adrenocorticotropic hormone secretion.
      3. **Drug interactions.** Aminoglutethimide induces the metabolism of warfarin, theophylline, digoxin, dexamethasone, and medroxyprogesterone; larger doses of these drugs may be needed.
  2. **Anastrozole and letrozole** (aromatase inhibitors)
    a. **Indication.** Metastatic breast cancer
    b. **Pharmacology.** These nonsteroidal inhibitors interfere with aromatase, the enzyme that converts androstenedione from the adrenals and peripheral tissues to estrone, which is further converted to estradiol.
    c. **Toxicity.** Antiestrogen effects, peripheral edema, thromboembolism, vaginal bleeding
    d. **Dose.**
      1. **Anastrozole** (Arimidex): 1 mg PO daily (supplied as 1-mg tablets)
      2. **Letrozole** (Femara): 2.5 mg PO daily (supplied as 2.5-mg tablets)
  3. **Mitotane** (*o,p'*-DDD, Lysodren)
    a. **Indications.** Adrenal carcinoma, ectopic Cushing's syndrome
    b. **Pharmacology**
      1. **Mechanism.** Causes adrenal cortical atrophy; the exact mechanism is unknown. Blocks adrenocorticoid synthesis in normal and malignant cells. Aldosterone synthesis is not affected.
      2. **Metabolism.** Degraded slowly in the liver and extensively distributed in fatty tissues. Its action is antagonized by spironolactone; the two drugs should not be administered together. Metabolites are excreted in the bile and urine.
    c. **Toxicity**
      1. **Dose-limiting.** Nausea and vomiting; adrenocortical insufficiency
      2. **Common.** Diarrhea, depression, lethargy, maculopapular rash
      3. **Occasional.** Orthostatic hypotension; abnormal LFTs; irritability, confusion, tremors; diplopia, retinopathy, lens opacity; myalgia; hemorrhagic cystitis, fever
    d. **Administration.** Plasma cortisol levels should be monitored periodically to assess the effectiveness of treatment and the possible development of adrenal insufficiency. Glucocorticoid and mineralocorticoid replacement therapy may be necessary.
      1. **Supplied** as 500-mg tablets
      2. **Dose modification.** Reduce dose for patients with hepatic impairment.
      3. **Dose:** 2 to 6 g PO daily in three divided doses; increase to 10 g daily as tolerated.
C. **Androgens**
  1. **Indications.** Breast carcinoma, short-range anabolic effect, stimulation of erythropoiesis
  2. **Toxicity and side effects** vary among preparations. Virilization, fluid retention, and hepatotoxicity, which is characterized by abnormal LFTs or cholestasis and is usually reversible, are frequent with certain preparations. May cause hypercalcemia in immobilized patients.
  3. **Administration.** Use with caution in patients with cardiac, hepatic, or renal disease.
    a. **Fluoxymesterone** (Halotestin and others): 10 to 40 mg/day in two to four divided doses (supplied as 2-, 5-, and 10-mg tablets)
    b. **Methyltestosterone** (Android and others): 50 to 200 mg/day in two or three divided doses (supplied as 10- and 25-mg tablets)
D. **Antiandrogens** (bicalutamide, flutamide, nilutamide)
  1. **Indications.** Prostate cancer in combination with medical therapy (see section VII.G) or orchiectomy that reduces testicular but not adrenal androgen production.
  2. **Pharmacology.** Nonsteroidal antiandrogens bind to cytosol androgen receptors and competitively inhibit the uptake or binding of androgens in target tissues. The drugs are almost totally metabolized.
  3. **Toxicity** (may be contributed to by the combined therapeutic component)
    a. **Common.** Impotence, gynecomastia, and other manifestations of hypogonadism, diarrhea
    b. **Occasional.** Nausea and vomiting, myalgia, depression; mild hypertension or pulmonary disorder (bicalutamide, nilutamide)
    c. **Rare.** Hepatitis, including cholestatic jaundice (all three), hemolytic anemia or methemoglobinemia (flutamide), iron-deficiency anemia (bicalutamide), interstitial pneumonitis, or visual disturbances (nilutamide)
  4. **Administration.** Usually given in combination with luteinizing hormone-releasing hormone (LHRH) agonist analogues (see section VII.G). Use with caution in patients with hepatic dysfunction.
    a. **Bicalutamide** (Casodex): 50 mg PO once daily (supplied as 50 mg tablets)
    b. **Flutamide** (Eulexin): 250 mg t.i.d. PO (supplied as 125-mg capsules)
    c. **Nilutamide** (Nilandron): 300 mg once daily PO for 30 days, then 150 mg daily (supplied as 50 mg tablets)
E. **Antiestrogens** (tamoxifen, toremifene)
  1. **Indication.** Breast carcinoma
  2. **Pharmacology:** Nonsteroidal agents that bind to estrogen receptors and may exert antiestrogenic, estrogenic, or both activities
  3. **Toxicity** (derived from tamoxifen, which is associated with the greater experience)
    a. **Common.** Hot flashes, menstrual changes, vaginal discharge, uterine bleeding; lowered serum cholesterol (especially low-density cholesterol); thrombocytopenia (mild and transient)
    b. **Occasional.** Retinopathy or keratopathy (reversible), cataracts; leukopenia, anemia; nausea, vomiting; hair loss (mild), rash; "flare" in first month of therapy of patients with bone metastases; thrombophlebitis or thromboembolism, particularly in patients with cofactors for thrombosis (e.g., inheritance of

factor V Leiden)

  c. **Rare.** Abnormal LFTs; altered mental state; slightly increased occurrence of endometrial adenocarcinoma on prolonged use
  4. **Administration**
    a. **Tamoxifen** (Nolvadex): 20 mg PO once daily (supplied as 10- and 20-mg tablets)
    b. **Toremifene** (Fareston): 60 mg PO once daily (supplied as 60-mg tablets)
F. **Estrogens** (diethylstilbestrol [DES])
  1. **Indications.** Breast carcinoma
  2. **Toxicity.** Nausea, uterine bleeding; hypercalcemic "flare"; thromboembolic disorders; abnormal LFTs, cholestatic jaundice (rare); chloasma, optic neuritis, retinal thrombosis; rash, pruritus; fluid retention, hypertension, headache, dizziness, hypertriglyceridemia
  3. **Administration**
    a. **Supplied** as 0.25-, 0.5-, 1.0-, and 5.0-mg tablets
    b. **Dose:** 1 to 15 mg PO daily in divided doses
G. **Luteinizing hormone-releasing hormone (LHRH) agonists**
  1. **Indications.** Prostate and breast cancer
  2. **Pharmacology.** LHRH agonist analogues decrease serum levels of luteinizing hormone and follicle-stimulating hormone and result in castration levels of testosterone in men and of estradiol in women within 2 weeks of treatment.
  3. **Toxicity and side effects**
    a. **Common.** Hot flashes, decreased libido; impotence and gynecomastia in men; amenorrhea and uterine bleeding in women
    b. **Occasional.** Hypercholesterolemia, local discomfort at site of injection
    c. **Rare.** GI upset, rash, hypertension, azotemia, headache, depression
  4. **Administration**
    a. **Leuprolide** (Lupron)
      1. **Supplied** as 7.5-, 22.5-, and 30-mg vials
      2. **Dose:** 7.5-, 22.5-, or 30-mg IM every 1, 3, or 4 months, respectively
    b. **Goserelin** (Zoladex)
      1. **Supplied** as 3.6- and 10.8-mg pellets in prefilled syringe
      2. **Dose:** 3.6 mg SC monthly or 10.8 mg every 3 months
H. **Progestins**
  1. **Indications.** Endometrial and breast carcinomas; or as an appetite stimulant in malignant cachexia; or for hot flashes in patients with breast carcinoma
  2. **Toxicity and side effects**
    a. Menstrual changes, uterine bleeding, hot flashes, gynecomastia, galactorrhea
    b. Fluid retention, thrombophlebitis, thromboembolism
    c. Nervousness, somnolence, depression, headache
  3. **Administration**
    a. **Medroxyprogesterone acetate injectable** (Depo-Provera)
      1. **Supplied** as vials containing 150 or 400 mg/mL
      2. **Dose for hot flashes:** 150 mg IM every 3 months
      3. **Dose for endometrial carcinoma:** 1 g IM weekly for six doses, then monthly
    b. **Megestrol** (Megace)
      1. **Supplied** as 20- and 40-mg tablets and 40 mg/mL suspension
      2. **Dose for breast cancer:** 40 mg PO q.i.d.
      3. **Dose for endometrial cancer:** 20 to 80 mg q.i.d.
      4. **Dose for appetite stimulation:** 400 to 800 mg PO daily as a single dose

VIII. Cytoprotective agents

A. **Amifostine** (Ethyol)
  1. **Indications.** Protection against cumulative nephrotoxicity from cisplatin-based therapies. The drug may also reduce cisplatin's cumulative neurotoxicity and hematotoxicity.
  2. **Pharmacology**
    a. **Mechanisms.** It is a prodrug that is dephosphorylated in tissues to an active free thiol metabolite that binds to and detoxifies reactive metabolites of cisplatin and scavenges free radicals.
    b. **Metabolism.** Rapidly metabolized to an active free thiol metabolite, which is further converted to a less active disulfide metabolite. The estimated plasma half-life is 8 minutes.
  3. **Toxicity**
    a. **Dose-limiting.** Hypotension (more than 60% of patients) is treated with fluid infusion and changes in posture.
    b. **Common.** Hypotension, nausea, and vomiting
    c. **Occasional.** Hypocalcemia, flushing, dizziness, somnolence, hiccups
    d. **Rare.** Transient loss of consciousness, allergic reaction
  4. **Administration.** Patients should be well hydrated before amifostine is administered. Antiemetics, including dexamethasone and a serotonin receptor antagonist, should be administered before amifostine.
    a. **Supplied** as 500-mg vials
    b. **Dose modification.** The infusion should be interrupted if systolic blood pressure decreases significantly.
    c. **Dose:** 910 mg/m^2 over 15 minutes, starting 30 minutes before chemotherapy (740 mg/m^2 if hypotension does not correct itself 5 minutes after interrupting the infusion)
    d. **Drug interactions.** Drugs that could potentiate hypotension should not be administered in conjunction with amifostine.
B. **Dexrazoxane** (Zinecard)
  1. **Indications.** To reduce the incidence and severity of doxorubicin cardiotoxicity
  2. **Pharmacology.** The drug is converted to a chelating agent that interferes with iron-mediated free radical generation that is thought to be responsible, in part, for anthracycline-induced cardiomyopathy.
  3. **Toxicity.** Added myelosuppression; pain at injection site
  4. **Administration.** This drug can be begun when the patient has received 300 mg/m^2 of doxorubicin and is expected to be continued on that therapy.
    a. **Supplied** as 250- and 500-mg vials
    b. **Dose modification.** None
    c. **Dose.** The dexrazoxane dose is 10 times the doxorubicin dose, which is given within 30 minutes of starting this chemoprotective agent.

IX. Monoclonal antibodies

A. **Monoclonal antibodies** have the advantage of relative selectivity for tumor tissue and relative lack of toxicity. Major problems using them for therapy are technical and the development of human antimouse antibodies (see "hybridomas" in Chapter 1, Cancer Biology and Oncogenesis: A Primer, section III.A).
  1. **Biologic effects.** Monoclonal antibodies can attack certain cells directly (e.g., malignant lymphocytes exposed to a selective monoclonal antibody are lysed in the presence of complement). Various radioactive and chemotherapeutic agents can be conjugated to monoclones, which deliver these agents specifically to cancer cells. Plant toxins (e.g., ricin, abrin), bacterial toxins (*Pseudomonas* endotoxin A, diphtheria toxin), or ribosome-inactivating protein can also be conjugated to monoclonal antibodies as *immunotoxins.* Growth factors (e.g., interleukins, epidermal growth factor, tumor growth factor) can sometimes be used as carriers for toxins; these constructs are called *oncotoxins.*
  2. **Clinical uses**
    a. Imaging of tumors using radioisotope-labeled monoclones
    b. Selectively "purging" bone marrow of cancer cells
    c. Treatment of specific tumors; rituximab and trastuzumab are available commercially
B. **Rituximab** (Rituxan)
  1. **Indications.** Relapsed or refractory low-grade or follicular CD20-positive, B-cell non-Hodgkin lymphoma
  2. **Pharmacology**

a. **Mechanisms.** The rituximab antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. *In vitro,* the Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis.

b. **Metabolism.** Rituximab has been detectable in the serum 3 to 6 months after completion of treatment. Administration results in a rapid and sustained depletion of circulating and tissue-based B cells. B-cell levels return to normal by 12 months after completion of treatment.

3. **Toxicity**

   a. **Dose-limiting.** Hypersensitivity reactions, serious cardiac arrhythmias

   b. **Common.** An *infusion-related symptom complex* responds to slowing infusion rate and consists of fever or chills (50%); hypotension, bronchospasm with dyspnea, and angioedema; nausea, vomiting, fatigue, headache, rhinitis, pruritus, urticaria, and flushing. These symptoms generally develop 30 minutes to 2 hours after beginning the infusion.

   c. **Occasional.** Severe granulocytopenia or thrombocytopenia; arthralgia, malaise; diarrhea, dyspepsia, taste perversion; hypertension, postural hypotension, tachycardia, bradycardia; lacrimation, paresthesia, hypesthesia, agitation, insomnia; hyperglycemia, hypocalcemia; pain in chest, back, or tumor site.

4. **Administration.** During the first infusion, the initial rate should be 50 mg/hour; if hypersensitivity or infusion-related events do not occur, increase the infusion rate in 50-mg/hour increments up to a maximum of 400 mg/hour. Subsequent infusions can be started at 100 mg/hour and escalated by 100 mg/hour at 30-minute intervals. Corticosteroids, epinephrine, and antihistamines should be available for immediate use in the event of a severe hypersensitivity reaction during administration. Slowing the infusion rate, diphenhydramine and acetaminophen, bronchodilators, or saline infusion may be useful for the infusion-related symptom complex.

   a. **Supplied** as 10 mg/mL in 10- and 50-mL vials

   b. **Dose modification.** Infusion-related reactions respond to stopping the infusion and then resuming at a slower rate.

   c. **Dose:** 375 mg/m^2 IV weekly for 4 weeks

C. **Trastuzumab** (Herceptin)

   1. **Indications.** Metastatic breast cancer that overexpresses the HER2 protein and that was previously treated with one or more chemotherapy regimens

   2. **Pharmacology.** The *HER2* (or *c-erb-B2*) proto-oncogene encodes a transmembrane receptor protein that is structurally related to epidermal growth factor receptor. Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to the extracellular domain of *HER2.* The humanized Ig-Gk antibody against *HER2* is produced by a mammalian cell (Chinese hamster ovary) suspension culture. It inhibits the proliferation of tumor cells that overexpress *HER2.*

   3. **Toxicity**

      a. **Dose-limiting.** Cardiomyopathy

      b. **Common.** An *infusion-related symptom complex* develops in about 40% of patients during the first infusion and infrequently with subsequent infusions; it responds to symptom treatment without altering the rate of infusion. Fever and chills occur most frequently; nausea, vomiting, pain, rigors, headache, dizziness, dyspnea, hypotension, rash, and asthenia may also occur. Diarrhea, nausea, or vomiting occurs in about 25%.

      c. **Occasional.** Hematosuppression

   4. **Administration.** Monitor electrocardiogram or ejection fraction in these patients during ongoing therapy.

      a. **Supplied** as 440-mg vial

      b. **Dose modification.** Use with extreme caution in patients with preexisting cardiac dysfunction or prior cardiotoxic therapy.

      c. **Dose:** initial dose, 4 mg/kg over 90 minutes; maintenance dose, 2 mg/kg/week over 30 minutes

X. Hematopoietic growth factors have had a major effect on cancer treatment. Their theoretical benefits have been transformed into widespread clinical use and increasing costs to treat the same diseases. Perceived and potential benefit, however, is not always translated into proven effectiveness. None of these agents have clearly improved survival.

A. **Erythropoietin** (EPO, rhEPO, epoietin-alfa, recombinant human erythropoietin; Epogen, Procrit).

   1. **Justification for use in the cancer patient.** Cancer patients in general have an inappropriately low EPO response for the degree of cancer-related anemia. EPO supplementation, often in high doses, has been shown in phase III studies to increase hemoglobin levels and decrease transfusion use. EPO has also been effective in improving quality-of-life measurements reported by the treated patients. The alternative to EPO is ignoring anemia until it threatens physiologic functions or increasing hemoglobin levels with red blood cell transfusions. The important financial issues involved (the relatively high cost of the drug and definition of the payor) are intimately related to the problem of justification of this form of treatment; these issues are fully recognized but are not judged here. The value of treatment with EPO remains controversial at this time.

   2. **Supplied** as 2000, 3000, 4000, 10,000, and 20,000 U in 1-mL vials

   3. **Toxicity.** Hypertension, particularly with renal failure; shunt clotting in dialysis patients; allergic reactions (rare); possible thrombotic vascular events in patients with vascular disease (rare)

   4. **Dose.** For patients with chemotherapy-induced anemia: 150 to 300 U/kg SC three times weekly (higher doses are not helpful). For patients with chronic renal failure or human immunodeficiency virus infection on zidovudine therapy: 50 to 100 U/kg SC three times weekly to start; maintenance dose is 25 U/kg three times weekly. This therapy may decrease the transfusion requirement within 8 to 12 weeks of starting treatment; the target hematocrit is 30% to 33%.

B. **Colony-stimulating factors** (CSFs)

   1. **Justification for use in the cancer patient.** CSFs have gained widespread use in the management of patients undergoing chemotherapy. However, most of the clinical use is not supported by controlled trials designed to demonstrate efficacy. The end points that support criticism of its use are overall survival, disease-free survival, and decreased days in the hospital. Unfortunately, survival has not been improved for most cancers treated with chemotherapy in combination with CSFs.

      a. **Justified uses for CSF:**

         1. Priming of autologous or allogenic progenitor stem cells for stem cell transplantation
         2. Reconstitution after priming of stem cells shortens hospital stays by about 3 days (can be started 5 days after high-dose chemotherapy)
         3. Induction therapy of acute myelogenous or lymphoblastic leukemias (shortens hospital stays by about 5 days)

      b. **Other uses for CSF:**

         1. Treatment of febrile neutropenia
         2. Primary prophylaxis of febrile neutropenia with routine chemotherapy
         3. Prophylaxis of febrile neutropenia when the patient previously experienced febrile neutropenia
         4. Treatment of afebrile neutropenia (shortens period of neutropenia by about 2 days)

   2. **Filgastrim** (granulocyte colony-stimulating factor [G-CSF], Neupogen) stimulates granulocyte colony-forming units (CFU).

      a. **Supplied** as 300-μg (1-mL) and 480-μg (1.6-mL) vials

      b. **Toxicity.** Transient bone pain (20% incidence) usually resolves without stopping treatment. Although splenomegaly is relatively common in patients receiving long-term therapy, it is rarely of clinical significance. Local inflammation at the injection site and mild LFT abnormalities may occur; other side effects are rare.

      c. **Dose:** 5 μg/kg/day SC or IV beginning no earlier than 24 hours after administering the last dose of chemotherapy. Administration is stopped when the absolute neutrophil count exceeds 10,000/μL; the white blood cell count decreases by 50% within 1 to 2 days. The dosage may be increased, but doses exceeding 10 μg/kg/day probably are not helpful.

   3. **Sargramostim** (granulocyte-macrophage-CSF [GM-CSF]; Leukine) stimulates granulocyte-macrophage CFU and megakaryocyte CFU.

      a. **Supplied** as 250- and 500-μg vials

      b. **Toxicity.** At low doses (5 μg/kg/day), side effects are similar to those caused by G-CSF. Fever, flu-like syndrome, and hypersensitivity reactions are more likely with GM-CSF preparations than with G-CSF. Diarrhea, asthenia, rash, malaise, and fluid retention (peripheral edema, effusions) may also occur. At transplantation doses, a capillary-leak syndrome and its wide range of related side effects can occur.

      c. **Dose:** 250 μg/m^2/day; the methods of administration vary among institutions. In acute leukemia, the dose is given about 11 days after completion of induction chemotherapy when the marrow is shown to be hypoplastic. In mobilization of progenitors in peripheral blood, it is given beginning immediately after infusion of progenitor cells. In myeloid reconstitution after bone marrow transplantation, it is given beginning 2 to 4 hours after bone marrow infusion.

C. **Platelet growth factors**

   1. **Justification for use in the cancer patient.** Interleukin-11 (IL-11) is the only commercially available thrombopoietic cytokine and has been approved for the prevention of thrombocytopenia in patients who experience severe thrombocytopenia (less than 20,000/μL) after previous chemotherapy (i.e., for "secondary prophylaxis"). The need for platelet transfusions are reduced with this drug, but not eliminated. IL-11 is not indicated after myeloablative therapy. Its effectiveness after drugs that cause delayed cytopenias (e.g., mitomycin, BCNU) is not yet known.

   2. **Oprelvekin** (IL-11, Neumega) differs from native IL-11 by a single amino acid.

      a. **Supplied** as 5-mg vials

      b. **Toxicity.** Reversible, mild to moderate fluid retention with dilutional anemia (responds to diuretics); transient atrial arrhythmias or visual blurring

c. **Dose:** 50 μg/kg SC daily beginning 6 to 24 hours after completion of chemotherapy and continuing until the platelet count is 50,000/μL or higher. Platelet counts usually begin to rise 5 to 9 days after starting dosing.

3. **Thrombopoietin.** The ligand for the *c-mpι* oncogene plays a central role in the control of megakaryocytopoiesis and thrombopoiesis; the scientific name for this molecule is *Mpl ligand.* Thrombopoietin is the native or biologic form of Mpl ligand. Recombinant human megakaryocyte growth and development factor (rHuMGDF) is a truncated form of Mpl ligand with identical biologic activity. The pegylated form (PEG-rHuMGDF) is more potent than the nonpegylated molecule but has been abandoned because of the development of neutralizing antibodies and other problems. The search for a clinically useful thrombopoietin goes on.

XI. Other biologic and investigational therapies

A. **Interferon-a** (IFN-a)
1. **Sources:** Lymphocytes, macrophages, and other cells
2. **Properties of IFN-a**
   a. Antitumor activity
   b. Antiproliferative activity
   c. Inhibition of angiogenesis
   d. Regulation of differentiation
   e. Interaction with growth factors, oncogenes, other cytokines
   f. Enhancement of tumor-associated antigens
   g. Natural killer (NK) cell activation, cytotoxic T-lymphocyte (CTL) activation, induction of major histocompatibility complex (MHC) class I
   h. Antiviral activity
3. **Clinical uses**
   a. Response rates reported to be 75% to 90% in previously untreated patients: chronic myelogenous leukemia (chronic phase), hairy cell leukemia, myeloproliferative disorders, cutaneous T-cell lymphomas
   b. Response rates reported to be 40% to 50% in low-grade lymphomas, multiple myeloma
   c. Condylomata acuminata, chronic granulomatous disease, hepatitis C, adjuvant therapy for melanoma
4. **Dose.** A wide range of doses and schedules have been used, depending on the condition (from 2 to 10 to 36 million U/m^2 are given SC for from 3 to 7 days weekly).
5. **Toxicities** (depend on dose and schedule). Flu-like symptoms (75% to 100%) may be dose-limiting, develop in 1 to 2 hours, and peak 4 to 8 hours after injection. Malaise, headache, rashes (40% to 50%), GI complaints (20% to 40%), mild leukopenia or thrombocytopenia, elevated LFTs (30%), neurologic complaints, chronic fatigue (can be dose-limiting)
6. **Supplied** as recombinant forms
   a. IFN-a2a (Roferon-A): 3-, 6-, 18-, and 36-million U/mL vials
   b. IFN-a2b (Intron-A): 3-, 5-, 18-, and 50-million U/mL vials
B. **IL-2** plays a major role in immune regulation. The primary action of IL-2 is to stimulate growth of activated T cells that bear IL-2 receptors. The binding of antigen in conjunction with IL-1 stimulates T cells to release IL-2, which signals further lymphocyte mitogenesis.
1. **Clinical uses.** Approved by the Food and Drug Administration for the treatment of metastatic renal cell carcinoma and melanoma
2. **Dose**
   a. High dose regimens administer 600,000 to 720,000 IU/kg every 8 hours for 5 consecutive days for two cycles separated by 7 to 10 days. The course of treatment is repeated for patients who respond.
   b. Low-dose regimens are being investigated. An example for renal cell carcinoma is 6 million U/m^2 by continous IV infusion (via 48-hour cassettes) for 4 days weekly for 4 weeks in conjunction with IFN-a, 6 million U/m^2 given SC twice weekly.
3. **Toxicity.** High-dose therapy with IL-2 is highly toxic; it induces vascular permeability and promotes secretion of other lymphokines (such as IFN- g) with their own sets of toxicities. These developments result in fluid retention and interstitial edema in several organ systems that appear to be reversible after administration of IL-2 ceases.
4. **Supplied** as recombinant IL-2 (aldesleukin, Proleukin) in 18-million IU vials
5. **Adoptive immunotherapy** involves the transfer of tumor-infiltrating lymphocytes (TILs) or lymphokine-activated killer (LAK) cells interacted with IL-2 to the host bearing the tumor. These cells have characteristics of non–MHC-restricted killer cells and are distinct from CTL and NK cells. Tumor regressions have been observed in 10% to 20% of patients with metastases from renal and other cancers.
   a. **CTLs** destroy other lymphocytes that have acquired viral or tumor antigens. IFN and IL-2 stimulate CTLs. The target cells must be of the same histocompatibility type as the cytotoxic T cell. **NK cells** (large lymphocytes with cytoplasmic granules) directly kill tumor cells. The activity and proliferation of NK cells are stimulated by a variety of lymphokines, including IFN and IL-2.
   b. **LAK cells** are collected by lymphocytapheresis and activated *ex vivo* by incubation with IL-2. Activated LAK cells acquire broad cytolytic activity against tumor cells. **TILs** can recognize tumor-associated antigens and accumulate in virtually all types of human tumors. Administration of TILs with IL-2 appears to be 50 to 100 times more effective than LAK cells with IL-2.
C. **Investigational therapies**
1. **Differentiating agents** induce cancer cells to mature along the expected pattern for the tissue of origin. Although a large number of agents have induced differentiation *in vitro,* the use of single agents to induce differentiation *in vivc* and regression of advanced cancer has been clinically disappointing; the singular exception is all-*trans*-retinoic acid in treating acute promyelocytic leukemia (see [Chapter 25]). Additionally, isoretinoin (13-*cis*-retinoic acid) has been effective in reversing oral leukoplakia and is being evaluated in various neoplasms of squamous epithelium. Many other agents showed promise and have been tested, including 1,25-dihydroxyvitamin D3, dimethyl sulfoxide, cytosine arabinoside, phorbol esters, interferons, cyclic adenosine monophosphate analogues, and others.
2. **Gene therapy** can be defined as a therapeutic technique in which a functioning gene is inserted into a patient's cells to provide a gene or gene product that is missing, to provide a new gene or gene product, to modify the immune response, or to remove or inactivate an existing gene. With the explosion of scientific advances in this area, new possibilities for cancer therapy have emerged. Some possibilities are the following:
   a. **Gene-modified TIL.** Although TILs can be specifically lytic, it appears that the secretion of cytokines, such as IFN- g and tumor necrosis factor (TNF), is the best correlate of the antitumor effectiveness of TILs. TILs depend on IL-2 for their continued survival. Clinical trials are underway using TIL transduced with the gene for TNF with the vision that transduction with the gene for IL-2 receptors may lessen the need for high doses of IL-2.
   b. **Cytokine genes** have been introduced into a variety of animal tumors in an attempt to increase immunogenicity. Examples of genes that have been inserted include those for IL-2, IL-4, TNF, IFN- g, and G-CSF.
   c. **Antisense genes** may be injected in tumors in an attempt to block expression of oncogenes.
   d. **Retroviral producer lines** may be injected into tumors in an attempt to introduce "suicide" genes into cancer cells.
   e. **Bone marrow cells** are being subjected to gene modification in an attempt to increase resistance to chemotherapeutic agents.
3. **Antisense oligonucleotides** are short fragments of DNA that are complementary to the "sense" strand of mRNA. These molecules theoretically can inhibit the function of mRNA, which normally is translated into protein in the cytoplasm by ribosomes. If the protein is vital for cellular growth and reproduction, its inhibition could result in diminished cell viability. The use of antisense oligonucleotides as inhibitors of gene expression represents another genetically based therapeutic approach to cancer.
4. **Circadian chronobiology.** Three major biologic rhythms have been defined that correspond to the periodic changes in the environment: the solar day (circadian rhythm), the lunar month (circumtrigentan rhythm), and the year (circannual rhythm). Circadian rhythms are observable and reproducible for many biochemical and physiologic events in human beings, including activity, pulse, temperature, blood pressure, certain serum chemistry values, cell proliferation, tumor cell proliferation, and drug pharmacology. The suprachiasmatic nucleus of the hypothalamus appears to be the site of important circadian pacemaker cells in mammals. Data suggest that therapeutic effect may be maximized and toxicity minimized for cytotoxic drugs administered at selected times of day.

Chapter 5 Supportive Care

Dennis A. Casciato and Barry B. Lowitz

I. Pain

A. **Occurrence and attitudes.** The incidence of pain in cancer patients increases with progression of disease and ultimately affects 70% of all patients and as many as 90% of those with advanced disease. Cancer therapies cause about 20% of the pain syndromes. About 50% of physicians in a recent multicenter study believed that they gave their cancer patients insufficient analgesic drugs for pain control, and 30% indicated they would not use maximally effective analgesic doses until they felt that the patient's life expectancy was less than 6 months. Ineffective analgesia is typically the result of inappropriate concerns by physicians and patients about addiction and development of tolerance. Cancer pain can be completely controlled by medication in about 80% of patients who are treated with a stepped therapeutic approach.

B. **Assessment of pain in cancer patients**
1. **Differential diagnosis of pain.** Pain is a nonspecific symptom that can result from unrelated benign diseases, effects of treatment, paraneoplastic syndromes, or the direct mechanical effects of the cancer. Pain determined to result from direct mechanical effects of a cancer must be assessed in terms of whether the underlying disease can be treated to relieve the pain. To provide effective pain treatment, differential diagnoses with proper history, physical examination, and appropriate laboratory studies are required.
2. **Patient self-assessment** is the most reliable guide to both the cause of the pain and the effectiveness of pain treatment. A log should be kept to track the times that the pain is worst, the intensity of the pain, the times and doses of pain medications or other analgesic measures, and the response to these measures.

   Different simple scales of pain intensity are used. One way to assess pain intensity is using a scale of 1 to 5 (1 is for absence of pain, 2 for barely noticeable pain, 3 for pain that interferes with sleep and limits concentration or other activities, 4 for pain severe enough to interfere completely with all normal activities, and 5 for intolerable pain). Another example is a pain scale of 0 to 10 (0 is for the absence of pain and 10 is for the most severe pain imaginable to the patient). The physician uses the log to adjust dosage and timing or analgesic medications or to change therapy.

3. **Chronic pain leads to medical (psychiatric) depression,** which progressively lowers the pain threshold and creates a "positive-feedback" cycle of pain and depression. Pain exhausts patients through loss of sleep, chronic fatigue, and inability to exercise; all of these problems cause or reflect depression. Assessment of pain includes assessment of symptoms of depression, including loss of energy, abnormal sleep patterns, loss of appetite, loss of interest, and decreased ability for "cognitive distraction." Some of these symptoms are mistaken for signs of progressive cancer. Because both pain and depression can be successfully treated, evaluation for depression is an essential part of pain management.

C. **Principles of pain management in cancer patients** when the underlying cause cannot be treated effectively
1. **Ideally, the goal of cancer pain management is complete relief of pain.** Even when this is not possible, maximizing pain control improves overall functioning, provides for more restful sleep, and relieves depression.
2. **Pharmacologic step management of cancer pain.** The World Health Organization has designed a three-step approach to the systemic pharmacologic management of pain.
   a. If there is an inflammatory component to the pain, nonsteroidal anti-inflammatory drugs (NSAIDs) are used (see section I.D). Adjuvant drugs are combined as indicated for associated symptoms (see section I.E). These analgesics are used in optimal doses and not "pushed to toxicity," which can cause organ damage.
   b. For mild or moderate pain that is not fully controlled or that is progressing with the above measures, combinations of opioids and nonopioid analgesics (see section F.1.d and section F.1.e) are used alone or combined with adjuvant drugs as indicated.
   c. For moderate pain or any pain not responding to the above steps, morphine or other related drugs with the same pharmacologic properties are used (see section F.1 and section F.2). Adjuvants are employed as needed. The morphine opioids do not cause any known dose-related damage to organs. The main precaution is that some of the adjuvant drugs can potentiate the respiratory suppression.
3. **Localized pharmacologic analgesics and nonpharmacologic interventions for pain,** although not commonly required, are an important part of the armamentarium for pain control. These range from injections of glucocorticoid-lidocaine into isolated painful soft tissue areas, to nerve blocks, ganglion blocks, and neurosurgical procedures (see section H.3).
4. **Placebos are never indicated for the treatment of cancer pain.** Placebos are drugs with no known direct pharmacologic activity; they produce pain relief less than half as often as pharmacologically active drugs. Their mechanism of action appears to be mediated by "psychological triggering" of endorphins, which are the "natural opioids" of the brain and affect the same receptors as morphine.
5. **Physical dependence and tolerance** are invariable but insignificant side effects of prolonged use of opiate analgesics in cancer patients. If a patient becomes free of pain, however, a program of gradual tapering of the dose must be employed to prevent acute withdrawal symptoms.

   It is essential that health care personnel and patients do not confuse addiction with opioid tolerance and physical dependence resulting from the effective treatment of pain because this misconception invariably results in underdosing and inadequate pain control. Addiction is an unrelated medical disorder, with complex behavioral components. Unlike addicts, patients who are withdrawn from narcotics that are no longer needed for pain control are not predisposed to relapse.

6. **Ineffective analgesia.** The major reason for ineffective analgesia is insufficient doses of prescribed analgesics.
   a. Physicians largely underdose patients because of excessive concern about the dose and side effects of narcotics and fear of patient addiction.
   b. Patients are often reluctant to report pain because of concerns about distracting physicians from treatment of the underlying disease and fears that pain means that the disease is worse.
   c. Patients may be reluctant to take prescribed narcotics because of concerns about becoming tolerant to pain medications or being thought of as an addict and worries about unmanageable side effects.
   d. Failure to control pain with adequate analgesic therapy, however, usually indicates the existence of factors other than focal tissue damage.
7. **We strongly recommend against using the following analgesics** for cancer patients: meperidine (Demerol), pentazocine (Talwin), butorphanol (Stadol), nalbuphine (Nubain), denocine (Dalgan), levorphanol (Levo-Dromoran), Brompton's cocktail, propoxyphenes (Darvon, Darvon-N), and placebos. All of these drugs have pharmacologic properties that makes them risky or ineffective.

D. **Nonnarcotic analgesics**
1. **Acetaminophen** (AMP, Tylenol and others), 650 mg PO q.i.d., is nearly as effective as aspirin in both analgesic and antipyretic actions. AMP does not have the anti-inflammatory, ulcerogenic, or antiplatelet activities of aspirin.
2. **Salicylates**
   a. **Aspirin** (ASA, acetyl salicylic acid) is the standard against which other NSAIDs are compared. This analgesic is significantly more effective than placebo in patients with pain from cancer. Aspirin should not be used in patients with a history of the syndrome of nasal polyps and asthma, gastritis, peptic ulcer disease, or bleeding diathesis (including severe thrombocytopenia or concomitant use of anticoagulants). Aspirin can inhibit platelet aggregation for 1 week or more.
   b. **Other salicylates** are not associated with the antiplatelet activity of ASA because they do not have the acetyl moiety, although they do have similar

gastrointestinal (GI) side effects. Cancer patients with arthritis or other inflammatory illnesses who cannot take NSAIDs may benefit from these agents. An example is choline magnesium trisalicylate (Trilisate), 1000 to 1500 mg PO t.i.d.

3. **NSAIDs** may be especially useful in bone metastases, paraneoplastic periostitis, benign or paraneoplastic arthritis, and reflex sympathetic dystrophy. These drugs all suppress platelet function and can cause gastric ulcers and GI bleeding (see section D.4). Prescribing misoprostol (Cytotec), 100 μg q.i.d., can ameliorate the GI effects. Omeprazole (Prilosec), 20 mg PO q.d., which is approved only in short courses for the treatment of gastroesophageal reflux and duodenal ulcer disease, may be considered for longer-term use in patients with advanced cancer who have a good pain response to NSAIDs but who continue to have problems with peptic ulcers. Some useful NSAIDs are the following:
   a. Ibuprofen (several), 400 to 600 mg PO q.i.d.
   b. Nabumetone (Relafen), 500 to 1000 mg PO b.i.d.
   c. Etodolac (Lodine), 400 to 600 mg PO b.i.d.
   d. Indomethacin (Indocin), 25 to 50 mg PO t.i.d., is associated with more severe and frequent side effects than other NSAIDs. However, it has a short half-life and appears to provide more frequent and rapid relief from paraneoplastic periostitis and reflex sympathetic dystrophy.

4. **"Preferential" COX-2 inhibitors.** Cyclooxygenase (COX) compounds exist throughout the body. COX-1 is present in most tissues as "housekeeper" enzymes; they maintain normal gastric mucosa and influence kidney and platelet function. COX-2 is induced and increases in response to inflammation. Both COX-1 and COX-2 convert arachidonic acid to prostaglandin and are inhibited by NSAIDs. A new generation of NSAIDs "preferentially" inhibits COX-2 and is associated with much less GI irritation and bleeding and appears to have less effect on platelet function than traditional NSAIDs. These agents may prove to be useful in cancer patients because of their more favorable toxicity profile. The U.S. Food and Drug Administration has released two such drugs:
   a. Celecoxib (Celebrex), 100 to 200 mg PO q.d. to b.i.d.
   b. Rofecoxib (Vioxx), 50 mg PO q.d.

E. **Adjuvant drugs for cancer pain management**

1. **Corticosteroids.** Peritumoral edema contributes to pain by pressure on or stretching of adjacent structures. Dexamethasone or prednisone may rapidly ameliorate headache from brain tumor or carcinomatous meningitis or liver pain from metastases stretching the liver capsule. They also improve mood and appetite and exert anti-inflammatory and antiemetic effects.

2. **Pamidronate,** 90 mg IV infusion over 3 hours every 4 weeks, is the treatment of choice for bone pain and fracture prevention from osteolytic lesions of multiple myeloma. It may also be helpful in controlling bone pain in up to 25% of breast cancer patients.

3. **Neuropathic pain syndromes,** particularly if the pains are lancinating or ticlike, can often be treated with tricyclic antidepressants alone or in combination with anticonvulsant drugs. These drug combinations are often effective in treatment of peripheral neuralgias, postherpetic neuralgia, and tic douloureux. Typical doses are as follows:
   a. Antidepressant drugs (see section E.4)
   b. Phenytoin (Dilantin), 300 to 400 mg/day
   c. Carbamazepine (Tegretol), 400 to 800 mg/day
   d. Valproic acid (Depakene), 200 to 400 mg PO b.i.d. or t.i.d.
   e. Gabapentin (Neurontin), 100 to 400 mg t.i.d.

4. **Antidepressants** have innate analgesic properties and potentiate the analgesic effect of opioids. Depressed patients may focus excessively on their pain, and chronic pain syndromes aggravate depression. Antidepressants are useful for pain that has significant emotional components and may be helpful in neuropathic pain. Several weeks of therapy are required to produce an effect. Most antidepressants can cause irritability, especially in patients with dementias, as well as hypomanic episodes and dysphoria in patients with bipolar disorders.
   a. Paroxetine (Paxil) is useful for depression disorder and panic attacks. It may precipitate hypomanic episodes and is contraindicated with monoamine oxidase (MAO) inhibitors. Start with 20 mg in the morning (10 mg in the elderly), and escalate the dose gradually up to a maximum of 40 each morning. If a manic episode develops, stop and restart at a lower dose or change drugs.
   b. Bupropion hydrochloride (Wellbutrin) is a mood "brightener" that acts differently from other antidepressants. It often helps in depression that is associated with mild to moderate chronic pain and appears to give patients a feeling of renewed energy and function. It is contraindicated in patients with seizures. Dosing is initiated at 100 mg (75 mg in the elderly) in the morning and then titrated to 200 mg, and then to b.i.d.
   c. Nortriptyline (Pamelor) has fewer sedative and anticholinergic side effects than the traditionally used amitriptyline (Elavil). The starting dose is 25 mg PO h.s. (10 mg PO h.s. in frail patients); the dose is slowly escalated to 50 to 100 mg PO h.s.

5. **Anxiolytic agents**
   a. **Benzodiazepines.** Anxious or agitated patients often perceive anxiety as a painful sensation. Diazepam (Valium), alprazolam (Xanax), or lorazepam (Ativan) may be used if narcotic analgesics alone are not effective. These drugs should be avoided in patients with dementia and may produce paradoxical agitated, confusional states in some patients.
   b. **Antihistamines,** such as hydroxyzine (Atarax, Marax), 25 to 100 mg PO q.i.d., may be useful in the anxious patient as a mild anxiolytic agent with sedating, analgesic, antipruritic, and antiemetic properties.
   c. **Patients with chronic dementia** may become agitated and confused when they develop pain. These patients often benefit from a regimen of haloperidol (Haldol), 1 to 3 mg/day, with analgesics. This drug frequently causes extrapyramidal symptoms, such as Parkinson-like syndromes, torticollis, and swallowing problems. Diphenhydramine (Benadryl) and benzotropine mesylate (Cogentin) rapidly reverse extrapyramidal symptoms.

F. **Opioids** alter the perception of pain and are the prototypical agent for central pain control. The only significant differences among the various opioids are duration of action and the dose needed to produce the same analgesic effect. The only significant risk from this class of drugs is respiratory suppression. These drugs induce tolerance, and essentially unlimited doses can be used for pain control, titered according to whether there is evidence of respiratory suppression. "Ineffectiveness" observed while using opioids usually indicates underdosing; the analgesic effect and the duration of that effect increase as the dose is increased.

Some opiates (e.g., pentazocine) are not useful because they have combined agonist and antagonist effects. Methadone and levorphanol are long-acting opiates that accumulate and have plasma half-lives that are significantly longer than their analgesic effectiveness. Similarly, metabolites of meperidine accumulate when this drug is administered for prolonged periods. "Fully agonistic" opioids do not reverse or antagonize other full agonists given simultaneously, are the most useful for cancer pain therapy, and are the only opioids discussed here.

1. **Short-acting opioids**
   a. **Instant-release morphine sulfate** (MS) remains the standard against which other analgesics are measured. No other drug is clinically superior for pain relief. MS is available in parenteral, tablet, oral liquid, suppository, and sustained-action forms. MS is commercially available in instant-release preparations as follows:
      1. MSIR: 15- and 30-mg tablets and capsules, 10-mg per 5 mL and 20-mg per 5 mL elixirs in 120 mL bottles, and 20-mg per mL elixir in 30 and 120 mL bottles
      2. Roxanol: 20-mg per mL elixir in 30-, 120-, and 240-mL bottles
      3. RMS: 5-, 10-, 20-, and 30-mg suppositories
   b. **Hydromorphone** (Dilaudid). The duration of action is only 1 to 2 hours for small doses (2 mg) given orally. As with other opioids, higher doses result in longer durations of effect. Dilaudid is available as 1-, 2-, 3-, and 4-mg tablets; 3-mg suppositories; and 1-mg per 5 mL solution in 1-pint bottles.
   c. **Codeine** (methylmorphine) is available alone and in several combinations with ASA or AMP. The effects of sedation, respiratory depression, and addictive potential are less problematic for codeine than for morphine.
   d. **Hydrocodone** is available in combination with ASA or AMP as follows:
      1. Vicodin (with AMP): 5-mg/500, 7.5-mg/750 ("ES"), and 10-mg/ 660 ("HP") tablets
      2. Lortab (with AMP): 2.5-mg/500, 5-mg/500, 7.5-mg/500, and 10-mg/500 tablets; 7.5-mg/500 per 15 mL elixir in 1-pint bottles
      3. Lortab (with ASA): 5-mg/500 ("ASA") tablets
      4. Lorcet (with AMP): 5-mg/500 ("HD"), 7.5-mg/650 ("Plus"), and 10-mg/650 ("10/650") tablets
   e. **Oxycodone** is available alone and in combination with ASA or AMP as follows:
      1. Oxy IR: 5-mg capsules
      2. Oxyfast: 20-mg/mL elixir in 30-mL bottles
      3. Roxycodone: 5-mg tablets; 5 mg per 5 mL solution in 500-mL bottles
      4. Intensol: 20-mg/mL elixir in 30-mL bottles
      5. Roxicet (with AMP): 5-mg/325 tablets; 5-mg/500 caplets; and 5-mg with 325 mg AMP per 5 mL solution in 500-mL bottles
      6. Percocet (with AMP): 5-mg/325 tablets
      7. Percodan (with ASA): 4.5-mg/325 tablets

2. **Long-acting opioids.** Patients started on these drugs must be tolerant (i.e., no longer having sedative or respiratory suppressant effects) to equivalent daily analgesic doses of short-acting opiates.
   a. **Sustained-release MS** is the drug of choice for preventing chronic pain in patients with cancer. The analgesic effect peaks in 2 to 3 hours and lasts for

12 hours; dosing more frequently than every 12 hours usually is not necessary if adequate doses are given. It is started at a dose of 60 to 100 mg PO every 12 hours (15 to 30 mg for frail patients). Sustained-release MS is commercially available as follows:
  1. MS Contin: 15-, 30-, 60-, 100-, and 200-mg tablets. MS Contin should not be crushed, halved, or chewed but can be administered rectally.
  2. Oramorph-SR: 15-, 30-, 60-, and 100-mg tablets

  b. **Sustained-release oxycodone** has similar analgesic effect and dosing (every 12 hours) as sustained-release MS. It is started at a dose of 10 to 20 mg every 12 hours and is commercially available as Oxycontin in 10-, 20-, 40-, and 80-mg tablets.
  c. **Fentanyl transdermal patch** (Duragesic) contains a reservoir of the drug and is applied to the skin. The patch should be changed every 3 days (sometimes every 2 days). The peak analgesic effect is delayed for up to 3 days after applying and persists up to 24 hours after removing the patch. Fentanyl is started at a dose of 25 μg. Multiple patches can be worn simultaneously to increase the dose. Duragesic is available as patches delivering 25-, 50-, 75-, and 100-μg/hour in packages of five patches.

3. **Side effects of opioid analgesics** result mostly from their effect on the central nervous system (CNS) and on smooth muscle tone.
  a. **Respiratory system.** Respiratory depression is a potentially life-threatening complication of narcotic overdose, but patients generally develop tolerance to the respiratory depressant effects of these agents.
    1. For subacute respiratory depression, withhold one or two opioid doses until symptoms resolve.
    2. For acute respiratory depression, administer **naloxone** (Narcan) slowly. Naloxone produces no respiratory depression but can precipitate a full-blown withdrawal syndrome accompanied by rapid recurrence of severe pain when given in too high a dose. The reversal by naloxone lasts 20 to 40 minutes.
    3. The usual dose of naloxone is 0.4 mg (400 μg) every 3 to 5 minutes until respirations are 10 to 20 breaths/min. Titrate the naloxone dose to improve respiratory function without reversing analgesia (e.g., 0.04 to 0.08 mg [40 to 80 μg] every 1 to 2 minutes).
    4. If a patient received an overdose of a long-acting opioid, repeat doses of naloxone may be required every few hours for 24 to 72 hours.
  b. **GI effects** include constipation, nausea, vomiting, and biliary colic.
    1. **Constipation** is a universal concomitant of opioid therapy and is treated prophylactically (see section IV.A.3). Rare patients with refractory obstipation may be given 3 to 5 mg of naloxone orally (the drug is absorbed poorly by this route).
    2. Nausea and vomiting are usually transitory and controllable. Prophylaxis is not necessary. Prochlorperazine (Compazine), metoclopramide (Reglan), or cisapride (Propulsid), used as needed, is usually sufficient to control symptoms.
  c. **CNS manifestations** include pupillary constriction, tremors, sedation, dysphoria, apprehension, apathy, mental confusion, hallucinations, and delirium. Narcotics may precipitate convulsions in patients with a medically controlled seizure disorder. Try decreasing the dose and increasing the frequency of administration of opioids.
    1. **Myoclonic jerks** are problematic in patients taking very high doses of MS (usually patients who are nearly refractory to its analgesic effect). Try decreasing the dose by using other analgesic techniques or using a different opioid. Alternatively, benzodiazepines, anticonvulsants, or dantrolene may be helpful.
    2. **Excessive sedation.** Administering caffeine may help. Alternatively, prescribe dextroamphetamine or methylphenidate (Ritalin), 2.5 to 10 mg PO, at breakfast and lunch.
    3. **Opiate-induced light-headedness and nausea,** particularly from codeine and its congeners, can be ameliorated with famotidine (Pepsid), 10 mg PO every 4 to 6 hours, with opioid doses.
    4. **Opioid encephalopathy** with delirium and confusion can last from a few days to 2 weeks and is often precipitated by contributing medical factors. Time and supportive care are required. Haloperidol, 0.5 to 1.0 mg PO or 0.25 to 0.5 mg IV or IM, may be helpful.
  d. **Other side effects**
    1. **Genitourinary system.** Urinary retention may necessitate bladder catheterization, particularly in the elderly.
    2. **Cardiovascular system.** Orthostatic hypotension and sinus bradyarrhythmias
    3. **Endocrine system.** Syndrome of inappropriate antidiuretic hormone (SIADH); decreased release of adrenal corticotropic and gonadotropic hormones from the pituitary gland

4. **Drug interactions with narcotic antagonists**
  a. **Sedatives** may result in increased CNS depression.
  b. **Phenothiazines** potentiate the analgesic effects of opiates.
  c. **MAO inhibitors** should not be administered with narcotics because the combination may produce hypotension, hypertension, delirium, convulsions, respiratory arrest, or death. Examples of MAO inhibitors include procarbazine (Matulane), phenelzine (Nardil), isocarboxazid (Marplan), tranylcypromine (Parnate), and pargyline (Eutonyl).
  d. **Curariform drugs** potentiate respiratory depression.

5. **Management of narcotic withdrawal.** The intensity of withdrawal symptoms is usually proportional to the duration of physical dependence. Symptoms develop within 2 to 48 hours after the last dose and usually peak at 72 hours. Opioid withdrawal is less life-threatening and dangerous than withdrawal from other classes of controlled drugs. Reassurance, education, and perhaps mild sedatives may be all that is required for patients who develop physical dependence during hospitalization and who are not going to continue on the drugs. Small doses of clonidine, 0.05 to 0.1 mg PO t.i.d. (or weekly skin patches of the drug), may reduce symptoms of withdrawal, especially tremors, hypertension, anxiety, and fevers.

G. **Administration of analgesics**
  1. **Dosage of opioids.** "Equianalgesic" dosing of opioids is a theoretical but flawed concept because of several pharmacokinetic problems. Inadequate dosage is the most common cause of ineffectiveness. *There is literally no maximum dosage of MS or other opioids in patients with advanced cancer.* Doses that would cause coma and death in a nontolerant person can be safely increased indefinitely as long as there is persistent pain and adequate respiration. Patients who have developed tolerance can derive excellent pain control with very high doses of oral or intravenous opioids or with changing the opioid or its route of administration (e.g., from oral to parenteral).
  2. **Route.** Short-acting opioids are best given orally for cancer pain but under several circumstances are administered subcutaneously, rectally, intravenously, and into the epidural, subarachnoid, and intraventricular spaces of the CNS. Fentanyl is administered transdermally. Opioids should not be given intramuscularly in patients with chronic cancer pain because the injection causes pain and the absorption of the drug is unreliable. When changing from the oral to the rectal route, begin with the previous oral dose and titrate upward. When going from the oral route to parenteral route, begin with lower doses.
  3. **Starting treatment.** For mild to moderate pain, first use aspirin, acetaminophen, or an NSAID with or without adjuvant drugs (see section D and section E). When pain persists, add a short-acting opioid (see section F.1). If the peak analgesic effect does not last 4 hours, increase the dose rather than shortening the dosing interval. If pain continues or becomes moderate to severe, increase the opioid potency or dose.
  4. **Treating constant pain in patients with advanced cancer.** Develop a regimen that prevents pain, as follows:
    a. **Establish tolerance with short-acting opioids.** Increase the dose and frequency until pain is controlled most of the day. If the drug is a fixed-ratio combination, beware of potential toxicity from ASA or AMP as the dose is increased; change to pure drugs as necessary.
    b. **After tolerance is established, add a long-acting opioid.** For chronic pain requiring frequent doses of short-acting opioids, initiate long-acting opioids (see section F.2) and give short-acting opioids for "breakthrough" pain. The long-acting opioids should be taken every 12 hours on a regular basis ("by the clock"), but patients should not be awakened to receive doses.
    c. **Add short-acting opioids as needed** for "breakthrough" pain control. Pure oral opioids (i.e., usually without ASA or AMP) are offered every 1 or 2 hours. Use the amount taken to estimate increases in the long-acting opioids.
    d. **The dose of long-acting opioid is gradually increased** to minimize or eliminate interval dosing. Sustained-release morphine and oxycodone are increased every 2 to 3 days and fentanyl patches every 5 to 6 days until the need for interval use of short-acting opioids is eliminated or reduced to three times a day or less.
    e. **Give the appropriate dose,** which is the amount of opioid that controls pain with the fewest side effects. Depending on response and side effects, increase or decrease doses by 25% to 50% of the previous dose.
    f. **Gradually taper opioids** to avoid withdrawal symptoms when the patient becomes pain free as a result of other treatments.
  5. **Parenteral administration of opioid analgesics** should be reserved for patients who cannot tolerate the enteral routes or who are in an acute pain crisis for which a rapid onset of action facilitates dose titration. The intravenous route is preferred.
    a. **Subcutaneous opioid infusion.** Infusions of subcutaneous MS may be given but become uncomfortable, particularly for emaciated patients. Subcutaneous infusion rates should not exceed 3 to 5 mL/hour; adjust concentrations of the infusate accordingly.
    b. **Patient-controlled analgesia** (PCA) using calibrated pump devices can be administered by either the subcutaneous or intravenous route. PCA is facilitated by using a computer-assisted drug-delivery system. Boluses are used to treat incident pains and to determine dose titration.
    c. **Intravenous opioid infusion.** Patients who have unremitting pain and who are expected to survive no longer than a few weeks may be treated with continuous intravenous opioid infusion. The starting hourly dose is usually 5 to 10 mg for MS or 0.25 to 1.0 mg for hydromorphone. Parenteral boluses are offered every 15 to 30 minutes. The dose rate is increased until analgesia is attained or decreased if patients develop excessive drowsiness or respiratory depression.
    d. **Infusion of opioid into epidural or subarachnoid spaces** decreases systemic opiate exposure by stimulating opioid receptors at the spinal cord and brain. The analgesic effect of MS is amplified 5- to 10-fold by the epidural route and 50- to 100-fold by the subarachnoid route. These methods may be

especially effective in patients with severe pain from bone metastases. An intrathecal test dose of MS is given at least 2 days before implantation of a subarachnoid pump to gauge efficacy. Narcotic withdrawal symptoms, respiratory depression, and CNS depression appear to be rare with this treatment.

These analgesic techniques, however, involve implanted pumps or externalized catheters, are invasive, and are expensive. They should be considered only for patients in whom aggressive local and systemic approaches have failed to relieve pain adequately or have been associated with intolerable toxicity.

H. **Other methods of pain management**
  1. **Psychological methods of pain control.** Behavioral modification, although not generally effective for moderate to severe chronic cancer pain, may be helpful for mild pain. Operant conditioning, hypnosis, guided imagery, and biofeedback are techniques that can be helpful for chronic mild pain, such as postoperative chest wall pain. *Cognitive distraction* is a useful adjunct for mild pain. This jargonistic term refers to helping patients focus on activities and social relationships of interest, which takes their mind off of the pain.
  2. **Physical methods of pain control,** such as hot or cold packs for muscle and joint pain, acupuncture, transcutaneous electrical nerve stimulation, various types of massage therapy, and exercise programs may be helpful additions to drug therapy in patients with mild to moderate chronic pain syndromes but are generally ineffective in treatment of severe cancer pain.
  3. **Neuroablative procedures** are not commonly used but are effective techniques for treating analgesic-resistant cancer pain in patients with life expectancy of less than a year. These procedures must be carried out by neurosurgeons or anesthesiologists experienced in these techniques.
      a. **Unilateral chordotomy** is the most effective neuroablative procedure and is particularly useful for patients with unilateral cancer pain below the shoulder. Radiofrequency lesions to spinothalamic tracts of the spinal cord are generally placed at the C1 to C2 level. Contralateral loss of superficial, deep, and visceral pain is produced in more than 75% of patients treated with percutaneous chordotomy. The duration of analgesia is limited to only a few months; incapacitating dysesthesia may develop after several months. In experienced hands, unilateral chordotomy is associated with low morbidity and mortality and minimal incidence of motor weakness or loss of bladder function. Sleep apnea, fecal and urinary incontinence, loss of orgasm, and muscle weakness, on the other hand, frequently complicate bilateral chordotomy.
      b. **Nerve blocks** may be useful in patients with pain restricted to a single somatic nerve or adjacent nerves (e.g., postthoracotomy pain may be relieved by subcostal blocks). Short-acting local anesthetics are initially used to determine the location for a permanent procedure.
      c. **Celiac plexus nerve block** is up to 85% effective for treating upper abdominal visceral pain, particularly from cancers of the pancreas or stomach. The procedure is often accomplished with needle placement under CT or fluoroscopic guidance. Pretreatment hydration and postoperative observation for 4 to 6 hours (with fluid replacement as necessary) can prevent transient hypotension from this procedure.
      d. **Partial celiac plexus sympathectomy** is useful for pain from pancreatic cancer and should be considered at the time of laparotomy for this malignancy.
      e. **Lumbar sympathetic blockade** can be attempted for pelvic visceral pain. This procedure affects sphincter tone or lower extremity strength uncommonly.
      f. **Spinal neurolysis** targets appropriate dorsal root ganglia. This procedure may be considered for unilateral chest wall pain or perineal pain.
      g. **Epidural corticosteroids and hypertonic saline** can be considered for pain from vertebral body metastases as well as for their more frequent use in pain from discogenic disease or spinal stenosis.
      h. **Hypophysectomy** relieves intractable pain from breast and prostate cancers, including those that have become resistant to hormonal therapy. The procedure results in hypopituitarism.
      i. **Cingulotomy** is effective in patients with intractable pain caused by widespread cancer and emotional factors that make the pain intolerable. The procedure is directed at the intensity and unpleasantness of pain and does not interfere with intelligence, personality, or initiative.

II. Oral symptoms

A. **Stomatitis from chemotherapy** can develop 2 to 10 days after treatment with many cytotoxic agents and during radiation to the head or neck. Resolution of symptoms usually occurs 2 to 3 weeks after completion of therapy but may persist longer. Sucking on ice chips or popsicles during the short infusion of certain cytotoxic agents (e.g., methotrexate) or taking oral glutamine preparations may prevent the development of stomatitis. Aggravating factors include poor oral hygiene (gingivitis, poorly maintained dentures), xerostomia, age- or radiation therapy–related mucus membrane atrophy, and aerobic or anaerobic bacterial infections. Infection with *Candida* species or herpesvirus can complicate or be confused with chemotherapeutic stomatitis; the index of suspicion for the infections is increased in patients with acquired immunodeficiency syndrome (AIDS) and in those taking high-dose or long-term glucocorticoids.
  1. **Symptoms and signs.** Stomatitis is usually first noted by the patient as sensitivity to citrus juice, hot food, or spicy food. Erythema and then aphthous ulcers develop. In severe cases, lesions progress to extensive ulceration and sloughing of the oral mucosa. *Candida albicans* or herpesvirus infection can have a similar appearance and must be considered if the mouth lesions are longer lasting or recognized by their characteristic appearance.
  2. **Treatment.** The following measures may relieve symptoms:
      a. Avoidance of foods that trigger the pain, most commonly very hard or hot foods
      b. Abstention from alcohol and tobacco
      c. Sucking on popsicles and cold beverages
      d. Frequent rinsing of the mouth with mild saline solution or baking soda mixed in water
      e. Sipping 5 to 15 mL of viscous 2% lidocaine (Xylocaine) for 30 seconds before meals and as needed
      f. Sipping 2.5 to 5.0 mL of liquid hydrocodone (e.g., Lortab solution) or cocaine (1% to 2%)
      g. Swishing and expectorating commercial suspensions
          1. Ulcerease: glycerin, sodium bicarbonate, and sodium borate
          2. BAX: lidocaine, diphenhydramine, sorbitol, and Mylanta
          3. Stomafate: sucralfate, Benylin syrup, and Maalox
      h. Applying choline salicylate gel to lesions every 4 to 6 hours
      i. Appropriate antimicrobial treatment for bacterial, monilial, or herpesvirus infections
B. **Xerostomia** is a complication of radiation therapy or radical surgery to the head and neck, of commonly used medications (such as antihistamines and opioids), and of mouth breathing. Treatments include the following:
  1. Sucking on hard candies (such as Life Savers, cinnamon, lemon drops) and regular use of chewing gum
  2. Adequate intake of water and electrolyte solutions, such as Gatorade
  3. Frequent mouth washing with cetylpyridinium (Cepacol)
  4. Pilocarpine hydrochloride tablets. Start with 5 mg t.i.d.; gradually titrate up to a maximum of 10 mg per dose every 4 hours while awake. This treatment must be given for 8 to 12 weeks to assess effectiveness. The lowest effective dose is used for maintenance therapy.
  5. Commercial preparations of artificial saliva, such as Salivart or Xerolube sprays
  6. Frequent application of a thin layer of petroleum jelly to the lips. Alternatively, the application to chafed lips of "Bag Balm" (traditionally used for cow udders) gives "amazing" results, according to irrefutable nurses.
C. **Abnormal taste** is a common symptom in patients with cancer. Patients often complain of a metallic taste or of food not tasting right or being without taste. Loss of taste, specifically for red meat, is frequent. There may be a low threshold for bitterness (urea) or a high or low threshold for sweetness. Both chemotherapy and radiotherapy can aggravate loss of taste. Zinc sulfate, 45 mg t.i.d., at the onset of altered perception of taste during radiotherapy to the head and neck and up to 1 month after completion of treatment may ameliorate the loss of taste acuity. Treatments for abnormal taste include the following:
  1. Reducing the urea content of the diet by eating white meats, eggs, and dairy products
  2. Masking the bitter taste of urea-containing foods by marinating meats, using more and stronger seasonings, eating food at cold or room temperatures, and drinking more liquids
  3. Helping overcome general poor taste by eating foods that are tart (lemonade frozen in ice trays, pickles, vinegar) or that leave their own taste (fruit, lemon drops, hard candy)
  4. Treatment of gingivitis, regular brushing and flossing of teeth, denture care and cleaning, and dental consultation
D. **Halitosis.** Treatments include the following:
  1. Optimal dental hygiene
  2. Gentle brushing of tongue with a soft toothbrush. The back of the tongue in particular collects malodorous bacteria and foods trapped in mucus but must be brushed quickly to avoid gagging.
  3. Ensuring adequate fluid intake
  4. Using Cepacol mouthwash, Breath Assure capsules, and charcoal tablets
  5. For oropharyngeal malignancies, treating xerostomia (see section II.B) and using 10% hydrogen peroxide gargles on awakening, after meals, and at bedtime
  6. Treating oral candidiasis and other infections appropriately
E. **Dysphagia**
  1. **Etiology.** Dysphagia may be caused by mechanical obstruction or neuromuscular defects and should be distinguished from odynophagia. Radiation therapy or reflux disease may also cause stricture formation and esophageal obstruction.
  2. **Management.** After there is agreement about treatment and feeding goals, treatment possibilities include the following:

a. **Patients with eating-related difficulty swallowing or aspiration** or any reason should be evaluated with a fluoroscopic barium swallow study, ideally done with a speech therapist present. Speech therapists then work with dietitians to design foods with the proper consistency for safe swallowing and sufficient caloric intake.

b. **Palliating an obstructed esophagus from esophageal cancer** (see Chapter 9, Esophageal Cancer, section VI.B)

c. **If an esophageal prosthesis becomes blocked,** the patient should sip small amounts of water and, every 30 minutes, dilute hydrogen peroxide. Alternatively, the tube can be flushed with cola.

d. **"Benign" obstruction caused by strictures from radiation therapy** require gradual dilation by gastroenterologists experienced in the technique to avoid esophageal rupture. This can take weeks to months; an interval gastrostomy tube placement must be considered. Many patients can have full restoration of normal swallowing. Antireflux regimens or reduction of stomach acid with famotidine (Pepsid), 10 mg b.i.d., or intermittent 4-week courses of omeprazole (Prilosec), 20 to 40 mg each morning, may be helpful.

e. **Excessive saliva production** when total esophageal obstruction produces sialorrhea and drooling can be treated with anticholinergics, alum mouthwashes, or irradiation of the salivary glands (400 to 1000 cGy).

III. Nausea and vomiting

A. **Etiology**

1. **Differential diagnosis.** Nausea and vomiting in cancer patients occur most often as a result of cytotoxic chemotherapy. Other causes include brain metastases, bowel obstruction, electrolyte imbalance (notably hypercalcemia), radiation therapy to the abdomen, and treatment with other drugs (narcotic analgesics, antibiotics).

2. **Cytotoxic drugs.** Drugs that are highly emetic include cisplatin, dactinomycin, anthracyclines, dacarbazine, nitrosoureas, nitrogen mustard, and high-dose cyclophosphamide (see Appendix B-1). The mechanisms for nausea and vomiting from chemotherapy are poorly defined but appear usually to be mediated by the CNS; some drugs may have peripheral activity. Acute chemotherapy-induced vomiting typically occurs 1 to 2 hours after treatment and usually resolves in 24 hours. Subacute vomiting occurs 9 to 18 hours after giving chemotherapy. Delayed vomiting occurs 48 to 72 hours after giving cisplatin (especially with doses of 100 mg/m^2 or more) and diminishes in 1 to 3 days.

3. **Psychological and behavioral factors** may induce or modify vomiting. Patients may vomit even before receiving chemotherapy (anticipatory vomiting) when the intravenous line is started, the syringe is seen, or even before leaving home on the day chemotherapy is scheduled. Emesis is more easily controlled, on the other hand, in patients with a history of chronic heavy alcohol use.

B. **Management**

1. **Prevention of vomiting.** It is best to prevent nausea and vomiting with adequate doses of antiemetics, particularly when drugs that are known to induce vomiting are used.

a. **Serotonin receptor** (5-HT3) **antagonists** bind to type 3 receptors of serotonin (5-hydroxytryptamine [5-HT]) and are the drugs of choice to prevent emesis generated by highly emetic regimens. 5-HT3 blockers alone achieve complete abrogation of emesis in about 60% of patients and achieve major control of emesis in 75% of patients.

1. **Dosage.** The following agents have about the same effectiveness, have improved efficacy with the addition of a corticosteroid, and are given 30 to 60 minutes before chemotherapy:

a. Ondansetron (Zofran), 8 or 32 mg IV

b. Granisetron (Kytril), 0.01 mg (10 μg) per kg IV or 1 mg PO

c. Dolasetron (Anzemet), 100 mg IV or PO

2. **Side effects** are mild headache, constipation, and transient transaminase elevations. Extrapyramidal side effects do not occur.

b. **Metoclopramide** (Reglan), a procainamide derivative, acts both centrally (at the chemoreceptor trigger zone) and peripherally (by stimulating gastric and small bowel motility, thereby preventing gastric stasis and dilation). This drug served a transitional role between the older agents and the newer 5-HT3 antiemetics.

1. **Dose:** 1 to 3 mg/kg IV every 2 hours for 2 to 6 doses

2. **Side effects** include mild sedation, dystonic reactions (especially in young patients), akathisia (restlessness), and diarrhea. The drug is given with lorazepam, diphenhydramine, and corticosteroids to prevent these complications.

c. **Corticosteroids** are effective for treating chemotherapy-induced vomiting by themselves or with 5-HT3 blockers. Recommended dosages are as follows:

1. Dexamethasone, 10 to 20 mg IV for one or two doses

2. Methylprednisolone, 125 mg IV for one or two doses

d. **Lorazepam** (Ativan), 1 or 2 mg IV or sublingually (SL) every 3 to 6 hours, is very useful in patients who are treated with emetogenic chemotherapy or who have refractory or anticipatory vomiting. The drug's amnesic effect is also helpful.

2. **Agents used for nausea**

a. **D-9-tetrahydrocannabinol** (THC) is the main active ingredient in marijuana and can relieve nausea and vomiting in some patients who do not respond to other antiemetic drugs. The drug should be prescribed cautiously for elderly patients and not at all for patients with cardiovascular or psychiatric illness.

1. **Dose:** 2.5- to 10-mg PO every 3 to 4 hours. THC is available as Marinol in 2.5-, 5.0- and 10-mg capsules.

2. **Side effects** include orthostatic hypotension, sedation, dry mouth, ataxia, dizziness, euphoria, and dysphoria. Maintaining a "high" is correlated with the antiemetic effect in younger patients.

b. **Antacids,** which perhaps work by speeding gastric emptying

c. **Antihistamines.** Promethazine (Phenergan), diphenhydramine (Benadryl), dimenhydrinate (Dramamine), and meclizine (Antivert) are given in dosages ranging from 12.5 to 50 mg PO every 6 hours.

d. **Scopolamine** (Transderm Scop). Patches changed every 3 days.

e. **Phenothiazines**

1. Prochlorperazine (Compazine), 5 to 20 mg PO every 4 to 6 hours

2. Thiethylperazine (Torecan), 10 mg PO t.i.d.

f. **Haloperidol** (Haldol), 0.5 to 1.0 mg PO every 4 to 12 hours

g. **Metoclopramide** (Reglan), 10 to 20 mg PO every 6 to 8 hours (if gastric stasis is suspected)

3. **Delayed vomiting**, occurring 1 to 2 days after treatment, is most often seen after high doses of cisplatin and is difficult to treat. The following may be tried:

a. **Dexamethasone alone:** 8 mg b.i.d. PO for 2 days, then 4 mg b.i.d. for 2 days

b. **Metoclopramide:** 0.5 mg/kg q.i.d. PO for 2 days with dexamethasone

c. **Ondansetron:** 4 or 8 mg b.i.d. to t.i.d. for 3 days with or without dexamethasone

4. **Anticipatory vomiting** is exceedingly difficult to palliate. Prevention of emesis when chemotherapy is first given is the best way to prevent anticipatory vomiting. Antiemetics should be prescribed generously, and chemotherapy should be given as late in the day as possible. Symptoms may improve with the following:

a. Sedatives, including antihistamines or benzodiazepines

b. Hypnosis by an experienced psychologist

c. Progressive muscle relaxation, which involves learning to relax by actively tensing and then relaxing specific muscle groups

d. Cognitive distraction

e. Relaxation techniques with guided imagery

f. Operant conditioning. For example, patients may be treated in an area and on a day different from their usual place and time.

IV. Colorectal symptoms

A. **Constipation**

1. **Etiology**

a. **Inactivity.** Prolonged bed rest, inadequate exercise, and neurologic problems resulting from spinal cord compression or cauda equina syndrome predispose to decreased motility of the bowel, hard stools, or impaction.

b. **Drugs.** Narcotic analgesics and vincristine are the most common offenders; others are calcium and aluminum antacids, anticholinergics, anticonvulsants, antidepressants, and abused laxatives or enemas.

c. **Metabolic abnormalities** include malignant hypercalcemia, hypokalemia, myxedema, and dehydration.

d. **Mechanical obstruction of the bowel** may be caused by fecal impaction, tumor, inflammatory strictures, or barium from contrast studies.

2. **Some preparations available** for the treatment of constipation in the United States are the following:

a. **Bulk producers.** Psyllium mucilloid (Metamucil, Konsyl) must be taken with adequate liquids.

b. **Stool softeners**

1. Docusate sodium (Colace): 50- and 100-mg capsules

2. Docusate calcium (Surfak): 50- and 240-mg capsules
    3. Mineral oil (Kondremul, Haley's MO); 30 to 120 mL/day
  c. **Peristalsis stimulants**
    1. Sennosides (Senokot): 8.6-mg tablet (or syrup)
    2. Bisacodyl (Dulcolax): 5-mg tablet, 10-mg suppository, enema
    3. Others: casanthrol, cascara sagrada, phenophthalein, castor oil
  d. **Combinations**
    1. Sennosides and docusate sodium (Senokot-S)
    2. Casanthranol and docusate sodium (Peri-Colace)
    3. Danthron and docusate sodium (Doxidan)
  e. **Saline or osmotic laxatives** with or without cascara sagrada
    1. Magnesium hydroxide (milk of magnesia): 15 to 30 mL PO h.s.
    2. Magnesium citrate: 10-oz solution, tablets, suppositories
    3. Sodium phosphates (Fleet Phospho Soda): PO or enema
    4. Lactulose (Cephulac): 45 to 60 mL per dose
    5. Polyethylene glycol (Go-LYTELY): 8 oz every 15 minutes
    6. Diatrizoate meglumine (Gastrografin): 250 mL enema
  3. **Prevention and management of narcotic-induced constipation.** Patients who are receiving regular dosages of narcotics (or vincristine) should be carefully questioned about bowel movements. They should be encouraged to drink liquids (i.e., water, prune juice, coffee) and to eat bran cereal daily.

  However, these measures plus stool softeners are usually insufficient, and bulk producers are poorly tolerated. The combination of docusate plus senna extract in parallel increasing doses is recommended to prevent narcotic-induced constipation. Brand name preparations (e.g., Senokot-S, Peri-Colace) can cost 10 times more than generic preparations of these agents.

    a. Start all patients who take narcotic analgesics on 2 tablets of Senokot-S (or the equivalent) at bedtime. If no bowel movement occurs in any 24- to 48-hour period, increase the dosage to 2, 3, or 4 tablets b.i.d. or t.i.d. as needed.
    b. If no bowel movement occurs in any 48- to 72-hour period, add Dulcolax, 2 tablets PO h.s. (or to t.i.d. if needed).
    c. If no bowel movement occurs in any 72- to 96-hour period, give an osmotic or saline laxative (see section IV.A.2.e).
    d. Clonidine, 0.1 mg PO b.i.d. to q.i.d., may be helpful for narcotic bowel. It can then be tapered when effective.
B. **Rectal discharge** may be caused by hemorrhoids, fecal impaction, tumor, radiation proctitis, and various rectal fistulas. After addressing the primary cause, inflammation may be reduced with corticosteroid suppositories or enemas. The skin of the perineum and genitalia must be protected and kept clean (without soap) and dry.
C. **Enterocutaneous fistulas** can be managed in the same manner as for surgical stomas with colostomy or ileostomy bags. The direction and advice of a stomal therapist is often warranted.
  1. The surrounding skin rapidly breaks down and limits bag attachment. Débrided skin should be kept clean using water with or without a mild soap; detergents and disinfectants aggravate the skin condition. Glucocorticoid creams (not ointments) can be used for local inflammation, and triple antibiotic cream can be used for infected areas. Several sealants are available to protect the skin from fistula discharge, including newer plastic coverings that permit air but not liquids to reach the skin and sprays, such as Opsite.
  2. Unless the volume of fecal material is large, it is sometimes possible to place a urinary catheter into the stoma, after assessing the anatomy by retrograde barium studies. The catheter can be used as a temporizing measure until abraded skin is sufficiently healed to provide secure attachment for a colostomy appliance.
D. **Distal colon and rectal cancerous fistulas involving the bladder or vagina** are best managed by a more proximal colostomy. This stops all drainage and allows long-term healing of inflamed tissues.
E. **Chemotherapy-induced diarrhea** (CID) can be debilitating and potentially life-threatening. The risk for CID is significantly greater with regimens that contain fluoropyrimidines or irinotecan (CPT-11). The cause of diarrhea is most likely a multifactorial process that results in an imbalance between absorption and secretion in the small bowel.

The opioids, loperamide (Imodium) and diphenoxylate (Lomotil), are most commonly used for CID. These agents reduce diarrhea by decreasing peristalsis in the small and large intestines. NSAIDs, clonidine, and cyproheptadine control the diarrhea associated with bowel inflammation, bronchogenic carcinoma, and carcinoid syndrome, respectively. Octreotide is effective in controlling the diarrhea associated with islet cell carcinomas, AIDS, and other secretory diarrheal syndromes. Octreotide also controls severe CID, but the optimal dose quantity and duration is unsettled, and the drug is expensive. The basis for treatment of CID is mostly anecdotal. Recommendations are as follows:

  1. **Avoid certain food products:** milk and dairy products, spicy foods, alcohol, caffeine, prune and orange juices, high-fiber foods, and high-fat foods.
  2. **Avoid certain medications:** laxatives, stool softeners, promotility agents (metoclopramide, cisapride).
  3. **Evaluate stool** for the presence of fecal leukocytes and pathogenic microbes in patients with persistent or severe diarrhea; treat accordingly.
  4. **Low-grade diarrhea** (National Cancer Institute [NCI] grades 1 and 2; see Appendix B-2).
    a. Observe for and correct any fluid and electrolyte imbalances.
    b. Loperamide given as an initial 4-mg dose followed by 2-mg every 4 hours. If diarrhea persists, increase the dose to 2-mg every 2 hours.
    c. Octreotide, 100 to 150 µg SC t.i.d., is given for patients who are refractory to high-dose loperamide therapy; treatment is continued until diarrhea resolves.
  5. **Severe diarrhea** (NCI grades 3 and 4; see Appendix B-2).
    a. Hospitalize patients who have significant dehydration, blood in the stool, or abdominal pain, and treat accordingly.
    b. Octreotide, 100 to 150 µg SC t.i.d., is given until diarrhea resolves. It is reasonable to increase the dose by 50-µg increments until diarrhea is controlled. Doses up to 2000 µg SC t.i.d. for 5 days have been used safely in CID.

V. Urinary symptoms

A. **Dysuria**
  1. **Etiology.** Inflammation of the urinary bladder or outlet
  2. **Management** includes treatment of infection if present and the following:
    a. Phenazopyridine (Pyridium), 100 to 200 mg PO t.i.d.
    b. Amitryptyline, 25 to 50 mg PO h.s. (especially for interstitial cystitis)
B. **Bladder spasm**
  1. **Etiology.** Vesicular irritation by cancer, postradiation fibrosis, indwelling catheter, cystitis, or anxiety
  2. **Management.** Cystitis is treated with antibiotics, catheter change, and bladder irrigation if a urethral catheter is present. Drugs of choice are as follows:
    a. Flavoxate (Urispas), 200 to 400 mg PO q.i.d.
    b. Oxybutynin chloride (Ditropan), 5-mg PO t.i.d. or q.i.d.
    c. NSAIDs are reportedly helpful.
    d. Hyoscyamine sulfate
      1. 0.125-mg tablets (Levsin), 1 or 2 tablets PO or SL every 4 hours
      2. 0.15-mg tablets (Cystospaz), 1 or 2 tablets PO q.i.d.
      3. 0.375-mg sustained release capsules (Levsinex, Cystospaz-M), 1 capsule every 12 hours
    e. Belladonna-opium suppositories (B & O Supprettes), one every 4 hours
    f. Propantheline bromide (Pro-Banthine), 15 mg PO h.s. or b.i.d.
    g. Blocks of the lumbar sympathetic plexus may be effective for the management of intractable bladder pain.
C. **Urinary hesitancy**
  1. **Etiology.** Malignant or benign prostate enlargement, infiltration of the bladder neck, presacral plexopathy, drugs, intrathecal block, bladder denervation by surgery, loaded rectum, inability to stand to void, and asthenia
  2. **Management.** Address the specific causes; a urethral catheter may be necessary. Drugs that may be useful include the following:
    a. Terazosin hydrochloride (Hytrin), 1- to 10-mg PO h.s.
    b. Bethanechol (Urecholine), 10 to 30 mg PO b.i.d. to q.i.d.

D. **Urinary obstruction by tumor**
1. **Bladder neck or urethral obstruction** can be very painful and should be relieved without delay. A transurethral catheter is the first line of treatment. For complete tumor obstruction, the urologist should place a transvesical catheter.
2. **Ureteral obstruction** by tumor can often be treated by stenting. In the presence of complete obstruction, nephrostomy can be considered if the patient is otherwise comfortable and there is some expectation that the underlying tumor will respond to therapy.
E. **Discolored urine** may be caused by food or drugs and is of no concern, except for the anxiety provoked in the patient.
1. **Pink or red urine:** beets, blackberries, rhubarb; doxorubicin (Adriamycin); phenophthalein, senna, cascara, danthron (e.g., in Doxidan); deferoxamine (Desferal); chlorzoxazone (Paraflex); phenothiazines; phenazopyridine (Pyridium)
2. **Brown or black urine:** phenacetin, salicylate; metronidazole (Flagyl); nitrofurantoin, chloroquine, quinine quinacrine, sulfonamides (yellow-brown); l-dopa, methyldopa (Aldomet); iron dextran (Imferon)
3. **Blue or green urine:** methylene blue, food coloring and other dyes; riboflavin; indomethacin, amitryptiline, danthron, mitoxantrone

VI. Respiratory symptoms

A. **Cough**
1. **Etiology.** The causes of cough are numerous.
2. **Management**
   a. Recommend that patients stop smoking. The antitussive effect of abstinence may require 4 weeks, however.
   b. Antihistamines are given for postnasal drip, bronchodilators for bronchospasm, diuretics for heart failure, and antibiotics for infection. Antitumor therapy should be given if practical.
   c. Improve the efficacy of the cough by asking patients to sit up to cough, and consider physiotherapy and postural drainage.
   d. Mucolytics include the following:
      1. Water by means of humidifier
      2. Inhalations of steam or compound benzoin tincture
      3. Guaifenesin (Robitussin), potassium iodide (SSKI), acetylcysteine (Mucomyst)
   e. Antitussives include the following:
      1. Dextromethorphan (Robitussin-DM)
      2. Benzonatate (Tessalon perles), 100 mg every 4 hours
      3. Scopolamine, 0.3 to 0.6 mg IM or SQ every 4 hours, or Transderm Scop patches
      4. Hydrocodone with phenyltoloxamine (Tussionex) or with homatropine (Hycodan). Both preparations contain 5 mg of hydrocodone per tablet or teaspoonful and are taken every 4 to 8 hours.
      5. Other opioid analgesics, including morphine
B. **Hiccups**
1. **Etiology**
   a. Diaphragmatic irritation from tumor infiltration, subphrenic abscess or empyema, hepatomegaly, and ascites
   b. Phrenic nerve irritation from mediastinal cancers
   c. Gastric distention of any etiology
   d. Uremia, esophagitis, or brain tumors
2. **Management**
   a. **"Home remedies" (pharyngeal stimulation):** 2 teaspoons of granulated sugar, two glasses of liquor, a cold key down the back of a hyperextended neck, a nasopharyngeal tube, and drinking a glass of cool water through a straw while plugging both the patient's ears with his or her fingers
   b. **Reduction of gastric distention:** nasogastric intubation, peppermint water (relaxes esophageal sphincter), or antiflatulents (simethicone)
   c. **Induction of hypercarbia** by breath-holding or using a paper bag
   d. **Potentially helpful pharmacologic measures**
      1. Baclofen (Lioresal), 5 to 20 mg PO every 6 to 12 hours (the only drug tested in a randomized, placebo-controlled manner)
      2. Chlorpromazine (Thorazine), 25 to 50 mg PO or IV every 6 hours
      3. Metaclopramide (Reglan), 10 to 20 mg PO every 4 to 6 hours
      4. Nifedipine, 10 to 20 mg PO every 8 to 12 hours
      5. Quinidine, 200 mg t.i.d.
      6. Benzonatate (Tessalon perles), 100 mg q.i.d.
      7. Ondansetron, 8 mg PO t.i.d. or IV bolus
      8. Anticonvulsants: phenytoin, carbamazepine, valproic acid
      9. Stimulants: amphetamines, methylphenidate
C. **Preterminal dyspnea**
1. **Etiology.** Patients with terminal cancer and pulmonary insufficiency from any cause often have panic attacks when developing shortness of breath. They fear they will stop breathing and suffocate while asleep.
2. **Management**
   a. For respiratory panic, calmly educate patients about breathing control and give diazepam orally.
   b. For shortness of breath associated with tachypnea, give morphine sulfate and corticosteroids orally.
   c. For air hunger, intravenous morphine sulfate and diazepam or lorazepam may be the only possible humane measures.
   d. For massive projectile hemoptysis, an occasional but fatal complication of lung cancer, give enough diazepam or morphine intravenously or rectally to render patients unconscious.
D. **"Death rattle"**
1. **Etiology.** Patients who are too weak to expectorate
2. **Management.** Place patients in the semi-Fowler's position. Oropharyngeal suction may be used in unconscious patients for cosmetic purposes when staff or visitors are present. Scopolamine or atropine in dosages of 0.3 to 0.8 mg SC every 2 to 4 hours may be helpful.

VII. Skin problems

A. **Pruritus**
1. **Etiology.** Generalized pruritus can develop as a result of the following:
   a. Scabies, dry flaky skin, or other primary skin conditions
   b. Biliary tract obstruction
   c. Paraneoplastic syndrome
   d. Cutaneous metastases or lymphomas
   e. Renal failure
   f. Psychiatric causes
   g. Iron deficiency, polycythemia vera, systemic mast cell disease
   h. Thyroid disease, hyperparathyroidism
   i. Hypersensitivity to drugs
   j. Intraspinal morphine
2. **Management.** Control of the underlying cancer may relieve itching. Drugs suspected of causing hypersensitivity reactions should be stopped. Factors that increase the perception of pruritus include dehydration, heat, anxiety, and boredom.
   a. **Instructions to patients.** Patients should be told to avoid traumatizing the skin by alcohol rubs, woolen clothing, or frequent bathing. Excessive bathing, especially with detergents and hot water, results in dry skin, which causes itching in itself. The use of baby oil, olive oil, lanolin, bland creams, emollient creams, or petroleum jelly should be encouraged. The skin should be "oiled" after each bath or shower, blotting in the agent while toweling dry. The use of soap should be stopped and situations that result in increased sweating avoided.
   b. **Local therapy**
      1. Bland cool compresses or calamine lotion
      2. Vioform-hydrocortisone cream b.i.d. or t.i.d. on inflamed areas
      3. Electron-beam radiotherapy is often effective in relieving pruritus from cutaneous lymphomas.
      4. Biliary drainage procedures for obstruction
   c. **Drug therapy**

1. Cyproheptadine (Periactin), 4 to 6 mg every 6 hours
2. Antihistamines
3. Diazepam (Valium), 5 to 10 mg b.i.d. or q.i.d.
4. Dexamethasone, 2 or 4 mg daily or b.i.d.
5. Methyltestosterone, 25 mg SL b.i.d., for cholestatic jaundice. The mechanism is unknown, but pruritus is frequently relieved.
6. Cholestyramine resin (Questran) is occasionally effective in patients with pruritus from biliary tract obstruction but causes severe constipation and malabsorption of foods and drugs.
7. Naloxone (Narcan) can relieve intraspinal morphine pruritus but may cause recurrence of pain and precipitate withdrawal symptoms.

B. **Preventive skin care in dying patients** is extremely important to their comfort. The following are recommendations of Twycross and Lack (see Suggested Reading):
   1. **Prevent decubiti by redistributing pressure**
      a. At home, obtain a camping mattress and fill it with water instead of air to create a waterbed.
      b. For wheelchairs, use an inflatable cushion or egg crate foam.
      c. Elbow and heel pads, sheepskin mats, self-adhering urethane foam, pillows, and bed cradles may be helpful.
      d. Turn or reposition patients frequently.
      e. Decubitus ulcers are sometimes impossible to prevent or treat in terminal patients, regardless of frequent and meticulous care. Cachexia, skin atrophy, incontinence, and pain on movement are some of the contributing factors. Caring and conscientious nurses may need physician reassurance that decubiti in this setting are impossible to prevent or treat.
   2. **Provide optimal hydration and hygiene**
      a. Avoid soap on dry fragile skin, creams and ointments in intertriginous areas, and trauma (from restraints, tape, and so forth).
      b. On normal skin, use mild soaps, pat dry, use gentle massage with bland cream, and use petroleum jelly on elbows and heels.
      c. On dry skin, use fine talc.
      d. On chafed areas, use silicone spray or Opsite.
      e. Change bed linen often.

C. **Hair loss**
   1. **Etiology.** Irradiation to the scalp and administration of certain cytotoxic drugs result in marked alopecia. Hair loss begins 2 to 3 weeks after these therapies are started. Hair usually regrows after therapy is discontinued. The relative risks of hair loss caused by chemotherapeutic agents are shown in Appendix B-1.
   2. **Management**
      a. **Emotional support.** Patients need to be forewarned. Hair loss should be discussed openly and sympathetically and its importance compared to the potential benefits of therapy. Inform patients about the relative risks of the specific regimen for alopecia. Explain that hair loss is preceded by scalp itching or pain and that hair is often curly when it regrows.
      b. **Wigs** should be obtained as soon as hair loss becomes evident (or before). Complimenting patients' appearance in a wig (if sincere) aids in adjustment. Prescribe a "scalp prosthesis" for insurance carriers.
      c. **Other measures.** Suggest the use of hats and colorful scarves, soft-bristle brushes, mild shampoos, and satin pillow cases. Discourage the use of blow-dryers, hot rollers, and exposure of the scalp to the sun.

VIII. Necrotic, malodorous tumor masses

A. **Pathogenesis.** Progressively growing tumor masses may erode through the overlying skin and ulcerate. The center of the mass becomes necrotic with formation and release of malodorous polyamines, such as vomitine. These polyamines are reactive and adhere to almost anything with which they come in contact, including skin, clothing, and hospital equipment, leaving a residual nauseating odor in the room. The smell worsens if the mass becomes infected with anaerobic organisms. The stench makes it difficult for others to enter the room. When visitors leave, the smell stays on their clothing and skin; as a result, patients become isolated from contact with others. Patients themselves often do not notice the odor.

B. **Management**
   1. **Radiation therapy** (RT). Large masses that may invade the overlying skin should be irradiated to prevent skin breakdown.
   2. **Amputation** may be necessary for tumors that do not respond to RT or chemotherapy (e.g., an extremity that is ravaged with sarcoma or a breast with massive carcinoma).
   3. **Skin metastases** confined to one small area of the body may be amenable to local resection. However, recurrences are likely.
   4. **Chemotherapy** or endocrine therapy should be used appropriately for the primary tumor.
   5. **Local care**
      a. **Frequent dressing changes** with highly absorbent, nonadhesive material.
      b. **Tumor bleeding** may be ameliorated by applying 1:1000 epinephrine solution to the tumor surface before applying the new dressing.
      c. **Flushing.** Necrotic tumor masses and fistulas should be generously irrigated at least three times daily with large volumes of 3% hydrogen peroxide.
      d. **Silver nitrate,** 1% solution soaked in large gauze pads, may be applied to necrotic areas by a gloved operator every day or two to help reduce oozing and odor. Absorbed silver may cause renal damage.
      e. **Maggots** actually débride necrotic tissue; however, the sight of maggots in wounds is usually more than nursing staff, physicians, and visitors can tolerate, even though patients often do not appear to notice them. Diethyl ether in generous amounts is applied to the tumor surface with 4-inch × 4-inch gauze; the gauze is wrung out onto the lesion so that reaches the deeper ulcerated areas. Maggots rapidly recur if treatment with ether is stopped.
   6. **Measures to control odor**
      a. **Isolate** patients with malodorous tumors in private rooms. An outward facing fan is placed to blow air out of the window. Normal areas of skin should be kept clean, and malodorous masses should be kept covered.
      b. **Room deodorizers** should be used. The deodorant aromas should be changed every few days to avoid conditioning of the staff, who soon identify the smell of the product with the rather thinly disguised stench of necrotic cancer.
      c. **Metronidazole** (Flagyl), 250 to 500 mg q.i.d., may be helpful, particularly if anaerobic bacterial infection is present.
      d. **Chloresium,** a 22% chlorophyll-copper complex in isotonic saline, is a true deodorizing agent and can be poured directly onto the necrotic tissues.
      e. **Disposable protective gowns and gloves** should be worn by caregivers.

IX. Fever

A. **Causes.** The diagnosis of tumor-induced fever is one of exclusion. It may develop in the course of nearly any malignancy but is especially common in the following conditions:
   1. Lymphomas and myeloproliferative disorders
   2. Retroperitoneal cancer
   3. Metastatic cancer to the liver
   4. Hepatocellular and renal cell carcinoma
   5. Gastric and pancreatic cancers
   6. Bone sarcomas

B. **Management**
   1. Controlling the underlying tumor, when possible, is the most effective means of controlling fever from tumors.
   2. Aspirin and acetaminophen may be alternated every 2 hours as necessary.
   3. Indomethacin, 25 to 50 mg PO t.i.d., is often helpful.
   4. Corticosteroids may be helpful but are generally not necessary.

X. Obstructive lymphedema

A. **Etiology.** Lymphedema may be caused by the malignancy, its metastases, or its treatment (surgery or RT).

B. **Management.** If surgery, RT, and chemotherapy are not indicated, the following may be tried:
   1. Prescribe diuretics such as Dyazide or Moduretic, 1 or 2 tablets daily; if ineffective, add a loop diuretic.
   2. Extremity pumps (e.g., Lymphapres, a 12-chamber device that has replaced the Jobst pump) used twice daily may be helpful.
   3. Use support stockings between pump applications.
   4. Elevate the affected limb if the lower extremity is involved.

5. Consider the use of massage by a physical therapist, a compressive sleeve overnight, and dexamethasone.

XI. Venous access problems

A. **Administering chemotherapy to patients with poor venous access**
   1. **Switching to oral agents.** Many of the available chemotherapeutic agents are absorbed, although incompletely, when given orally.
   2. **Difficulty finding veins** may be alleviated by several techniques:
      a. Hang the arms (wrapped in hot, moist towels, with tourniquets lightly applied) for 10 minutes below the level of the heart.
      b. Use a blood pressure cuff expanded halfway between systolic and diastolic pressures. Tight tourniquets are never helpful.
      c. Search other places to find veins, such as the upper arm or legs.
      d. Advise patients to drink plenty of liquids on the day before treatment and to wear a sweater on the day of treatment to keep the arm warm.
      e. Place hot packs over the site before venipuncture.
   3. **Vein training.** Patients with inaccessible veins are instructed to sit in a chair with the arms held below heart level and to squeeze tennis balls, Nerf balls, or household sponges three times daily for 10 minutes or until fatigued. The arms may be wrapped periodically with warm towels.
   4. **Other methods** for securing venous access include arteriovenous fistula (see section XI.C) and right atrial Silastic catheters (see section XI.E).
B. **Heparin lock.** A plugged, short catheter may be used in patients requiring intermittent intravenous infusions. The catheter is flushed regularly with heparin.
C. **An arteriovenous fistula** may be established in patients who have inaccessible veins and a reasonably long expected survival. Administration of viscous solutions through the shunt promotes thrombosis.
D. **Hypodermoclysis.** Dehydration in patients with difficult venous access can be treated with parenteral fluids administered by clysis. A 21-gauge needle is inserted at a slight angle to the skin of the lateral thigh and then further inserted 1 to 2 inches into the subcutaneous tissue. One vial (150 U) of hyaluronidase (Wydase) is administered through the needle; the enzyme should not be infused into inflamed or cancerous areas. Ringer's lactate solution and mineral additives can then be given at a rate of 100 to 150 mL.
E. **Prolonged central venous catheterization.** Polymerized silicone rubber (Silastic) catheters inserted into the right atrium through the cephalic vein can provide prolonged venous access for administering intravenous fluids, blood products, and drugs and for sampling blood. Both external and subcutaneously implanted types are available.
   1. **A nonfunctioning catheter** is usually the result of obstruction of the catheter tip by either the right atrial wall or a clot. Repositioning the patient usually dislodges the catheter from the atrial wall. A chest radiograph should be taken to evaluate the position of the catheter tip, if it is questionable.
      a. Heparin, 3 mL of 1:1000 solution, should be injected into the line with a tuberculin syringe to provide extra pressure; leave it in place for 15 to 60 minutes before flushing. Repeat the procedure four more times or until successful.
      b. Urokinase, 5000 IU (Abbokinase Open-Cath) may also be tried if a clot is suspected.
      c. An infusion of urokinase directly into the dysfunctional catheter may also successfully dissolve clots. The dose is 40,000 U/hour for 1 to 12 hours. Patients should be observed for bleeding for 48 hours.
   2. **Complications.** Catheter-related deaths are rare. The most frequent problems are severing the catheter (if external), infections, and clotting. Differences in the incidence of documented infections between external catheters and subcutaneous ports are arguable; if infections do occur, they may be treated successfully with antibiotics without removing the catheter in the appropriate circumstances (see Chapter 35, section II.G). There are no differences in the incidence of clotting between external and subcutaneous catheter devices.
   3. **Indications for removing venous catheters** include persistent fever, entrance-site infection, air leak, axillary or jugular or superior vena cava thrombosis, or pleural effusion (due to misplacement of the catheter into the pleural space).

XII. Nutritional support

A. **Mechanisms of malignant cachexia** are poorly understood and are reviewed by Nelson and colleagues (see Suggested Reading). The characteristics of cancer cachexia that differ from starvation cachexia include equal mobilization of fat and skeletal muscle (rather than preferential mobilization of fat), normal or increased basal metabolic rate (rather than decreased), increased liver size and metabolic activity (rather than atrophy), normal or increased glucose turnover (rather than decreased), and increased protein breakdown (rather than decreased). Related factors include but are not limited to the following:
   1. **Metabolic abnormalities in cachexia of malignancy**
      a. **Carbohydrates:** insulin resistance, glucose intolerance; increased gluconeogenesis, Cori's cycle activity, glucose turnover, and serum lactase.
      b. **Fats.** Decreased lipoprotein lipase; increased fatty acid mobilization and turnover, serum lipid levels, and glycerol turnover
      c. **Proteins:** Decreased skeletal muscle anabolism; increased skeletal muscle catabolism and protein turnover
   2. **Decreased intake**
      a. **Anorexia.** Many tumors are associated with anorexia, typically manifested by an aversion to meat. Some patients experience decreased or altered sense of taste and smell.
      b. **Mechanical obstruction** of any portion of the intestinal tract makes oral intake impossible. In advanced stages, tumors of the head and neck or ovary frequently make eating impossible.
      c. **Nausea and vomiting.** See section III.
      d. **Diagnostic studies** often require fasting; if such studies are not conducted efficiently, patients can become nutritionally compromised.
   3. **Increased losses**
      a. **Biochemical abnormalities.** See section A.1.
      b. **Diarrhea.** Severe diarrhea or malabsorption syndromes are associated with carcinoid syndrome, gastrinoma, medullary thyroid carcinoma, pancreatic carcinoma, small bowel lymphatic obstruction, excessive bowel resection, certain cytotoxic agents, and radiation enteritis.
      c. **Lactase deficiency** is common in protein starvation and after some chemotherapies, making milk products unsuitable.
   4. **Natural history.** Increasing loss of body protein leads to progressively worsening anemia, hypoalbuminemia, hypotransferrinemia, loss of cell-mediated immunity, decreased work tolerance, decreased deep-breathing ability, increased risk for pneumonia, inability to ambulate, and then inability to sit up. Other signs include hair loss, scaling skin, brittle nails, and decubitus ulcer. Death occurs when 30% to 50% of body protein stores are lost.
B. **Assessment of nutritional status.** Serial measurements of the following parameters provide prognostic information about the risk for sepsis and death:
   1. **Weight and serum albumin concentration.** Substantial protein-calorie malnutrition is characterized by a recent loss of more than 10% of the stable pre-illness weight and by significant hypoalbuminemia (less than 3.0 g/dL). Albumin has a serum half-life of about 3 weeks, and albumin levels change in direct proportion to improvement or deterioration of nutritional status.
   2. **Transferrin** has a half-life of about 1 week and changes more rapidly than albumin with changes in nutritional state. Serum transferrin is also less affected than albumin by factors unrelated to nutritional state, such as hydration and infection.
   3. **Skin tests.** Poor nutrition with weight loss of more than 10% of usual body weight results in anergy and depression of immune competence. Nutritional status and immunocompetence are adequate if two or more of the following skin test antigens produce a positive intradermal reaction: tuberculin, mumps, *Candida* species, and streptokinase-streptodornase.
   4. **Nutritional requirements.** The healthy person requires 2000 to 2700 (25 cal/kg) calories per day distributed as follows: 15% protein (1 g/kg body weight), 50% carbohydrate (3 g/kg), and 35% fat (1 g/kg). To achieve a positive nitrogen balance and sustain weight, cachectic patients require hyperalimentation with 2700 to 4000 calories and twice the recommended daily allowance of amino acids and essential nutrients.
C. **Treatment of anorexia and cachexia**
   1. **Palliative care of the anorectic or cachectic patient.** Progressive weight loss is part of the biology of progressive cancer. Nutritional therapy does not prolong survival if the tumor cannot be controlled. However, most patients and families believe that nutritional status is essential, regardless of the underlying disease.
      a. Physician "interest" in dietary support often provides psychological palliation, especially when active cancer treatment is not helpful. This posture gives patients and families the feeling that they are doing something positive. Useful techniques include referral to dietitians, and "folksy" dietary advice, such as the use of caloric supplements and the measures described in section C.2, below. The physician must recommend against unhealthful diets and potentially toxic doses of "health food" preparations.
      b. It is important that the physician support the wishes of the dying patient who is becoming exhausted by well-meaning family members and friends trying to force food intake. Coach such patients to tell the family members and friends that, while the intentions are appreciated, being pushed to eat is exhausting and adding to their misery. The physician should reiterate the futility and harmful psychological effects of forcing food. The refusal to eat is the patient's biology and decision.
   2. **Some measures that may be helpful** in patients who refuse food include the following:
      a. Provide small frequent feedings, up to six times a day, as tolerated.
      b. A small helping looks better on a small plate; do not use large dinner plates.
      c. Have food available whenever the patient is hungry.
      d. Have the patient dress for meals and sit at the table, if possible.

    e. Attend to stomatitis, dry mouth, and foul taste (see <u>section II</u>).

    f. Vitamins may be used if not excessive. Vitamin C is ineffective therapy against tumors but is usually harmless unless substituted for proven therapy or if the doses ingested produce dysuria, diarrhea, or satiety.

    g. Do not routinely weigh the patient.

3. **Appetite stimulants** that may be helpful include the following:

    a. Metoclopramide (Reglan), 10 mg PO before meals and h.s., may relieve anorexia, nausea, and early satiety, particularly when caused by dysmotility. Side effects include dystonic reactions and restlessness.

    b. Dexamethasone, 4 mg in the morning after food, particularly in patients who need an anti-inflammatory agent for pain control. Side effects include proximal myopathy, fluid retention, mental status changes, and immunosuppression.

    c. THC, 2.5 to 7.5 mg after breakfast and lunch, starting with the lower dose, which is then escalated. Side effects include dizziness, fluid retention, somnolence, and dissociation, particularly in the elderly.

    d. Cyproheptadine, 2 to 4 mg before meals, is inexpensive and may be helpful.

    e. Megestrol acetate, 400 to 800 mg/day (10 to 20 mL/day of Megace Oral Suspension, which contains 40 mg/mL in 240-mL bottles). Side effects include high cost, edema, hypertension, and hyperglycemia.

    f. Antidepressants may be useful with anorexia due to depression.

    g. Hydrazine sulfate does not decrease anorexia.

4. **Other measures**

    a. Dental relining improves chewing abilities and facial appearance.

    b. An old photograph helps the new caregivers recognize the essential humanness of the emaciated patient.

    c. New photographs of the patient with family, friends, and caregivers helps legitimize the value of this "new" person.

    d. The patient should have at least one new set of well-fitting clothes, if affordable.

D. **Hyperalimentation in cancer patients.** Nutritional deficiency leads to decreased immunocompetence, poor wound healing, and decreased tolerance to antitumor therapy. For cancer patients whose prognosis warrants nutritional support, enteral feeding (EF) or parenteral hyperalimentation (PH) may be given.

1. **Indications for EF.** "If the gut works, use it." Patients who have a functional GI tract but are unable to ingest adequate nutrients orally are candidates for EF. EF is far less expensive, more physiologic, and associated with fewer complications than PH.

2. **Indications for PH**

    a. The patient has a curable neoplasm but is likely to have a protracted recovery from treatment (such as extensive bowel resection), or

    b. The patient is cured of tumor but is awaiting surgical intervention and has residual nutritional problems (e.g., enterocutaneous fistulas), or

    c. The patient requires prolonged postoperative nasogastric suction (more than 4 to 7 days) for conditions that necessitate avoidance of oral intake.

    d. Patients with severe malabsorption, vomiting, esophageal obstruction from benign causes, or severe dysphagia not amenable to dietary manipulation

    e. Patients with chemotherapy-associated severe diarrhea or prolonged stomatitis leading to weight loss

3. **Contraindications to hyperalimentation**

    a. **Contraindications to EF** are intractable vomiting, upper GI bleeding, or intestinal obstruction.

    b. **Hyperalimentation is not useful** for patients with the following conditions:

        1. Minimal nutritional deficits, or

        2. Weight loss caused by progressive cancer that is unlikely to respond to therapy, or

        3. Aggressive tumors that respond dramatically to therapy (e.g., lymphoma and small cell lung cancer)

    c. **PH is strongly discouraged** in most patients receiving chemotherapy because the 12% complication rate is unacceptable. Complications include pneumothorax, thrombosis, and catheter-related septicemia.

E. **Enteral feeding** provides liquid formula diets into the GI tract orally or by means of feeding tubes. Gastrotomy tubes and other tube enterostomies are used when a nasogastic feeding tube cannot be placed or is not tolerated by the patient. Percutaneous endoscopic placement has the advantages of speed and minimal surgical incision.

1. **Preparations.** Many enteral products are available, but a standard formula is usually sufficient for patients with an intact digestive system. Isotonic solutions that contain high nitrogen and a medium caloric density (1 to 2 kcal/mL) are satisfactory in 90% of patients. Preparations that contain a high concentration of amino acids are often unacceptable for patients with cancer-related meat aversion.

High-calorie preparations are often offered as caloric supplements, but they often cause diarrhea and are so rich that many patients refuse them. Asking patients for flavor preference, diluting each can with an equal amount of water, and serving no more than half this amount *on ice* can make these preparations more acceptable to patients. This cooled dilution can provide up to an additional 1,000 cal/day when given *after* patients have eaten what they can of a meal, between meals, and at bedtime as tolerated.

2. **Administration.** Start tube feedings with a full-strength solution at about 30 mL. Increase the infusion rate to tolerance by increments of 10 to 25 mL over 12 to 24 hours for 2 to 3 days.

3. **Complications of EF**

    a. **Frequent complications and corrections**

        1. Vomiting and bloating: reduce the flow rate.

        2. Diarrhea and cramping: reduce the flow rate; dilute the solution; treat with an antidiarrheal drug; consider a different type of solution. Diarrhea is especially likely in patients who have been given broad-spectrum antibiotics.

        3. Hyperglycemia: reduce the flow rate; give insulin.

        4. Edema: usually requires no treatment; diuretics may be used.

        5. Offensive smell or taste: add flavorings.

        6. Nasopharyngeal discomfort: encourage the use of sugarless gum, gargling with warm water and mouthwash, topical anesthetics.

        7. Abnormalities of serum levels of sodium, potassium, calcium, magnesium, or phosphorus: adjust the formula's ingredients.

    b. **Infrequent complications and corrections**

        1. Congestive heart failure: administer fluids more slowly and treat cardiac decompensation.

        2. Fat malabsorption: use low-fat formulas; add pancreatic enzymes.

        3. Elevated serum transaminase: decrease carbohydrate content of formula.

        4. Acute otitis media: administer antibiotics; change nasogastric tube to other nostril.

        5. Clogged tube lumen: flush with water or replace tube.

    c. **Rare complications that necessitate discontinuing therapy**

        1. Aspiration pneumonia (unlikely to occur if the head of the bed is elevated to 45 degrees, volume overload is avoided, and the cough reflex is intact)

        2. Esophageal erosion from nasogastric tube

        3. Acute purulent sinusitis

        4. Hyperosmolar coma

Suggested Reading

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Chapter 6 Psychosocial Aspects of Cancer Care

Barry B. Lowitz

When I thought I was learning to live, I was but learning to die.
   LEONARDO DA VINCI

I. Psychological responses to the diagnosis of cancer tend to reflect premorbid mechanisms of coping and interacting. The presence of cancer disrupts virtually every aspect of the life of the patient and family. Premorbid psychiatric problems become intensified and "telescoped." Physicians and other health care personnel have an active role in helping patients and families to cope and function.

A. **Common losses experienced by cancer patients**
   1. Loss of health and physical integrity (resulting from disease, disfigurement, and discomfort)
   2. Loss of friends and loved ones (including separation to receive treatment, rejection by some friends or family members)
   3. Inability to perform routine activities (such as self-care, job, and hobbies)
   4. Loss of finances (resulting from cost of treatment and loss of job)
   5. Loss of self-esteem
   6. Loss of religious convictions ("What did I do wrong to deserve this?")
B. **Common reactions**
   1. **Symptoms and signs**
      a. **Hostility-anger** is the most common reaction and is typically manifested by displacement of anger about the disease onto doctors, relatives, and others. Patients and families frequently blame their current problems on mismanagement by previous health-care personnel.
      b. **Anxiety** is manifested by agitation, short concentration span, sleep problems, or compulsive behavior. It often worsens the subjective sensation of pain.
      c. **Guilt** may be manifested by blaming others for the illness. Patients or family members commonly ruminate over what they might have done to cause the illness. Family members often feel that if they had taken other actions, the illness would not have developed.
      d. **Entitlement** is manifested by petulant and demanding behavior. Patients feel that they deserve special treatment as compensation for their losses.
      e. **Compliance** with medical treatment develops when patients understand their disease and develop a sense of acceptance. Noncompliance is a regressive behavior that signals anxiety, depression, or unhealthy denial.
      f. **Depression** is an appropriate response if it is not severe. Depression is manifested by flat affect, insomnia, anorexia, withdrawal, and psychomotor retardation. Depression is often mistaken for dementia; establishing the differential diagnosis is essential to improve patients' ability to function.
      g. **Dependency** is a very common reaction to advanced malignancy and can immobilize patients.
      h. **Psychoses** that require pharmacologic intervention may develop.
C. **Evaluation.** Changes in behavior by either the patient or the patient's loved ones are the usual clues that problems exist. Assess the following:
   1. **Emotional risk factors**
      a. Prior emotional problems
      b. How the patient handled prior significant losses or hostilities (similar strategies will probably be used again)
      c. Presence of concomitant stresses
      d. Nature of interpersonal relationships
      e. Patient's attitude toward self
   2. **Alterations** in how a typical day is spent.
   3. **Support** given by family, friends, religious institution, employer, and others.
   4. **The severity of depression.** Determine specific concerns, such as financial or family problems, that result from the illness.
   5. **Changes in sexual activity** and interest
D. **Management**
   1. **General techniques.** The physician should be a sympathetic listener who is open, understanding, and available. Specific attention should be directed as follows:
      a. Determine specific goals with the patient (e.g., travel, family events).
      b. Confront patients with depression or anxiety directly ("You look depressed"; "You look upset").
      c. Explain the medical problems clearly and consistently.
      d. Be flexible with therapeutic options, second opinions, and the patient's wishes.
      e. Denial may be a healthy psychological defense mechanism and should be supported if it does not interfere with the welfare of patients or their families.
      f. Patients and their families must be informed that sexual activities are not harmful and that cancer is not contagious. Many patients lose interest in sexual activity and require support from the physician; this is not abnormal, even in healthy people.
      g. Antidepressant medication can be very effective for sleep disorders, loss of interest, and unexplained fatigue. Unless medically contraindicated, an empirical trial of antidepressants for 4 to 6 weeks can be beneficial.
   2. **Psychiatric consultation** should be requested when the patient is extraordinarily difficult to manage. Expert consultation is essential when patients are immobilized by anxiety or depression, or are psychotic. Such consultations should seek psychiatric diagnoses, suggestions for behavior modification, and recommendations for psychopharmacologic therapy. The continued care of the patient, however, should remain in the hands of a member of the patient's established health care team.

II. Discussing diagnosis, treatment, and prognosis

A. **General approach**
   1. All patients need to be fully informed about their illness, its prognosis, and options for therapy. The best way to inform a given patient depends on the patient's age, premorbid personality, economic situation, family or social factors, concomitant illnesses, and other determinants of his or her unique psychosocial makeup.
   2. The diagnosis of cancer should be presented to the patient as soon as tissue confirmation is obtained. The physician should meet the patient privately and allow enough time to discuss the diagnosis and answer questions. Care should be taken to *preserve eye contact* during this discussion.
   3. The physician's candor in discussion of the diagnosis creates trust and helps patients view further staging procedures as a positive approach to the disease.
   4. Patients should be encouraged to make a list regularly of any general questions they or their families have and to bring this list to the next appointment.
   5. Explanation of the diagnosis may have to be repeated. A patient often hears only what he or she wants or is ready to hear. Some deny ever being told the diagnosis even when it is discussed several times. If such denial does not interfere with medical care or cause psychosocial problems, the patient need not be repeatedly confronted.
B. **Virtually all patients should be told the diagnosis.** Honest discussion removes the trauma of speculation. The diagnosis of cancer engenders a sequence of symptoms, complications, tests, treatments, and hospitalizations that disrupt the patient's enjoyment of life. Time becomes precious. There are finances to plan, vacations to take, acquaintances to rekindle, things to be said, and dreams to fulfill. Life planning mandates patients' awareness of the diagnosis. Even patients with chronic brain syndrome probably should be told the diagnosis on the chance that they can comprehend at least part of what they are told.
C. **Common problems**
   1. **Patients who deny the diagnosis** and want another opinion should be supported. The physician should tell these patients that they may want a second opinion and that their seeing another practitioner will not jeopardize the present relationship. The primary physician should offer to provide copies of all records for the second-opinion doctor to review.
   2. **Families who oppose the patients' knowing the diagnosis** should be answered honestly. Patients must be told regardless of the family's apprehension.

The task then becomes dealing with the family's anxiety and assisting them in accepting the need for the patient to be fully informed. Certain cultures disdain having the elderly informed of the diagnosis of cancer; associated linguistic limitations may preclude the physician from accomplishing the previously given recommendations.

3. **Questionable ability to cope.** Some patients' ability to cope with the knowledge of the diagnosis may be legitimately questioned. A qualified mental health person may be able to assess the patient and help establish a way for the patient to be accurately informed and helped to cope with the stress.
4. **Passive patients**
   a. Patients who ask no questions at the time of diagnosis may also be denying facts. All patients should be asked directly for questions and be instructed to write them down for further discussion. It is important to discuss the necessary diagnostic studies and management. Overly quiet patients should be encouraged to come back more frequently to avert poor follow-up or even suicide attempts.
   b. Patients who cooperate with therapy and ask few or no questions may want the physician and family to make the difficult decisions. Be certain that patients truly wish to have others involved in making decisions. Limit information for these patients to potentially unpleasant symptoms of therapy.
5. **Discussing the prognosis.** Rigid prognostication for a given patient is impossible. "The doctor gives me *X* months to live" is inappropriate for a patient to think or say. Doctors do not have "crystal balls" and realistically cannot set a "date for the execution." Doctors should avoid making guarantees and commitments that cannot be kept. The doctor should stress the variable course and unpredictability of disseminated cancer.

III. Preparing patients for cancer treatment
Most of the current technologies are complex, frightening, potentially mutilating, and toxic. Many difficult decisions must be made among unpleasant choices. Most patients and their families must actively participate in making these decisions.

A. **Organizations.** Patients who require ostomies (i.e., ileostomy, colostomy, or ureteral diversion) should be visited preoperatively by a stomal therapist and a member of one of the ostomy clubs. These clubs, although not technically oriented, are supportive of patients and families and can share patients' feelings and concerns. Laryngectomy patients can be similarly prepared by speech therapists and patient clubs that can be contacted through the American Cancer Society. Patients who require amputation may benefit from meeting with recovered amputees and physical therapists both before and after surgery. Patients with breast cancer may be helped by the American Cancer Society Reach for Recovery Program, which can help reinforce the goal of a return to normal function. The patients' spouse should be included as an active participant in all discussions of the disease and treatment.
B. **Radiation therapy.** It is essential that the radiation therapist fully inform and prepare patients in advance concerning what to expect. The treatment environment (e.g., the "Radiation Hazard" signs, the whirring sound of a linear accelerator, and feeling isolated) should be described to help allay anxiety.
C. **Chemotherapy.** Patients who are to receive chemotherapy should be informed by the oncologist about the side effects and about the frequency and duration of treatment. The patients' primary physician should be encouraging and hopeful.

IV. Social pressures affecting cancer treatment
Pressures from family members and well-meaning friends are dominant forces in management decisions affecting cancer patients. These forces often directly conflict with scientific standards of care and rational medical ethics. The physician may not be able to remedy the causes of the problems but can minimize their effects.

A. **Patients' families and loved ones**
   1. **Children.** Even young children should be kept informed about what is happening to their loved ones. Children often fantasize and may think that something they did caused the illness. Emotional instability may be manifested as regressive behavior (such as loss of toilet training), night terrors, school problems, or other behaviors. If children are not informed, they may feel abandoned, isolated, and even more responsible. Professional counseling is necessary for many children. If the patient is close to death, the children should not be kept away. Frequent hospital visits are important both for the patients and the children.
   2. **The concerned family.** Family members must be active participants in the care of the patient. A single family member or the patient should be appointed as spokesperson and should be educated about the patient's illness, the diagnostic plans, and the family's responsibilities. Concerned friends and family members often repeatedly ask the same questions, and a spokesperson can be a great help. Family conferences with the physician may alleviate that difficulty.
   3. **The difficult family** may be identified by their having previously sought opinions from many different specialists, "none of whom were any good." Characteristically, they flatter, demand excessive consultations, and question treatment methods. If the physician tries to define limits, the family may respond by accusing him or her of insensitivity or may involve the physician in litigation. The root of these behaviors is often excessive panic or guilt. Some ways to handle these situations are as follows:
      a. **Do not be dogmatic** about the approach of past physicians. Families should be reassured that the past care was reasonable and appropriate (if it was); no two physicians do exactly the same things.
      b. **Family conferences are helpful.** The physician will not able to interact with each and every family member every time they have a question, but will be able to do so through an agreed-upon spokesperson.
      c. **The patient is a victim** of such a family; the patient loses continuity of medical care to satisfy the panic or guilt of the family. If possible, talk this over with the patient directly. Most patients respond positively to the suggestion of bringing the family to the bedside in your presence and having the patient direct the family to change their behavior.
B. **Disagreement between patient and family about management** may involve cancer therapies, medical support, requests for other opinions, and so on. Two situations are commonly encountered in the practice of oncology: (1) The family wants the patient left alone to "die with dignity," and the patient wants to "keep fighting"; or, (2) the patient wants to be left alone and the family will not give up. These problems must be approached conjointly to avoid social, and possibly legal, disasters.
   1. Present the options to patients in a private meeting or with the closest family members. Make it clear to patients that they must make the final decision.
   2. When patients have reached a decision, have a conjoint meeting with them and their families to ensure that everyone knows and respects their wishes. It is important that patients state their wishes directly to the family in your presence. This protects families from having recriminations about doing too much or not enough later on, and makes it clear you are following the patient's informed direction. Such meetings should be documented in the patient's chart.
C. **When other opinions, experimental therapies, or more toxic therapies are sought**
   1. **Second opinions** should be encouraged for all patients and families who broach the subject. A word of caution: The second opinion sometimes recommends an aggressive therapy of which you disapprove rather than a sound treatment approach that differs from yours. This disparity can lead to an endless chain of second opinions as patients agonize over the best decision. Although most physicians who give second opinions will respect your relationship with the patient, a few will libel you and actively condemn what you have done or are planning to do for the patient. An egocentric colleague or a tertiary care center that is "a bit short on patients" can be a risk for both the patient and you.
   2. **Family members and well-meaning friends** often pressure patients into undertaking aggressive treatments that have not been adequately evaluated or have proved only marginally effective.
      a. These treatments are characteristically toxic and expensive, involve additional radiologic and laboratory studies to monitor the effects of therapy, and require additional medications to treat the side effects of the "breakthrough" therapy. When compared with a more standard approach, the combined diagnostic and therapeutic assault is not generally indicated. Unfortunately, patients are often made to feel that they owe it to their loved ones to "give it a chance."
      b. The physician must make it clear that the goal of treatment in patients with incurable cancer is palliation. Palliation means improvement of symptoms and function but does not mean reduction in size of an asymptomatic lesion or reduction in blood levels of a tumor marker. Highly toxic chemotherapy or aggressive or "innovative therapies" have little role in palliation. A gentle but direct approach is often necessary to keep patients out of harm's way.
   3. **Management of patients participating in clinical trials**
      a. Experimental therapies that are organized as formal clinical trials stand in stark contrast to "creative oncology." Formal studies are approved by an Institutional Review Board, which protects human subjects who are undergoing experimental treatment. Such formal trials are the only valid method for determining the effectiveness or ineffectiveness of a new cancer treatment.
      b. Primary oncologists and primary care physicians should have an ongoing role with patients, during and after the experimental therapy. The primary doctors must have a copy of the protocol in the patients' chart.
      c. The side effects and cost of participating in a clinical trial must be weighed against the patient's hope that the treatment may prove effective.
D. **When families seek "quack" methods of cancer therapy**
   1. **Seeking the cure.** Patients and their families often become desperate and willing to try anything. They often fear conventional cancer therapies and may become convinced that the "medical establishment" is depriving them of a cure. Patients easily fall prey to quacks who may even be licensed physicians.
   2. **Compromise.** Families or patients may seek unconventional therapy even while complying with conventional medical therapy. Unless the physician states his or her disapproval explicitly, families may think he or she approves. The physician should also state in advance that he or she will not accept that any improvement in the patient's condition results from the unacceptable modes of therapy. The physician should know which agents the patient receives as part of outside treatment; these agents may be actual antineoplastic drugs, and their administration may compound the toxic reactions from other prescribed chemotherapy. If the patient prefers to abandon medical treatment completely, the physician should assure the patient and family that the physician will be available if needed.
   3. **Confrontation.** The issue of cancer quackery must be confronted and fought with facts.

a. Explain that increased morbidity occurs without competent, comprehensive medical supervision.
b. Point out the excessive costs involved.
c. Explain the reasons positive results occur with ineffective agents.
   1. A small percentage of many tumor types regress spontaneously; these are the only results reported.
   2. Patients who are "cured" by unproved methods often do not have cancer at all; biopsy specimens were never taken.
   3. The disappearance of reversible, nonmalignant disease can look like a cancer response.
   4. Some distributors of ineffective treatments use radiation therapy and chemotherapy in addition to the medically unacceptable remedy but ascribe responses to the latter.
d. Explain that many unscrupulous entrepreneurs use psychological techniques to sell worthless products to desperate people who may be told such things as, "A powerful governmental agency (or the American Medical Association) is suppressing the use of a great cancer cure for reasons known only to themselves." The physician should acknowledge that although the legitimate medical profession does not have all the answers, this does not imply that someone else does.

E. **The media**
   1. **Journalism** can cause great harm to many individuals, but the harm to society of prior restraint or censorship of the media has been consistently proved far more dangerous.
   2. **Medical journalism.** Most people know about an illness only by what they hear from their physicians, other medical professionals, and the media. A journalist's job is to write news and not necessarily to provide information. A story that reports negative results for a therapy or insufficient testing of a therapy is information but not news, and such stories are rarely published. On the other hand, the excitement of a researcher who has found some positive early results or the happiness of a patient who appears to have benefited from an unusual therapy is infectious for a journalist; such stories are frequently published. Furthermore, journalists are often "sitting on the door step" of research institutions. They often publish news articles about "breakthrough" treatments before they appear in medical journals or are appropriately evaluated by the research community. News is mistaken for information by most people, and the physician has a formidable job in helping patients to make informed decisions.
   3. Media "breakthroughs" are often embarrassing to the physician. Patients feel that any competent physician should "know these things." The best way to deal with this is to tell the patient directly that you are not familiar with the treatment but will find out more about it and help them evaluate it. Most patients and families appreciate this kind of honesty. Those who do not are often medicolegal risks.

V. Interacting with the dying patient

A. **The problem of methodology.** Care of the dying patient requires artful methodology. Inexperienced doctors feel uncomfortable interacting with these patients, do not know what to say, and often avoid meaningful contact.
   1. **We all die uniquely.** Each patient has unique fears or anxieties about death. However, many experts in thanatology have documented that patients are less afraid of death than of being abandoned.
   2. **Emotional reactions in the dying patient** include denial and isolation, anger, bargaining, depression, and acceptance. There are, however, no regular and predictable stages of dying. Most patients fluctuate among these stages for varying periods of time, sometimes denying their illness, sometimes angry, sometimes depressed. The stage of acceptance, if ever present, is often transitory; when it does occur, it is usually brief, just before demise, and associated with the voluntary separation of patients from friends and relatives.

B. **Techniques in thanatology.** The role of the physician is to minimize the psychological discomfort of the patient. Because time is of the essence, a crisis intervention model can be employed.

Support defenses that tend to minimize the patient's discomfort.
   Counteract harmful defenses.
   Avoid isolating the patient.
Maintain an honest relationship to maximize patient trust.

   1. **Provision of clinical data.** Knowing the disease's progress and the details of laboratory and x-ray films and discussing management plans help many patients gain some sense of control over their disease.
   2. **Passive support.** There is little point in forcing discussions about death unless the patient shows anxiety, is depressed, or volunteers the subject. In-depth psychiatric analysis is also best avoided unless analysis itself is a useful defense for the patient.
   3. **Support of attitude**
      a. Most people feel that a positive attitude is beneficial to their condition. Cancer patients often spontaneously adopt this view, and it should be supported by the physician. The risk is that when events turn for the worse, some people feel guilty that the change was their fault for not being able to maintain a positive attitude. The best intervention is to tell patients how well they have done and that they probably would have fared much worse if they had a negative attitude.
      b. Some people may benefit psychologically and perhaps physically from relaxation techniques such as acupressure and muscle testing, mental imaging of their bodies destroying the tumors, self-hypnosis, and so forth. We actively encourage patients who want to try these methods of "holistic medicine" so long as they do not interfere with proven methods of treatment or endanger the patients' health.
   4. **Support of hope.** Hope is never false. A positive attitude on the part of the physician provides comfort. Hopeful patients may spend more of their time thinking about living than about dying. Patients hope for more than just longer life; they hope to function well, be free of pain, and not be isolated from contact with other people or their physician. Even when the cancer ceases to respond to treatment, the physician can support these hopes.
   5. **Discourage harmful defenses**
      a. **Anger out of control.** Patients who are frustrated about their disease often manifest anger toward family, friends, and medical personnel. This can also be a method that patients use to "protect" the family from loss and guilt; patients wrongly believe that if they are grumpy, they will not be missed as much. Confront the patient directly: "You have a right to be angry at your disease, but your family and I are on your side. We all have to work together to treat your illness. Being angry with me [us] is not helping anyone." This technique may provide patients the defense of objectifying the disease as something separate from themselves.
      b. **Manipulative behavior** often reflects a pre-illness personality disorder but may be the only way the patients can avoid isolation. Physicians can often recognize manipulative behavior when they feel angry with these patients and feel guilty for feeling angry. Acceptable patient behavior must be defined in these circumstances. This definition and the consequences of unacceptable behavior should be discussed with the staff and the family.
      c. **The "hateful" patient** can present formidable problems in care. These patients make the staff angry by passive-aggressive behavior, accident proneness, manipulation of drug use, and giving conflicting descriptions of their understanding of the disease and its treatment to various staff members. They tend to play people off against each other. These activities can be very destructive. It may be helpful to refer the patient for counseling; maintain a strictly technical relationship with the patient, and place firm limits on physician availability; confront the patient directly, "Your behavior makes it difficult for me to give you proper care"; note a few specifics. If there is no improvement, the patient probably should be instructed to find another physician. Be sure to document the reasons for referral in the medical records.
   6. **Managing a patient's sense of isolation**
      a. **Physical isolation**
         1. For patients who are left alone at home during the day and who call the doctor several times a week, recommend a day-care or occupational therapy center. Arrange for regular visits by the family.
         2. Patients who are afraid not to be under continuous medical supervision should be asked directly if they have this concern. Arrange for hospice or nursing home care. Assure patients that nurses will contact the doctor for any problems.
         3. If patients who have been stable seek acute medical admission, with or without objective evidence of worsening, this often represents a grave sign of imminent deterioration or of serious problems at home and is an absolute indication for acute hospital admission.
      b. **Psychosocial isolation**
         1. **The garrulous patient.** Some patients talk incessantly at each visit and behave as if the doctor were their captive audience. If the physician defines and sticks to time limits for each visit, he or she is less likely to resent or isolate such patients.
         2. **The depressed or agitated patient.** When patients appear depressed or anxious, confront the patient gently but directly, "You seem down today," or, "You seem upset." Encourage ventilation of feelings.
         3. **The fearful patient.** The patient says, "I think I'm dying." The physician should ask if the patient is frightened or concerned about familial economic problems or the family's ability to cope after his or her death. The physician should ask if there is some way to help. Sometimes these questions allow the patient to focus on particular problems beyond the fears all share about death.
   7. **When treatment options are expended**
      a. When little more can be done to control the tumor, patients should be informed of this and told that further therapy may only make them more ill. These patients should continue to be followed closely and solicitously even if they are not receiving specific anticancer treatment.

   b. Attention should then be focused on achieving goals other than tumor control, such as relief of pain, control of other symptoms, and enjoyment of family life.

   c. Some patients express desire for chemotherapeutic agents after appropriate drugs have failed. Occasionally, drugs with some effectiveness may be used in doses too low to produce side effects for placebo effect; cost should be minimized, and the family should be informed about the rationale for treatment.

  8. **When there is nothing to say**

   a. **Presence and interest** are the most important commodities physicians have to offer in these settings. Soft touching, limited physical examination, and allowing the patient to speak freely may be comforting. Be a good listener and maintain eye contact. Personal feelings and sensitive words should be expressed. If the physician does not know what to say, he or she should either admit it to the patient or say nothing.

   b. **Words are rarely helpful** to conscious patients who are frightened and aware that they are about to die. Parenteral sedatives or narcotics may alleviate some anxiety, but merely being there and holding the dying patient's hand probably palliates the psychological discomfort of dying.

C. **The team approach.** A patient's dying can drain individual staff members. A team approach to the care of dying patients can diffuse the impact and benefit the patient. The responsibility for preventing patient isolation and monitoring patients' emotional reactions belongs to the nurse, psychologist, lay consultants, hospital team, families, and friends, as well as to the physician. If a patient needs spiritual support, the clergy should be consulted. If there are estate problems or social problems, social services or attorneys should be consulted. It is important that one health care provider, usually the physician, is in charge to provide coordination and continuity.

VI. Physicians' reactions Emotional problems of physicians, especially oncologists, frequently arise from regular exposure to death together with difficulty coping with their own aging and mortality. Physicians may wonder whether they will survive long enough to enjoy the fruits of many years of labor, to experience recognition for their work, or to be remembered for it after they die. These questions arise earlier in life for those taking care of dying people and may take on pathologic significance.

A. **Signs of emotional problems in physicians**
1. Feeling helpless in treating patients; feeling overwhelmed that few patients with advanced cancer can be cured
2. Increasing feelings of guilt for not having been able to keep a patient alive; carrying a sense of inadequacy or depression
3. Feeling hopeless about the prospects of cancer treatments
4. Feeling remorse for unfulfilled dreams; working harder but starting to feel that medical practice has harmed enjoyment of life and medical altruism has been repaid by pain felt for sacrificing family, pleasures, and self
5. Tending to buffer themselves from patients with house staff, colleagues, or a too-busy practice ("I cannot take it anymore")
6. Becoming inappropriately aggressive or optimistic in therapy when it is evident that it will not benefit a patient; developing the "general complex," whereby physicians feel they are fighting a war against the unfairness of nature that they cannot win
7. Feelings of chronic fatigue or exhaustion, especially associated with inability to limit time and energy given to patient care

B. **Acting on symptoms.** These signs in physicians and other members of the health care team must be taken seriously because patients and staff can both be adversely affected. Positive action is required.
1. A vacation or change in work milieu may be indicated. Vacation schedules should be compulsively kept; everyone, including thanatology personnel, needs some time for bereavement.
2. Practice may have to be stopped altogether to preserve mental health.
3. Psychiatric consultation should be sought for prolonged depression or anxiety, sleep disturbance, feeling that people are turning away, excessive consumption of alcohol or other drugs, or evidence of emotional impairment or chronic stress.

Chapter 7 Head and Neck Cancers

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Principles

Head and neck cancers comprise a heterogeneous group of tumors exclusive of intracranial lesions. Tumors from various sites of origin have distinct behavior patterns and prognoses and require different management. Each primary site is considered separately after a discussion of common features.

I. Epidemiology and etiology

A. **Incidence.** Primary head and neck malignant tumors constitute 5% of all newly diagnosed cancers in humans and result in about 16,000 deaths per year. One to three cases occurs annually per 100,000 population in the United States. The incidence of squamous cell carcinoma is significantly higher in male patients (male-to-female ratio, 3:1 to 4:1).

B. **Etiology.** Substantial alcohol intake and cigarette smoking are major risk factors for head and neck cancers. A variety of hereditary, environmental, occupational, and hygienic factors are of lesser importance. Conditions associated with increased incidence of specific head and neck cancers are discussed in their respective sections.

C. **Multiple cancers.** Second primary cancers in the upper respiratory passage are present in about 5% of patients with head and neck cancers at the time of diagnosis. Eventually, secondary cancers occur in 20% of all of these patients. This development is most frequent in patients who continue to consume alcohol and smoke cigarettes. The multiplicity of neoplasms suggests that the entire respiratory mucosa may be predisposed to develop malignant tumors, a so-called field defect. These patients may also develop cancer of the lung.

II. Pathology and natural history

A. **Histology.** Squamous cell carcinomas constitute at least 95% of head and neck cancers, except those in the hard palate and salivary glands. Minor salivary gland adenocarcinomas can occur throughout the upper aerodigestive tract. Tumors with other histologies are infrequently seen.

B. **Metastases.** Head and neck cancers spread predominantly by local invasion of adjacent tissues and dissemination through lymphatic channels. Hematogenous dissemination, most commonly to the lungs, is a relatively late phenomenon.

III. Diagnosis

A. **Common symptoms or signs**
   1. Mass, often painless
   2. Mucosal ulcer, often with mass
   3. Localized (often referred) pain in the mouth (teeth), throat, or ear
   4. Odynophagia or dysphagia
   5. Visual disturbances related to cranial nerve palsies, proptosis, blindness
   6. Hearing loss, usually unilateral, and often associated with serous otitis
   7. Persistent unilateral "sinusitis," nasal obstruction, or bleeding
   8. Unilateral tonsillar enlargement in adults
   9. Five to 10% of white plaques (leukoplakia) may be cancer *in situ.* This condition must be differentiated from *Candida* species infection (can be wiped off) and lichen planus (fine white lines often related to denture irritation).

B. **Laboratory investigation.** The pretreatment diagnostic evaluation of head and neck cancer must both document the extent of disease and exclude a coincident second primary cancer in the upper aerodigestive tract. A chest radiograph and a computed tomography (CT) or magnetic resonance imaging (MRI) scan from the base of the skull to the thoracic inlet are included in the evaluation of location and extent of the cancer.

C. **Endoscopy** includes direct visualization of the nasopharynx, larynx, hypopharynx, cervical esophagus, and proximal trachea. In patients without obvious tumors, biopsies may be performed during endoscopy of high-risk areas: the nasopharynx, pharyngeal tongue, tonsillar fossa, and pyriform sinus. Endoscopy is useful in the following circumstances:
   1. To document the presence, site, and extent of tumors in the upper aerodigestive tract
   2. To search for other primary cancers in patients with already recognized cancers in the upper aerodigestive tract
   3. To evaluate patients with metastases of unknown origin (MUO) to neck lymph nodes

D. **Evaluating patients with probable MUO to neck lymph nodes.** A premature biopsy of a suspect node can compromise both treatment and likelihood of cure if the origin is head and neck cancer. Management of patients with MUO is discussed in Chapter 20.
   1. **Criteria for endoscopy in patients with cervical adenopathy**
      a. The enlarged node is firm and nontender or growing, and there is no evidence to suggest inflammatory disease (e.g., no response to a 2-week course of antibiotics).
      b. The patient is at high risk for cancer (older than 40 years of age and a history of tobacco or alcohol abuse).
      c. No primary tumor is found on visual, digital, and mirror examination.
   2. **Biopsy of the suspect node** should be done only when:
      a. Fine-needle aspiration cytology fails to reveal the diagnosis, and
      b. Thorough physical examination fails to reveal a primary tumor, and
      c. CT or MRI examination does not disclose a primary tumor, and
      d. Endoscopy fails to reveal a primary site

IV. Staging system and prognostic factors

A. **Staging classification.** The TNM staging system for head and neck cancers is widely used. The definitions for the system, histopathologic grades, and stage groupings are shown in Table 7.1.

Table 7.1 TNM staging and stage grouping for head and neck cancers [a]

B. **Discordant clinical and pathologic evaluation of stage.** In some instances, biopsies of an apparently invasive cancer are interpreted as cancer *in situ,* cellular atypia, or dysplasia. This histologic interpretation requires additional biopsies, particularly at the margin of the gross tumor, because the initial biopsies may not have been representative of the lesion. If these biopsies are not conclusive, the entire gross tumor may be excised, if practical, for more complete examination. After the primary cancer has been positively identified, treatment planning can proceed based on likely extension of the tumor into adjacent tissues.

C. **Prognostic factors**
   1. **Primary site.** The site of origin of a cancer in the head and neck strongly influences the prognosis. For example, a cancer 1 cm in greatest dimension on a true vocal fold is more curable than a primary lesion of similar size arising subglottically or in the pyriform sinus.
   2. **Extent of tumor.** The local extent of the primary tumor and metastases is an important prognostic indicator and is reflected in the TNM staging system.
   3. **Histologic grade.** Epidermoid carcinomas of the upper aerodigestive tract are usually subdivided by grade (Table 7.1). Tumor grade correlates somewhat with biologic behavior; less well-differentiated primary cancers tend to grow more rapidly and be more locally or regionally extensive at the time of initial diagnosis.

V. Prevention

A. **Abstinence.** The limiting or elimination of alcohol and tobacco consumption (including chewing tobacco) and good oral hygiene remain the mainstay of prevention for most head and neck cancers.

B. **Chemoprevention.** Isoretinoin (13-*cis*-retinoic acid) can reverse severe oral leukoplakia. Continued maintenance therapy with attendant toxicity (rashes, conjunctivitis, hypertriglyceridemia) is required to sustain the effect. Isoretinoin also appears to reduce the occurrence of second neoplasms in patients treated for primary head and neck squamous cell carcinomas; the drug does not prevent recurrence of the original neoplasm, however.

VI. Management

A. **Principles of treatment.** Before commitment for therapy of all patients, there should be input from members of a multidisciplinary group that includes a surgeon, radiation oncologist, medical oncologist, and dentist. Patients must be frequently examined after treatment. Recurrent or persistent tumors can usually be recognized within 2 years of initial treatment.
   1. **Anatomic barriers,** such as bone and peripheral nerves, may be a greater deterrent to surgical removal than to irradiation. Thus, cancers arising in the mucosa of the nasopharynx or posterior pharyngeal wall are usually irradiated by choice because of anatomic barriers. In other primary sites, such as the vocal fold and retina, the extreme morbidity of loss of voice or sight associated with obtaining a tumor-free margin surgically usually makes radiation therapy (RT) preferable.
   2. **Surgery.** The primary cancer should be widely excised with tumor-free margins of normal tissues. Preservation of function (i.e., swallowing or speech) is a prime consideration. Cosmesis is secondary to adequate resection. Ipsilateral neck dissection is often an extension of this operation.

   Tumor extension into bone requires sophisticated partial resection, when appropriate, or complete resection followed by an insertion of a prosthesis or some type of flap construction. When the primary tumor is closely adjacent to or involves the mandible, an *en bloc* resection of the primary tumor, cervical nodes, and intervening mandible may be done (called *composite resection*).

   3. **RT** can control cancers arising in the head and neck with preservation of an intact anatomic part and consequently with preservation of function and cosmesis.
      a. **The volume** at the primary tumor site must include a margin outside of all cancer cells and so is comparable to that which would be removed surgically. The anatomic sites of actual or likely spread of cancer, such as the regional lymph nodes, are frequently included in continuity with the primary tumor site. The primary and high-risk sites may be treated simultaneously or consecutively by the same or different methods.
      b. **Large total doses** (i.e., 6500 to 7500 cGy) of radiation, approaching the tolerance of normal tissues, are usually required to eradicate squamous cell carcinomas arising in the mucosa of the head and neck. Occasionally, the usual daily dose of 180 to 200 cGy may be delivered at less than 24-hour intervals (accelerated fractionation), or several smaller increments may be used every 24 hours (hyperfractionation).

B. **Treatment of the primary cancer**
   1. **T1 or T2 cancer at the primary site.** Either RT or surgery can usually treat small malignancies with equal success. The choice of modality depends on the tumor's location, accessibility, and histologic grade and the patient's vocation, health, and treatment preference. Tumors of high grade are often best treated with RT. Deeply invasive tumors and tumors adjacent to or invading bone are often best managed surgically.
   2. **T3 or T4 cancer at the primary site.** The management of T3 lesions should usually combine surgery with preoperative or postoperative RT. Neither sequence has been demonstrated to be clearly superior. If surgery is not considered feasible, patients may be treated with either high-dose RT alone or RT preceded by or followed by chemotherapy. The addition of chemotherapy to RT is still being investigated.
   3. **Postoperative RT.** After the removal of all grossly detectable cancer, doses of 4500 to 6000 cGy result in a very high frequency (90% to 95%) of tumor control with few detectable sequelae. Advantages of this sequence include an appraisal of tumor extent that is unaltered by irradiation and performance of surgery in unirradiated tissue with possibly fewer technical problems and more rapid healing. Such planned use of RT should begin as soon as wound healing permits. **Postoperative RT is indicated** when:
      a. The cancer is poorly differentiated, or
      b. The cancer is histologically identified at or near the surgical margins, or
      c. There is extensive involvement of the lymphatics by tumor, or
      d. Multiple cervical lymph nodes contain cancer, or
      e. The tumor extends through the capsule of the node into surrounding tissues

C. **Treatment of cervical lymph nodes** is determined by the site and extent of the primary tumor, the proposed treatment modality for the primary lesion, and the N staging of the cervical nodes. A primary resection for proven or suspected metastases to cervical lymph nodes should involve *en bloc* removal of all lymph nodes and adjacent normal tissues.
   1. **Neck dissection** (ND) may be a "radical neck dissection" or one of a variety of partial neck dissections. Less extensive dissections include removal of tumor-involved lymph nodes that do not respond adequately to primary irradiation. Definitions and indications vary among surgeons.
      a. **A classic radical ND** removes *en bloc* all tissue from the mandible to the clavicle, from the anterior border of the trapezius to the midline strap muscles, and between the superficial layer of the deep cervical fascia (platysma) and the deep layer of the deep cervical fascia. Among the resected structures are the sternocleidomastoid muscle, internal jugular vein, and 11th cranial (accessory) nerve.
      b. **A modified radical ND** spares certain structures, usually the accessory nerve or the sternocleidomastoid muscle. It is usually reserved for the treatment of patients with clinically negative cervical lymph nodes, planned postoperative neck irradiation, or minimal tumor in neck nodes. The most common variant is the supraomohyoid dissection, which removes nodes from levels 1, 2, and 3.
      c. **A partial ND** results in only partial removal of the lymph nodes. In its extreme, a partial ND involves removal of only a solitary nodal mass.
   2. **Patients without enlarged cervical lymph nodes** have an incidence of tumor-containing nodes as high as 60%. Exceptions to this high incidence include cancers of the vocal fold or paranasal sinuses, small lip cancers, and low-grade salivary gland malignancies. For most other head and neck cancer sites, the homolateral cervical nodes should be treated with either RT or ND, even if not grossly involved with metastases.
   3. **Patients with enlarged cervical lymph nodes**
      a. **ND** is usually is performed whenever the primary site is treated surgically. **RT should follow ND** when:
         1. Any node is larger than 3 cm in greatest dimension, or
         2. Any of the conditions listed in section B.3 are present
      b. **RT** is usually the treatment of choice for primary carcinomas of the nasopharynx, pharyngeal tongue, soft palate, or tonsillar region or when the tumor-involved nodes cannot be resected. **ND should follow RT** when the tumor-involved nodes do not completely grossly respond to RT or when the tumor-involved nodes were initially unresectable but become resectable.

D. **Role of chemotherapy in head and neck cancers.** Many nonrandomized studies and early reports have shown impressive response rates for head and neck carcinomas treated with various chemotherapeutic regimens, but no clear improvement in overall survival. Responses to chemotherapy are best with high-grade tumors. The patient's nutritional status, performance status, and comorbid conditions greatly affect the significance of the response.
   1. **Single agents.** Methotrexate, bleomycin, carboplatin, cisplatin, vinorelbine, epirubicin, and 5-fluorouracil (5-FU) are active single agents, each achieving

significant tumor reduction in 15% to 30% of patients.

2. **Combination chemotherapy regimens.** The most useful regimens combine cisplatin and 5-FU (PF regimen) without leucovorin or with it (PFL regimen). Adding other drugs to this combination has not improved results. Representative regimens, which are given every 21 to 28 days, include the following:

   a. **PF**

   Cisplatin, 100 mg/m^2 IV on day 1
   5-FU, 1000 mg/m^2/day by continuous IV infusion (CIV) for 5 days (total, 5 g/m^2)

   b. **PFL**

   Cisplatin, 25 mg/m^2 IV on days 1 through 5 by CIV (total, 125 mg/m^2)
   5-FU, 800 mg/m^2/day on days 2 through 6 by CIV (total, 4 g/m^2)
   Leucovorin, 500 mg/m^2 on days 1 through 6 by CIV (total, 3 g/m^2)

3. **Beneficial effects of chemotherapy** have been best demonstrated in laryngeal and nasopharyngeal carcinomas.

   a. **Laryngeal carcinoma.** Chemotherapy followed by definitive RT achieves laryngeal preservation in a high percentage of patients with advanced cancer but does not improve overall survival. The precise contribution of chemotherapy to this benefit, however, is uncertain.

   b. **Nasopharyngeal carcinoma.** Studies in the Western world of patients with N2 and N3 disease have shown improved 3-year relapse-free survival and overall survival when compared with those treated with RT alone. Studies in Asia, however, have failed to demonstrate a benefit from the addition of chemotherapy to intensive RT programs.

4. **Induction chemotherapy** (before surgery or RT) for locally advanced disease

   a. Induction chemotherapy results in tumor regression in 60% to 90% and in complete responses (CRs) in 25% to 70% of patients with locally advanced head and neck cancers, many of which can be pathologically documented. Patients with CRs have better survival than those with partial responses, but this is not a valid statistical comparison.

   b. Patients who achieve a CR with chemotherapy may require only additional RT (i.e., surgery may not be necessary). The appropriate sequence of chemotherapy, RT, and surgery has not been well defined.

   c. Induction chemotherapy results in a decreased frequency of subsequent distant metastases, but survival data are conflicting. Although individual reports have supported using 5-FU and cisplatin induction chemotherapy for stage III and IV head and neck carcinomas without distant metastasis (i.e., with substage M0), meta-analyses of phase III trials show no advantage in either locoregional control or survival.

5. **Simultaneous chemoradiotherapy** is popular and shows promise for locally advanced head and neck cancers but is difficult to evaluate. Such treatment is considered for patients in good general condition and with good performance status because it can be associated with substantial toxicity.

   a. Locoregional control is achieved in 35% to 70% of patients treated with chemoradiotherapy versus 15% to 45% of patients treated with conventional or hyperfractionated RT. Three-year survival with chemoradiotherapy may be better than with RT alone. Extension and confirmation of these observations is necessary before this approach becomes widely adopted.

   b. A regimen used at Duke University with "acceptable" toxicity is given during the first and sixth weeks of RT, and for two cycles after the completion of RT.

   Cisplatin, 12 mg/m^2/day by CIV for 5 days (total, 60 mg/m^2), and
   5-FU, 600 mg/m^2 by CIV for 5 days (total, 3 g/m^2)

6. **Postoperative adjuvant chemotherapy** decreases the occurrence of distant metastases and may increase survival in high-risk groups (including those who achieved a response to preoperative chemotherapy) but has no effect on disease-free survival or overall survival.

7. **Local recurrence and metastatic disease.** Combination chemotherapy with PF achieves response rates of about 45% (reported range, 10% to 75%), but the duration of response is short (usually less than 2 months). No combination improves survival rates. Patients with disseminated head and neck cancers usually die within 6 months.

E. **Persistent tumor.** When a cancer reappears at the previously treated primary site, it results from incomplete destruction of all tumor cells. Although this is often called *recurrence,* it is actually regrowth of a persistent tumor. If a discrete new tumor arises separately from a previously treated primary site, it represents a new or second cancer. Irradiation or additional surgery can often salvage surgical failures. Surgery is usually the treatment of choice to salvage RT failures; such attempted surgical rescue is associated with increased morbidity related to late radiation-induced tissue changes.

F. **Adverse effects of treatment**

   1. **Complications of radical surgery**
      a. Cosmetic and functional deformity
      b. Speech impediment or loss
      c. Aspiration pneumonia
      d. Shoulder or arm weakness, paresthesias, and pain with ND

   2. **Toxicity of chemotherapy administered with RT** may be significant
      a. Severe stomatitis, diarrhea
      b. Nephropathy, fluid and electrolyte imbalance, divalent cation deficiency
      c. Neuropathy
      d. Malnutrition
      e. Pancytopenia
      f. Hospitalizations to treat complications

   3. **Adverse effects of RT.** The frequency and severity of sequelae of RT are related to the specific sites irradiated, the condition of the normal tissues before irradiation, the total and incremental doses, the pattern of application, the quality of the radiation, concurrent disease, and the use of medications.

      a. **Acute, self-limiting sequelae**
         1. **Skin and conjunctival "reactions"** include erythema, discoloration, and rarely superficial ulceration. These sequelae disappear after a few weeks.
         2. **Epilation** of the scalp may be permanent or temporary depending on the total dose. The regrown hair may be of a different character than the original in color and density. Permanent epilation of the face (beard) or eyebrows requires relatively high doses. Eyelashes may be permanently lost with lower doses.
         3. **Mucositis** in the oral cavity, hypopharynx, or cervical esophagus may result in dysphagia.
         4. **Edema** involving the endolarynx may cause hoarseness.
         5. **Lhermitte's syndrome** is transitory and consists of electric shock–like sensations in the upper or lower limbs, precipitated by flexion of the neck. This is related to inclusion of the cervical spinal cord in a tissue volume taken to relatively high doses.
         6. **Serous otitis media,** which may follow irradiation of the middle ear, resolves spontaneously.

      b. **Chronic sequelae**
         1. **Xerostomia** is secondary to irradiation of the salivary glands, primarily the parotids, to high doses. Partial suppression and change of consistency of the saliva may be permanent.
         2. **Myelopathy** of the cervical spinal cord is the most dreaded long-term sequela. This condition follows exposure to very high doses (less than 1% incidence at 6000 cGy in 200-cGy daily increments).
         3. **Cataracts** may follow irradiation of the lens. This sequela, which is more common in elderly patients and those with diabetes, usually can be avoided by careful technical application. Cataracts due to irradiation can be successfully treated surgically.
         4. **Ulceration** of soft tissue is a rare long-term consequence and is usually related to irradiation to a high total dose, often in conjunction with surgery.
         5. **Necrosis of the mandible** is infrequent and can be nearly eliminated by careful irradiation techniques and good dental care.

G. **Supportive care**

   1. **Adequate nutrition** can be maintained by diet supplements between meals, nasoesophageal or gastrostomy tube feedings, or hyperalimentation.

   2. **Opportunistic infections** frequently occur in debilitated patients during therapy and must be treated. Oral candidiasis is the most common infection in head and neck cancer patients (see Chapter 35, section VI.B).

   3. **Dental care**
      a. All patients who are likely to receive high doses of radiation to the oral cavity, including a portion of the mandible or the salivary glands, should have a dental consultation before therapy.
      b. Fluoride gel treatment during and after the period of RT reduces dental problems.
      c. Dentures should not be worn during RT and for a period of 6 to 9 months after its completion. These dentures should have a soft lining and not result in local sites of pressure.

4. **Psychological support**
   a. Reiterate the appropriateness and necessity of particular treatments.
   b. Explain postsurgical reconstruction and rehabilitation.
   c. Reinforce patient avoidance of alcoholic beverages and tobacco.
   d. Emphasize the maintenance of good oral hygiene.
   e. Emphasize the importance of long-term follow-up.

VII. Special clinical problems

A. **Increasing induration of neck or facial tissues in a previously irradiated area** may indicate persistent cancer. If involved by carcinoma, the skin is usually tense, brawny, and purplish in color, often fixed to the underlying tissues or bone, and usually associated with an enlarging mass. Occasionally, no discrete masses are palpable, but the involved tissues are firm to stony hard. In contrast, postirradiation induration is usually flat, smooth, and confined to areas of high dose. A biopsy is often hazardous. Treatment can usually be undertaken using clinical criteria without tissue diagnosis.

B. **Unsightly cosmetic facial defects** pose major problems for both patients and those who must interact with them. Health professionals should combine a professional, detached view of physical defects with compassion.

C. **Massive facial edema** is an occasional end-stage problem in advanced head and neck cancer and is usually caused by venous or lymphatic obstruction in the neck or mediastinum. These patients usually die from cerebral edema, hemorrhage, or inanition.

D. **Arterial rupture with exsanguination** may result from tumor erosion through the carotid or other major arteries and is usually rapidly fatal. RT should be attempted in patients with tumor adjacent to a major vessel. It may control the tumor, stimulate fibrosis, and avert or delay this disaster.

E. **Airway obstruction** can be a cause of death for patients with untreated or uncontrolled cancer of the upper respiratory passages.
   1. **Emergency tracheostomy** may be required in patients with a severely compromised upper air passage (e.g., stridor) before treatment.
   2. **Prednisone**, 40 to 60 mg/day PO, may provide temporary relief for some patients when other modalities have been ineffective. Patients who cannot swallow can receive methylprednisolone, 40 mg SC.
   3. **Antibiotics** for the treatment of superimposed infection may relieve airway or swallowing difficulties and reduce accompanying foul odors.
   4. **Chemotherapy** may be used in patients who have already received maximum tolerable doses of radiation in an attempt to achieve tumor reduction.

F. **Inability to swallow** may be a complication of uncontrolled head and neck tumors. Alimentation support is probably not warranted in patients whose cancer is refractory to RT and chemotherapy because prolonged survival may be accompanied by airway obstruction, facial edema, or intractable pain.

G. **Infection** of bulky, necrotic tumors may be associated with fever, pain, or swelling and may be caused by normal mouth flora. Symptomatic relief can sometimes be obtained using a broad-spectrum antibiotic (e.g., metronidazole).

Specific Head and Neck Cancers

The relative occurrence, sex predominance, most common site, and histology of the constituents of head and neck cancers are compared in Table 7.2.

Table 7.2 Features of head and neck cancers by site of origin

I. Lip (sites: vermilion border and mucosal surfaces)

A. **Natural history**
   1. **Risk factors** include smoking, long-standing hyperkeratosis, sun and wind exposure, chronic irritation, and xeroderma pigmentosum.
   2. **Presentation.** Ninety-five percent occur on the lower lip. The presenting sign or symptom is usually a recurrent scab, sore, blister, or ulcer with or without a mass.
   3. **Lymphatic drainage.** First to submental and submaxillary nodes, and then to upper anterior cervical (jugular) and intraparotid nodes. Lymphadenopathy is seen in 5% to 10% of patients at presentation and is related to the size of the primary cancer.

B. **Differential diagnosis**
   1. Keratoacanthoma is a self-limiting, exophytic lesion of sun-exposed skin that may mimic squamous cell carcinoma. It arises rapidly and resolves spontaneously within months.
   2. Infected hyperkeratosis
   3. Leukoplakia
   4. Syphilitic chancre

C. **Staging of lip carcinomas.** See Table 7.1 for TX, T0, Tis, N, and M stages, for histopathologic grades, and for stage groupings.

   T1 Tumor £2 cm

   T2 Tumor >2 cm but £4 cm

   T3 Tumor >4 cm

   T4 Tumor invades adjacent structures (e.g., through cortical bone, inferior alveolar nerve, floor of mouth, skin of face)

D. **Treatment of primary lesions.** Because lip carcinoma is often detected early, it is equally curable by surgery, various irradiation techniques, or chemosurgery. Therefore, the choice of therapy is determined by the condition of tissues, expected cosmetic results, patient's age, comfort, convenience, and treatment costs. Treatment modalities are as follows:
   1. **Leukoplakia, severe dysplasia, and small carcinoma *in situ*:** vermilionectomy (lip shave)
   2. **T1 and Tis (lesions £ 1 cm):** RT or surgical excision
   3. **T1 to T4 (lesions >1 cm):** RT is cosmetically preferred, but excision and reconstruction give similar curative results.
   4. **Commissure involvement:** RT is cosmetically and functionally preferable if the commissure is involved.

E. **Treatment of regional nodes**
   1. **Clinically negative neck.** Observe or irradiate the first echelon of nodes in large or poorly differentiated primary tumors.
   2. **Clinically positive neck.** ND with or without contralateral suprahyoid dissection. Postoperative RT is given based on the findings of ND.

F. **Recurrences.** Most treatment failures occur locally.
   1. **Surgical failures** are best treated with RT or additional surgery and RT failures with surgery.
   2. **Delayed neck dissections** for subsequently appearing cervical metastases do not appear to affect survival.

G. **Local tumor control rate** exceeds 90% for cancers up to 3 cm and is 75% to 80% for larger cancers.

II. Oral cavity (sites: floor of mouth, oral tongue, buccal mucosa, gingiva, alveolar ridges, retromolar trigone, hard palate)

A. **Natural history**
   1. **Risk factors** include smoking, excessive consumption of alcohol, poor oral hygiene, prolonged focal denture irritation, betel nut chewing, and syphilis
   2. **Presentation.** Most oral cavity cancers first appear as a painless ulcer or mass. If symptomatic, patients complain of local pain; difficulty chewing, swallowing, eating, or speaking; or that dentures do not fit well.
   3. **Lymphatic drainage** involves the upper jugular and submandibular nodes. The likelihood of bilateral adenopathy increases as the lesion approaches the midline. Lymphadenopathy occurs in about 40% of patients at presentation.

B. **Diagnosis.** Obtain x-ray films of the chest and mandible to detect distant metastases and bone erosion or mental nerve foramen enlargement (an indication of perineural infiltration); panoramic views of the mandible are preferred.

C. **Staging of oral cavity carcinomas.** See Table 7.1 for TX, T0, Tis, N, and M stages, for histopathologic grades, and for stage groupings.

   T1 Tumor £2 cm

   T2 Tumor >2 cm but £4 cm

T3 Tumor >4 cm

T4 Tumor invades adjacent structures (e.g., through cortical bone, into deep muscle of tongue, maxillary sinus, skin). Superficial erosion alone of bone or tooth socket by a gingival primary is not sufficient to classify the lesion as T4.

  D. **Treatment of primary lesions**
    1. **Oral tongue and floor of mouth carcinoma**
      a. **Very small lesions (¾1 cm).** Surgical excision, interstitial RT, or external RT through the peroral cone; the neck is not treated electively.
      b. **T1 or T2 lesions.** Surgery, if location allows a wide excision without functional deformity; or, combination external and interstitial RT. The choice between surgery and RT is made according to the patient's health and psychological, social, and occupational factors.
      c. **Extensive lesions.** RT alone or combination RT and surgical resection. Surgery (alone or with RT) is preferred for mandibular invasion or attachment, verrucous carcinoma, or unreliable patients.
      d. **Local tumor control rate** exceeds 90% for T1 and T2 tumors.
    2. **Gingiva and hard palate carcinoma.** Most tumors of the upper gingiva and hard palate are salivary gland adenocarcinomas. Gingival and palatal lesions involve bone early on. Surgery is usually preferred.
      a. **Early lesions.** Surgery
      b. **Advanced lesions.** Surgery and RT
      c. **Local tumor control.** Small tumors are usually locally controlled. The control rate of T4 lesions is about 40%.
    3. **Buccal mucosa carcinoma**
      a. **T1 lesions.** Surgery or RT
      b. **T2 or T3 lesions.** RT
      c. **T4 lesions.** Surgery and RT, if feasible
      d. **Local tumor control rate** exceeds 90% for T1 lesions but drops to 50% to 60% for extensive tumors.
    4. **Retromolar trigone carcinoma**
      a. **Early lesion.** Surgery
      b. **Advanced lesion** (usually involves bone). Surgery, often with RT
      c. **Local tumor control.** Most T1 and T2 tumors are controlled.
  E. **Treatment of regional nodes**
    1. **Clinically negative neck**
      a. **T1 primary.** Observe if the patient is reliable and the lesion is low grade.
      b. **T2 to T4 primary, or a high-grade lesion**
        1. If primary lesion is treated surgically, perform elective ND.
        2. If primary lesion is treated with RT, treat nodes with RT.
        3. If primary lesion is treated with both modalities, the cervical nodes can be treated with either modality.
    2. **Clinically positive neck nodes**
      a. If the primary lesion is treated surgically, do ND.
      b. If the primary lesion is treated with RT, irradiate the neck and do ND for residual enlarged nodes or nodes originally larger than 3 cm.
      c. If the cervical lymphadenopathy is fixed, begin treatment with RT. If the nodes become mobile during RT, do a neck dissection after 5000 cGy. If the nodes remain immobile, complete the full course of RT.
    3. **Indications for neck irradiation after ND**
      a. Multiple tumor-containing nodes, or
      b. Node greater than 3 cm or tumor extends outside capsule, or
      c. High-grade malignancy

III. Oropharynx (sites: base of tongue, anterior and posterior tonsillar pillars, glossotonsillar sulci, lateral and posterior pharyngeal walls; extends from the plane of the inferior surface of the soft palate to the plane of the superior surface of the hyoid [or floor of the vallecula])

  A. **Natural history**
    1. **Presentation**
      a. Cancers arising in the pharyngeal tongue may be clinically silent until extensive. The lesion may be entirely submucosal and recognizable only by induration.
      b. Tonsillar and pharyngeal tongue tumors frequently are initially recognized by nodal metastases.
      c. Symptoms include odynophagia (referred), local pain, otalgia, dysphagia, and trismus (an indication of deep infiltration of muscle by tumor).
    2. **Lymphatic drainage.** Lesions of the pharyngeal tongue and tonsillar fossa metastasize to the upper jugular nodes. The incidence of nodal metastases at the time cancer is detected varies with the primary site.
  B. **Diagnosis.** These lesions can be visualized and are palpable. A CT scan or MRI of the neck is helpful to detect masses in the tongue and vallecula and to visualize a pharyngeal wall mass, abnormal thickening, or enlarged lymph nodes.
  C. **Staging of oropharyngeal carcinomas.** See Table 7.1 for TX, T0, Tis, N, and M stages, for histopathologic grades, and for stage groupings.

T1 Tumor £2 cm

T2 Tumor >2 cm but £4 cm

T3 Tumor >4 cm

T4 Tumor invades adjacent structures (e.g., pterygoid muscles, mandible, hard palate, deep muscle of tongue, larynx)

  D. **Treatment of primary lesions**
    1. **Soft palate carcinoma.** Forty to 50% of patients have cervical nodal metastases at the time of diagnosis.
      a. **Small lesions.** Usually RT
      b. **Large lesions.** RT alone is preferred because extensive surgical resection can result in compromise of ability to speak and swallow.
      c. **Local tumor control rate** is 80% to 90% for T1 to T2 tumors and 75% to 80% for T3 to T4 tumors.
    2. **Tonsillar region carcinoma.** Nodal metastases are detected in 70% of patients at the time of diagnosis.
      a. **Early lesions.** Surgery (composite resection with ND) or RT
      b. **Advanced lesions.** Surgery and RT
      c. **Local tumor control rate** exceeds 85% for T1 and T2 cancers, 50% to 75% for T3 cancers, and 25% for T4 cancers.
      d. **Approximate 5-year survival.** Invasion of the pharyngeal tongue or trismus markedly decreases likelihood of cure.

Stage	Five-year survival (%)	Nodes	Five-year survival (%)
T1,T2	70	All N0	80
T3,T4	20	All N1	45
		All N3	10

    3. **Anterior tonsillar pillar carcinoma** (may be included in oral cavity carcinoma) is better differentiated histologically and has less of a propensity for early metastasis than other oropharyngeal sites.
      a. **Early lesions.** Surgery or RT
      b. **Advanced lesions,** particularly if deeply infiltrative or involving the base of tongue or bone, are treated with surgery or combined surgery and RT
      c. **Local tumor control rate** exceeds 85% for T1 to T2 cancers
    4. **Pharyngeal tongue carcinoma.** Lymphadenopathy is detected in 80% of patients at presentation and is bilateral in nearly 50%.
      a. **Early lesions** (uncommon). Surgery or RT
      b. **Advanced lesions** (across the midline). RT alone because the alternative of total glossectomy in unacceptable to most patients
      c. **Local tumor control rate** is about 75% for T1 cancers, 60% for T3 cancers, and 15% for T4 cancers.
    5. **Pharyngeal wall carcinoma.** Most lesions that extend well onto the posterior wall are not curable by surgery.
      a. **Early lesions.** RT
      b. **Advanced lesions.** Combined RT and surgery
      c. **Local tumor control rate** ranges from 30% to 50% for T2 to T3 cancers; T1 cancers are rare.
  E. **Treatment of regional nodes.** Because most of the cancers of this region require RT as primary or adjuvant therapy, RT rather than surgery is commonly used

in the treatment of cervical node metastases.
1. **N0 and N1.** If surgery is used to treat the primary site, then ND is done; if RT is used to treat the primary, then RT is used for the neck.
2. **N2A.** Similar to N0 and N1, but ND is often required for residual disease.
3. **N2B.** RT, followed by modified ND
4. **N3A.** RT and ND, if possible
5. **N3B.** Treat each side individually
6. **Indications for RT after ND**
   a. Multiple tumor-containing nodes, or
   b. Node greater than 3 cm or tumor perforating the capsule, or
   c. High-grade pathology
F. **Follow-up of oropharyngeal carcinoma.** Careful and frequent follow-up visits are essential for the following reasons:
   1. Surgical salvage of RT failures can be successful.
   2. Incidence of subsequent second malignancies is 5% to 10%.

IV. Nasopharynx (sites: from the posterior choana to the level of the free border of the soft palate)

A. **Natural history.** Nasopharyngeal carcinoma is the second most common malignancy in southern China and is high in incidence among some native American populations. Nonkeratinizing nasopharyngeal carcinomas are uniformly associated with Epstein-Barr virus; patients usually have increased levels of immunoglobulin A antibody to the viral capsid antigen and early antigen.
   1. **Pathology.** About 85% are squamous cell carcinomas or its lymphoepithelial variants (Schmincke's or Regaud's tumor), 10% lymphomas, and 5% other histologic types (undifferentiated carcinoma, melanoma, plasmacytoma, angiofibroma of childhood).
   2. **Presentation.** Nasopharyngeal tumors spread directly through the pharyngeal space to the structures in or near the cavernous sinus and the foramina of the middle cranial fossa (including the gasserian ganglion and its branches). Destruction in the parasphenoid bones and nerve compression can result in severe pain and nerve palsy. Cranial nerve VI, which passes around the brain stem and along the cavernous sinus, is usually the first nerve to be affected, resulting in a lateral rectus muscle paresis.
      a. **Common symptoms and signs.** Enlarged neck nodes, headache, epistaxis, nasal obstruction (often unilateral), unilateral decreased hearing secondary to eustachian tube obstruction, sore throat (inferior extension), and pain on neck extension.
      b. **Retrosphenoidal syndrome** usually starts with the sixth cranial nerve and subsequently involves cranial nerves II through VI. Symptoms include unilateral ophthalmoplegia, pain, ptosis, trigeminal neuralgia, and unilateral weakness of muscles of mastication.
      c. **Syndrome of the retroparotid space** results from nodal compression of cranial nerves IX through XII and of sympathetic nerves at the base of the skull. Symptoms include difficulties with swallowing, taste, salivation, and respiration; weakness of the trapezius, sternocleidomastoid muscles, homolateral tongue, and soft palate; and Horner's syndrome.
   3. **Lymphatic drainage.** Because the tumor is relatively anaplastic and the nasopharynx has a rich lymphatic network, these carcinomas may spread to lymph nodes when the primary tumor is small.
      a. First involved are the retropharyngeal and lateral pharyngeal nodes, followed by the upper cervical nodes. Involvement of the high, posterior cervical nodes is characteristic.
      b. Lymphadenopathy is present in 80% of patients at presentation; 50% is bilateral.
B. **Diagnosis.** Carefully examine regional lymph nodes. Rhinoscopy, indirect nasopharyngoscopy, and triple endoscopy are performed. A CT scan or MRI of the base of the skull, pharynx, and neck is essential.
C. **Staging of nasopharyngeal carcinomas.** See Table 7.1 for TX, T0, Tis, N, and M stages and for histopathologic grades.
   1. **Primary tumor stage**
   T1   Tumor confined to nasopharynx
   T2   Tumor extends to soft tissues of oropharynx or nasal fossa
     T2a   Without parapharyngeal extension
     T2b   With parapharyngeal extension
   T3   Tumor invades bony structures or paranasal sinuses
   T4   Tumor with intracranial extension or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit
   2. **Stage groupings**
   I   T1 N0 M0
   IIA   T2a N0 M0
   IIB   T1,2a N1 M0; T2b N0, N1 M0
   III   T1,2 N2 M0; T3 N0,1,2 M0
   IVA   T4 N0,1,2 M0
   IVB   Any T N3 M0
   IVC   Any T Any N M1
D. **Treatment of primary tumors**
   1. **RT** alone (bilateral) is used for both the primary tumor and the regional nodal metastases.
   2. **Surgery** is not feasible because of the inadequacy of the surgical margins at the base of the skull and the frequent involvement of the retropharyngeal and cervical nodes bilaterally.
E. **Treatment of regional nodes.** RT is the treatment of choice. Neck dissection is reserved for adenopathy that persists or regrows after irradiation in patients with apparently controlled primary tumors.
F. **Gross reappearance of the cancer** at the primary site can be retreated with additional external-beam RT or the placement of a removable radioactive source in the nasopharynx. Such retreatment is only moderately successful and may often produce long-term side effects.
G. **Local tumor control rate** exceeds 90% for T1 to T3 primary cancers. Control of cervical adenopathy by RT is equally successful.
H. **Chemotherapy for nasopharyngeal carcinoma.** See Principles, section VI.D.3.

V. Hypopharynx (sites: pyriform fossa, lateral and posterior hypopharyngeal walls, postcricoid region; the hypopharynx extends from the plane of the superior border of the hyoid bone, or floor of the vallecula, to the plane of the lower border of the cricoid cartilage)

A. **Natural history**
   1. **Presentation.** Odynophagia, dysphagia, and referred otalgia are common presenting symptoms. Late clinical findings include cough, aspiration pneumonia, hoarseness, and neck masses.
   2. **Direct extension.** These tumors behave aggressively with early direct extension; they are usually detected in an advanced stage.
   3. **Lymphatic drainage** involves the retropharyngeal and midjugular nodes. Lymphadenopathy is present in 80% of patients at presentation.
B. **Diagnosis.** Indirect laryngoscopy, direct laryngoscopy, and CT scan or MRI of the neck are performed.
C. **Staging of hypopharyngeal carcinomas.** See Table 7.1 for TX, T0, Tis, N, and M stages, for histopathologic grades, and for stage groupings.
   T1   Tumor limited to one subsite of hypopharynx and ≤2 cm
   T2   Tumor involves more than one subsite of hypopharynx or an adjacent site, or measures >2 cm but ≤4 cm without fixation of hemilarynx
   T3   Tumor is >4 cm or with fixation of hemilarynx
   T4   Tumor invades adjacent structures (e.g., thyroid or cricoid cartilage, carotid artery, soft tissues of neck, prevertebral fascia or muscles, thyroid or esophagus)
D. **Treatment of primary lesions**
   1. **Pyriform sinus tumors**
      a. **Small, exophytic lesions** (particularly in upper pyriform sinus). RT
      b. **Other early T1 or T2 lesions.** Total or partial laryngectomy, and partial or total pharyngectomy and RT combined
      c. **T3 to T4 lesions.** Laryngopharyngectomy and RT. If inoperable because of involvement of the posterior pharyngeal wall or massive neck disease, treat with RT alone.
   2. **Posterior pharyngeal wall tumors.** RT alone
   3. **Persistent or recurrent disease.** Salvage is poor.
E. **Treatment of regional nodes**
   1. **Clinically negative neck.** Prophylactic RT or ND
   2. **Clinically positive neck.** Combined ND and RT

F. **Tumor control.** Many T1 and T2 tumors can be locally controlled. The likelihood of control of cervical node metastases varies with the size and number of nodes.

VI. Larynx

A. **Natural history.** Although cancer of the larynx represents only 2% of the total risk for cancer in humans, it is the most frequent head and neck cancer except for skin cancer. There is a direct etiologic relationship to cigarette smoking. Alcohol ingestion probably is less important as an etiologic agent than for other head and neck cancers. The clinical presentation depends on the primary site and extent of the cancer. Tumors arising from the true vocal folds, which are usually diagnosed when smaller, are less likely to infiltrate surrounding tissues or to metastasize to regional lymph nodes than are tumors arising subglottically or supraglottically.

1. **Presentation.** Persistent hoarseness is the usual presenting symptom for patients with cancers arising on the true vocal folds (glottis). At other primary sites, sore throat with dysphagia or nonpainful, regional adenopathy may develop.

2. **Lymphatic drainage**
   a. **Glottic (true vocal fold) carcinomas.** The true vocal folds are devoid of lymphatics. Therefore, cervical node metastases develop only when the tumor has extended to adjacent structures.
   b. **Supraglottic carcinomas.** This group of tumors are drained by a rich lymphatic network. About 40% to 50% of these patients develop regional adenopathy involving the upper (subdigastric) or middle internal jugular nodes (levels 2 and 3).
   c. **Subglottic carcinomas.** Lymphatics, which are sparse, extend through the cricothyroid membrane to the pretracheal (Delphian) nodes or the lower internal jugular nodes.

3. **Curability** is related to the site of origin, ranging from most curable to least curable as follows: true vocal fold cancers; tumors arising from the false folds, epiglottis, ventricles, aryepiglottic folds; tumors arising in the subglottis (infrequently controlled).

B. **Diagnosis**
1. **Studies.** Indirect laryngoscopy, performed during deep breathing and phonation, can determine the mobility of the vocal folds and arytenoids. Direct laryngoscopy facilitates biopsy and may provide better visualization of the ventricles and subglottic larynx. CT and MRI are useful to determine tumor extent, particularly when the thyroid cartilage and pre-epiglottic space are involved.

2. **Differential diagnosis**
   a. Hyperkeratosis
   b. Laryngocele
   c. Polyps (which appear as glistening, pedunculated masses)
   d. Papillomas (which are white, grapelike growths)

C. **Staging of laryngeal carcinomas.** See Table 7.1 for TX, T0, Tis, N, and M stages, for histopathologic grades, and for stage groupings.

1. **T1 and T2 for glottic carcinomas**
   T1   Tumor limited to the vocal folds with normal mobility (may involve anterior or posterior commissures)
     T1a   Tumor limited to one vocal fold
     T1b   Tumor involves both vocal folds
   T2   Tumor extends to supraglottis or subglottis, or with impaired vocal fold mobility

2. **T1 and T2 for supraglottic carcinomas**
   T1 Tumor limited to one subsite of supraglottis with normal fold mobility
   T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis without fixation of the larynx (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus)

3. **T1 and T2 for subglottic carcinomas**
   T1 Tumor limited to the subglottis
   T2 Tumor extends to vocal folds with normal or impaired mobility

4. **T3 and T4 for glottic, supraglottic, and subglottic carcinomas**
   T3 Tumor limited to the larynx with vocal fold fixation (for supraglottic tumors: and/or invades postcricoid area or preepiglottic tissues)
   T4 Tumor invades through the thyroid cartilage or to other tissues beyond the larynx (e.g., soft tissues of neck, thyroid, trachea, pharynx, esophagus)

D. **Treatment principles for laryngeal carcinomas**
1. **Treatment of primary site**
   a. **The overriding requirement** for treatment is preservation of the patient's life, voice, and swallowing reflex. These considerations have led to the increasing use of RT alone or more limited surgical procedures combined with RT.
   b. **Salvage (total) laryngectomy** is usually required for patients in whom more conservative treatments fail.
   c. **Deeply infiltrative tumors** are more difficult to evaluate because of accompanying distortion and edema. Laryngectomy is therefore favored in many of these patients.
   d. **Sequential chemotherapy and definitive RT** is effective for achieving laryngeal preservation in a high percentage of patients with advanced cancer in both glottic and supraglottic lesions without compromising overall survival. It is not known, however, whether administering higher doses of RT alone would achieve the same result.
   e. **Sequelae of therapy**
     1. Total laryngectomy necessitates tracheostomy and loss of normal voice. About 50% to 70% of patients develop satisfactory esophageal speech.
     2. RT of the larynx is rarely associated with painful chondritis and edema of the laryngeal structures.

2. **Treatment of regional nodes.** Glottic carcinomas are treated without ND, unless cervical nodes are palpable (less than 10%). Supraglottic and subglottic carcinomas usually require some form of cervical node therapy. Clinically positive nodes are generally managed with ND.

E. **Glottic carcinoma** (sites: true vocal folds, including the anterior and posterior commissures)
1. **Treatment of primary tumor**
   a. **Tis.** RT or "cord-stripping" for focal areas of disease
   b. **T1 to T2.** RT is preferable to surgery (either cordectomy or vertical laryngectomy). Involvement of the arytenoid or more than one third of the opposing fold is a contraindication to hemilaryngectomy. Postoperative RT is given after hemilaryngectomy if the tumor is close to the surgical margins.
   c. **T3.** Lesions that fix the true vocal folds can be divided into two groups: relatively smaller lesions, which respond to irradiation (local control is 50% to 60% with possible surgical salvage) and extensive tumors (bilateral, compromised airway) that require surgery and usually postoperative RT.
   d. **T4.** Total laryngectomy and RT

2. **Treatment of persistent or recurrent disease**
   a. Surgery for RT failure. The surgical salvage rate for early glottic cancer is about 85%.
   b. RT or total laryngectomy for failure of partial laryngectomy or cordectomy
   c. RT for failure of total laryngectomy. Salvage rates are poor. (RT usually should be used as a postoperative adjuvant.)

3. **Tumor control**
   a. **T1.** Greater than 80% with RT and approaches 100% with surgical salvage
   b. **T2.** From 60% to 70% with RT and approaches 90% to 100% with surgical salvage
   c. **T3.** From 60% to 65% with RT and 75% with surgery plus RT. Ultimate control of 80% to 85% with surgical salvage. From 60% to 65% voice preservation with primary RT
   d. **T4.** From 40% to 45% with laryngectomy. Up to 50% with RT and surgical salvage.

F. **Supraglottic carcinoma** (sites: epiglottis, aryepiglottic folds, vallecula, arytenoid, false folds)
1. **Treatment of primary tumor**
   a. **T1.** RT or supraglottic resection
   b. **T2 to T3.** RT frequently controls exophytic cancers. Surgery, which is reserved for RT failures, is favored for infiltrative disease or lesions involving the base of the epiglottis or false folds. Surgical procedures include supraglottic or total laryngectomy.
   c. **T4.** Surgery and RT

2. **Indications for postoperative RT**
   a. Bulky or infiltrating lesions, or
   b. Close or positive operative margins, or
   c. Multiple positive lymph nodes, or
   d. Deep connective tissue, thyroid cartilage, or perineural involvement, or
   e. Poorly differentiated histology

3. **RT treatment failures** usually require total laryngectomy. The surgical salvage rate is 80% for RT failures.
4. **Local tumor control rates** are 90% to 95% for T1 and T2 lesions, about 80% for T3 lesions, and 40% to 50% for T4 lesions.
G. **Subglottic carcinoma** (sites: extends from 10 mm below the free margin of the vocal fold [inferior limit of the vocalis muscle] to the lower margin of the cricoid cartilage)
  1. **Treatment of primary tumor**
    a. **Early lesions.** RT or total laryngectomy
    b. **Advanced lesions.** Total laryngectomy and RT
    c. **Approximate 5-year survival rate** without evidence of disease is less than 25%.

VII. Nasal cavity and paranasal sinuses

A. **Natural history.** Although cancers often involve both the nasal cavity and paranasal sinuses at the time of diagnosis, it is important to separate those cancers limited to the nasal fossa from those arising in the sinuses. Most tumors of the nasal cavity and paranasal sinuses are squamous cell carcinomas. Some adenocarcinomas, sarcomas, plasmacytomas, lymphomas, minor salivary gland tumors, and olfactory neuroblastomas also occur.
  1. **Presentation.** Symptoms and signs often mimic inflammatory sinusitis and include local pain, tenderness, toothache, bloody nasal discharge, loosening of teeth, and interference with fit of dentures. Other symptoms are visual disturbances, proptosis, nasal obstruction, trismus, and a bulging cheek mass that can ulcerate through the skin and palate.
  2. **Lymphatic drainage** involves the retropharyngeal, submaxillary, and upper anterior and posterior cervical nodes. At the time of presentation, lymphadenopathy is present in 15% of patients who have early disease and in more patients with advanced disease.
B. **Diagnosis**
  1. **Studies.** Rhinoscopy, endoscopy, sinoscopy, and CT scan or MRI of the involved structures are performed. Bone destruction on radiographs is the hallmark of malignancy, although it can also occur in certain benign conditions (e.g., papilloma, osteomyelitis).
  2. **Differential diagnosis**
    a. Inverting papilloma of the nasal cavity
    b. Destructive mucocele of the sinus
    c. Allergic fungal sinusitis
  3. **Staging.** The reader is referred to a current staging manual for staging of these tumors.
C. **Treatment of primary lesions**
  1. **Paranasal sinuses**
    a. **Surgery** is usually indicated because of the frequency of osseous involvement. The desire to obtain a wide margin beyond the tumor is tempered by a reluctance to produce serious sequelae. If disease extends through the periorbita, orbital exenteration is performed. Reconstructive and cosmetic surgery using prosthetic devices is often necessary.
    b. **RT** is nearly always necessary because the resection margins are often minimal or positive and the neoplasm is frequently of high grade.
  2. **Nasal cavity tumors**
    a. **Early lesions.** RT is preferable if surgery will produce a deformity. Surgery is favored if bone is destroyed or if the lesion is a sarcoma.
    b. **Advanced lesions.** A combination of surgical resection and RT is most commonly used. RT alone is used for lymphomas, plasmacytomas, rhabdomyosarcomas, lethal midline granuloma, malignant histiocytosis, and olfactory neuroblastoma (see Chapter 19, section VIII). Adjuvant chemotherapy is used for rhabdomyosarcoma, Ewing's sarcoma, osteogenic sarcoma, and neuroblastoma.
    c. **Local tumor control rate** approaches 100% for stage I tumors.
  3. **Nasal vestibule carcinomas**
    a. **Early lesions.** RT is preferable if surgery will produce a deformity.
    b. **Advanced lesions.** RT alone
    c. **Recurrent or persistent disease after RT.** Surgery, cryosurgery, chemosurgery, and laser surgery have all been advocated.
    d. **Local tumor control rate** exceeds 90% for small tumors.
  4. **Ethmoid sinus carcinoma.** Surgery and RT. Approximate 5-year survival rate is 30%.
  5. **Frontal and sphenoid sinus carcinomas.** RT alone. Results are dismal.
  6. **Maxillary antrum carcinoma.** Fenestration before surgical extirpation provides tissue biopsy, decreases tumor bulk through curettage, and allows for drainage of necrotic debris during treatment. Treatment is as follows:
    a. **Early lesions.** Surgery alone
    b. **Advanced lesions.** Surgery with either preoperative or postoperative RT.
    c. **Very advanced lesions.** Chemotherapy initially, then surgery and RT
    d. **Unresectable disease.** Chemotherapy and high-dose RT
    e. **Recurrences.** Surgery, RT, or chemotherapy, alone or in combination, is used. Salvage is very poor.
    f. **Approximate 5-year survival** is 60% for patients with T1 or T2 lesions and 30% to 40% overall.
D. **Treatment of regional nodes**
  1. **T1,2 N0.** No treatment
  2. **T3,4 N0.** Prophylactic upper neck RT
  3. **Any T N1,2,3.** If surgery is part of the management of the primary lesion, then ND is done. If RT is being used primarily, partial ND may still be necessary for initial large or residual tumors.
E. **Sequelae.** Most failures are local. Subsequent cosmetic surgery or prosthetic reconstruction should await healing and a reasonable likelihood of local control. Delayed homolateral cataract may follow RT.

VIII. Salivary glands

A. **Natural history.** The parotid gland accounts for 80% of the salivary gland neoplasms in adults. About 75% of parotid tumors are benign. In contrast, nearly half of tumors arising in the submaxillary or minor salivary glands are malignant.
  1. **Histology of malignant tumors**
    a. Mucoepidermoid tumors (high and low grade)
    b. Adenoid cystic carcinoma (high and low grade)
    c. Undifferentiated carcinoma
    d. Malignant mixed tumors (epithelial and mesenchymal components)
    e. Adenocarcinoma
    f. Squamous cell carcinoma (considered to be high grade)
    g. Acinic cell tumors
    h. Malignant lymphoma
  2. **Presentation.** Most malignant salivary gland tumors appear as a painless swelling. Local pain (particularly along the distribution of an adjacent nerve) and development of nerve palsy are highly indicative of malignancy.
  3. **Tumor spread.** The malignant neoplasms tend to spread by direct extension and infiltration, but high-grade tumors also metastasize distantly or to regional nodes. Adenoid cystic carcinomas tend to infiltrate along nerve trunks; they may recur months or years after initial therapy (see Chapter 19, section VI).
  4. **Lymphatic drainage**
    a. **Parotid gland tumors** metastasize to intraparotid, submaxillary, and upper cervical nodes.
    b. **Submaxillary gland tumors** metastasize to subdigastric, submaxillary, and upper jugular nodes.
B. **Diagnosis**
  1. **Studies.** A CT scan or an MRI should be obtained.
  2. **Differential diagnosis.** Most salivary gland swellings are caused by inflammation or ductal obstruction. The intraparotid lymph nodes receive afferent lymphatic drainage from the skin of the face, scalp, ear, and buccal mucosa. Symptoms and signs to differentiate benign from malignant parotid masses are shown in Table 7.3.

C. **Staging of major salivary gland carcinomas.** Regional lymph node (N) and distant metastases (M) classifications are shown in Table 7.1.
  1. **Primary tumor stage**
  TX Primary tumor cannot be assessed
  T0 No evidence of primary tumor

  T1 Tumor £2 cm without extraparenchymal extension
  T2 Tumor >2 cm but £4 cm extraparenchymal extension
  T3 Tumor >4 cm but £6 cm or having extraparenchymal extension without seventh cranial nerve involvement
  T4 Tumor invades base of skull or seventh nerve or is >6 cm
  2. **Stage groupings for major salivary gland carcinomas**
  I T1,2,3 N0 M0
  II T3 N0 M0
  III T1,2 N1 M0
  IV T4 N0 M0; T3,4 N1 M0; any T N2,3 M0; any T any N M1
D. **Treatment of parotid gland carcinoma.** Wide surgical excision (total parotidectomy) is the standard treatment. However, there is a tendency to use less radical surgery in combination with postoperative RT to spare the facial nerve (when not involved by the cancer) while decreasing the possibility of local recurrence. For example, superficial lobectomy may be considered if it is the only lobe involved.
  1. **Prophylactic ND** is performed for high-grade parotid tumors, but not for low-grade tumors.
  2. **Postparotidectomy sequelae**
    a. Facial nerve palsy
    b. Auriculotemporal syndrome of gustatory sweating
  3. **Use of radiotherapy**
    a. **Postoperative RT** is generally given to the tumor site when:
      1. The tumor is high grade, or
      2. Resection margins are positive or close, or
      3. Tumor is peeled off the facial nerve or there is histologic evidence of perineural involvement, or
      4. Tumor invades deeply, or
      5. Tumor excision is for recurrence
    b. **Curative RT** is attempted only if the patient is unresectable or medically inoperable.
    c. **Recurrent benign tumors.** RT is advocated after reexcision (or after the initial treatment if the resection margins are positive).
  4. **Chemotherapy** (see section E)
E. **Treatment of submaxillary gland carcinoma**
  1. **Surgery.** Wide resection of contents of submaxillary space (including nerves, surrounding muscle, and periosteum) with ND
  2. **Postoperative RT** indications are similar to those for the parotid gland.
  3. **Chemotherapy** for salivary gland cancers has not been extensively investigated. Doxorubicin, fluorouracil, and methotrexate used alone or in combination occasionally result in substantial tumor response.
F. **Results of treatment**
  1. **Malignant salivary gland tumors**
    a. **Local control rate.** Overall, 75%; high-grade and squamous cell carcinoma, 30%; low-grade carcinoma, 80%
    b. **Survival rate.** Recurrences can occur 10 or 15 years after treatment. Therefore, 5-year survival statistics are not reliable.
  2. **Benign mixed tumors** have a recurrence rate of 25% after lumpectomy and 2% after lobectomy. One fourth of recurrences are malignant.

Suggested Reading

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Chapter 8 Lung Cancer

Martin J. Edelman and David R. Gandara

I. Epidemiology and etiology

A. **Incidence.** Lung cancer is the most common visceral malignancy, accounting for roughly one third of all cancer deaths, and is the most common cause of cancer-related death in both men and women. Annually there are 172,000 new cases in the United States. Although rates for men are decreasing, there is a continued increase for women. Even more disturbing is a recent increased incidence of non–small cell lung cancer (NSCLC) in relatively young nonsmoking women.

B. **Etiology**
   1. **Smoking.** Cigarette smoking is the cause of 85% to 90% of lung cancer cases; the risk for lung cancer in smokers is 30 times greater than in nonsmokers. Smoking cigars or pipes doubles the risk for lung cancer compared with the risk in nonsmokers. Passive smoking probably increases the risk of lung cancer about two-fold, but because a proportion of the risk associated with active inhalation is about 20-fold, the actual risk is small.
      a. The risk for lung cancer is related to cumulative dose, which for cigarettes is quantified in "pack-years." One in seven people who smoke more than two packs per day die from lung cancer. The incidence of death from lung cancer begins to diverge from the nonsmoking population at 10 pack-years.
      b. After cessation of smoking, the risk steadily declines, approaching, but not quite reaching, that of nonsmokers after 15 years of abstinence for patients who smoked for less than 20 years. With the decline in smoking in the United States, a large percentage of new diagnoses of lung cancer occur in former smokers.
      c. The risk of the major cell types of lung cancer is increased in smokers. Some adenocarcinomas, especially in women, are unrelated to smoking.
   2. **Asbestos** is causally linked to malignant mesothelioma. Asbestos exposure also increases the risk for lung cancer, especially in smokers (three times greater risk than smoking alone). Thus, the risk for lung cancer in smokers who are exposed to asbestos is increased 90-fold.
   3. **Radiation exposure** may increase the risk for small cell lung cancer (SCLC) in both smokers and nonsmokers. Radon has been associated with up to 6% of lung cancer cases.
   4. **Other substances** associated with lung cancer include arsenic, nickel, chromium compounds, chloromethyl ether, and air pollutants.
   5. **Lung cancer** is itself associated with an increased risk for a second lung cancer occurring both synchronously and metachronously. Other cancers of the upper aerodigestive tract (head and neck, esophagus) are associated with an increased risk for lung cancer because of the "field cancerization" effect of cigarette smoking.
   6. **Other lung diseases.** Lung scars and chronic obstructive pulmonary disease are associated with an increased risk for lung cancer.

II. Pathology and natural history

A. **Small cell carcinoma** (15% of lung cancers). SCLC comprises several histologic subtypes: oat cell, polygonal cell, lymphocytic, and spindle cell. The natural histories of these subtypes are virtually identical.
   1. **Location.** More often central or hilar (95%) than peripheral (5%)
   2. **Clinical course.** Patients with SCLC often have widespread disease at the time of diagnosis. Rapid clinical deterioration in patients with chest masses often indicates SCLC.
      a. **Hematogenous metastases** commonly involve the brain, bone marrow, or liver. Pleural effusions are common.
      b. **Relapse** after radiation therapy (RT) or chemotherapy occurs in the sites initially affected as well as in previously uninvolved sites.
   3. **Associated paraneoplastic syndromes** include the syndrome of inappropriate antidiuretic hormone (SIADH; most common), hypercoagulable state (common), ectopic adrenocorticotropic hormone (ACTH) syndrome (uncommon), and Eaton-Lambert (myasthenic) syndrome (rarely seen with any other tumor). Hypercalcemia occurs rarely in SCLC, even in the presence of extensive bony metastases.
B. **NSCLC.** The other histologic variants (squamous, adenocarcinoma, large cell) of lung cancer are grouped together as NSCLC because of similarities in presentation, treatment, and natural history.
   1. **Squamous cell carcinoma** (30% of lung cancers)
      a. **Location.** Previously, squamous cell carcinoma was thought to occur in a predominantly peripheral location, whereas adenocarcinoma occurred centrally. Studies indicate a changing radiographic presentation, with the two cell types now having similar patterns of location.
      b. **Clinical course.** Compared with other kinds of lung cancers, squamous cell lung cancers are most likely to remain localized early in the disease and to recur locally after either surgery or RT.
      c. **Associated paraneoplastic syndromes.** Hypercalcemia resulting from ectopic production of parathyroid hormone-related peptide (PTH-RP) is the more frequent syndrome. Hypertrophic osteoar-thropathy (occasional), paraneoplastic neutrophilia (sometimes associated with hypercalcemia), prominent joint symptoms (occasional), or hypercoagulability is also seen.
   2. **Adenocarcinoma and large cell carcinoma** (60% of lung cancers). Adenocarcinoma is the most common cell type occurring in nonsmokers, especially young women. Most cases, however, are smoking associated. The incidence of this histology has increased in recent years.
      a. **Location.** These tumors present as peripheral nodules more commonly than squamous cell carcinoma.
      b. **Clinical course.** More than half of patients with adenocarcinoma, apparently localized as a peripheral nodule, have regional nodal metastases. Adenocarcinomas and large cell carcinomas have similar natural histories and spread widely outside the thorax by hematogenous dissemination, commonly involving the bones, liver, and brain.
      c. **Associated paraneoplastic syndromes** include hypertrophic osteoarthropathy, hypercoagulable state, hypercalcemia due to PTH-RP or cytokines (HHM), and gynecomastia (large cell).
C. **Uncommon tumors of the lung**
   1. **Bronchial carcinoids** may present with local symptoms from airway obstruction, ectopic ACTH production, or carcinoid syndrome (see Chapter 15, section II).
   2. **Cystic adenoid carcinomas** ("cylindroma") are locally invasive cancers. Locoregional recurrence is most common, but they may also metastasize to other areas of the lung and to distant sites (see Chapter 19, section VI).
   3. **Carcinosarcomas** are large lesions that have a tendency to remain localized and are more often resectable than other lung malignancies.
   4. **Mesotheliomas** are caused by exposure to asbestos and occur in the lung, pleura, peritoneum, or tunica vaginalis or albuginea of the testis. A history of asbestos exposure of any duration at any time is *prima facie* evidence that it caused the mesothelioma.
      a. **Histopathology.** Mesotheliomas consist of several histologic variants: sarcomatous, epithelioid, and others that have the histologic appearance of adenocarcinoma. The latter type can be distinguished from other adenocarcinomas by the absence of mucin staining and the loss of hyaluronic acid staining after digestion by hyaluronidase.
      b. **Clinical course.** The diffuse (usual) form of mesothelioma spreads rapidly over the pleura and encases the lung. It may develop multifocally and invade the lung parenchyma. Distant metastases are not common and usually occur late in the course. If there is a sarcomatous pattern, liver, brain, and bone may be involved.

III. Diagnosis and further evaluation
The diagnostic evaluation should proceed in an orderly manner to establish an accurate diagnosis and stage of disease. If lung cancer is suspected on the basis of the signs and symptoms described in the following subsections, an initial limited laboratory and radiologic evaluation is indicated. The primary effort should be directed at establishing a histologic diagnosis because this will determine the need for, and type of, additional tests as well as therapeutic options.

If NSCLC is diagnosed, the subsequent staging evaluation is directed to determine which modalities of therapy (surgery, radiotherapy, or chemotherapy) should be employed. In the past, surgery has been the mainstay of therapy for NSCLC and remains the primary mode in early-stage (I and II) disease. Therefore, the initial evaluation determines whether the tumor is potentially **resectable** (the tumor can be surgically removed with clear margins) and **operable** (the patient is physiologically capable of withstanding such a procedure). The fundamental question must also be asked: What are the long-term results for surgical resection of any given stage of NSCLC? If surgery is not warranted, then the next question is whether the patient is a potential candidate for nonsurgical management with curative intent (i.e., chemoradiotherapy).

If SCLC is diagnosed, the evaluation is directed at determining whether the patient has limited- or extensive-stage disease because stage dictates prognosis and the appropriate therapeutic approach. Generally, the therapeutic approach to SCLC involves chemotherapy with or without radiotherapy. Only occasionally does surgery play a role in this disease.

A. **Symptoms and signs**
   1. **Symptoms.** A history of smoking, new or changing cough, hoarseness, hemoptysis, anorexia, weight loss, dyspnea, unresolving pneumonias, chest wall pain, or symptoms of paraneoplastic syndromes are suggestive of lung cancer. These symptoms frequently inspire a smoker to quit just before the diagnosis of lung cancer.
      a. Patients with cancers located in the lung apices or superior sulcus (Pancoast's tumor) may have paresthesias and weakness of the arm and hand as well as Horner's syndrome (ptosis, miosis, and anhidrosis) caused by involvement of the cervical sympathetic nerves.
      b. Evidence of metastatic disease includes bone pain; neurologic changes; jaundice, bowel, and abdominal symptoms with a rapidly enlarging liver; subcutaneous masses; and regional lymphadenopathy.
   2. **Physical findings.** In addition to local findings in the chest and lungs, physical examination should be directed at determining whether there is metastatic disease, which would both provide staging information and, in the case of superficial cutaneous or lymph node involvement, allow for easier biopsy. Particular attention should be paid to the head and neck for concomitant cancers; to lymph node areas in the supraclavicular fossa, neck, and axilla for metastases; and to the abdomen for hepatomegaly.
B. **Laboratory studies**
   1. **Radiographs**
      a. **Chest radiograph.** If a mass is present, old x-ray films should be obtained for comparison. Persistent infiltrates, particularly in the anterior segments of the upper lobes, are suggestive of cancer.
      b. **Computed tomography (CT) scan of the chest and abdomen** through the level of the adrenal glands. CT of the chest for the staging of lung cancer is clearly superior to chest radiographs and has been reported to have an overall accuracy of 70%. Mediastinal lymph nodes are generally considered abnormal when larger than 1.5 cm in diameter and normal when smaller than 1.0 cm; nodes between these two limits are indeterminate. If 1.5-cm is used to categorize mediastinal lymphadenopathy as abnormal, sensitivity of CT is relatively poor, but specificity is excellent. CT scanning provides information about the extent of invasion of the primary tumor, the presence of pleural effusion, and lymph node status. Magnetic resonance imaging (MRI) rarely adds additional information.
         1. **Adrenal masses.** Unsuspected adrenal metastases are common in NSCLC and alter management if the patient otherwise appears to have early-stage disease. Nonmalignant adrenal masses are also common (adrenal adenomas), however, and care must be taken not to deprive a patient of an otherwise curative procedure based on an isolated adrenal mass. It is sometimes possible to distinguish between metastatic disease and adenomas based on the density characteristics. If the diagnosis is unclear and the adrenal is the only site of suspected metastases, biopsy is indicated.
         2. **Other single areas that are suspect** for, but not diagnostic of, malignancy (i.e., liver, brain) warrant a similar approach. See also [section VII.B](#).
C. **Obtaining pathologic proof of lung cancer.** Before embarking on other studies, a diagnosis of lung cancer must be proved histologically. Pursuit of the diagnosis should start with the least invasive procedure that gives histologic proof of malignancy.
   1. **Sputum cytology,** which was once routine practice, has been largely replaced by the flexible fiberoptic bronchoscope. Even in the best series, repeated sputum cytology is positive in only 60% to 80% of centrally located NSCLC and 15% to 20% of peripheral NSCLC.
   2. **Flexible fiberoptic bronchoscopy** should be performed in all but the smallest and most peripheral lesions. Two thirds of all cancers can be directly visualized. Additional tumors are evident only as extrinsic bronchial narrowing, which may be diagnosed through the bronchoscope by transbronchial biopsy in some cases. Inspection of the airways by bronchoscopy also rules out endobronchial lesions from a second bronchogenic carcinoma.
   3. **Suspicious cutaneous nodules** may undergo biopsy to establish a histologic diagnosis and for staging.
   4. **Lymph nodes.** Enlarged, hard, peripheral lymph nodes represent another potential site for biopsy. Blind biopsy of nonpalpable supraclavicular nodes is positive for cancer in less than 5% of cases. The finding of granuloma in lymph nodes can be misleading; some patients have cancer concomitant with sarcoidosis or granulomatous infections.
D. **Subsequent evaluation.** After the histologic diagnosis of lung cancer, the evaluation should focus on determining whether disease is confined to the chest and may therefore be treated with curative intent (limited-stage SCLC and stages I to III NSCLC) or whether the patient has distant disease. In appropriately selected patients, the following diagnostic studies may assist in making this determination. *In the absence of abnormalities evident from history, physical examination, and routine blood studies, these studies are likely to be normal.*
   1. **A bone scan** should be obtained in all patients with SCLC. In NSCLC, a bone scan is obtained if there is bone pain, elevated alkaline phosphatase, hypercalcemia, or mediastinal adenopathy.
   2. **Bone radiograph** (plain film) of painful areas
   3. **Spinal MRI** for patients who have suspected epidural metastases in the spinal canal or suspected lung cancer with back pain or brachial plexopathy. In patients with back pain and suspected lung (or any other) cancer, the workup should be performed on an urgent or emergent basis to allow for rapid therapeutic intervention with steroids, RT, or surgery.
   4. **Brain CT or MRI** should be obtained as part of routine staging for patients with SCLC, which is associated with a 10% incidence of neurologically asymptomatic brain metastases. These studies are not recommended for staging patients with stage I or II NSCLC in the absence of clinical signs. Patients with stage III and IV NSCLC who are under consideration for aggressive multimodality therapy or chemotherapy should undergo central nervous system (CNS) scanning.
   5. **Mediastinoscopy** is useful in the following circumstances:
      a. For *routine* preoperative staging of NSCLC (radiologic assessment alone of the mediastinum is inadequate)
      b. In patients with mediastinal masses, negative sputum cytology, and negative bronchoscopy
      c. To evaluate mediastinal lymphadenopathy. Hyperplastic nodes related to postobstructive infection are common. Mediastinoscopy may permit the patient to be considered for curative resection. Mediastinoscopy is not indicated if mediastinal nodes are smaller than 1 cm.
   6. **Percutaneous and transbronchial needle biopsy** are frequently used to diagnose lung cancer. Some argue that if NSCLC is found by these techniques and medical resectability is assumed, mediastinoscopy or thoracotomy inevitably follows in the absence of evidence of metastatic disease, and therefore the procedure is unnecessary. Furthermore, if cancer is suspected and the needle biopsy reveals a granuloma, the cancer may have been missed. If the diagnosis is SCLC, however, thoracotomy may be avoided. Additionally, medically inoperable patients with negative bronchoscopy still require a tissue diagnosis.
   7. **Positron emission tomography** (PET). PET scanning is an emerging technology based on the differential uptake of radiolabeled glucose (fluorodeoxyglucose [FDG]) by neoplastic tissues compared with normal tissue. PET scanning has demonstrated superiority to CT scanning and probable equivalence to mediastinoscopy in the evaluation of mediastinal nodes. Although its availability is limited, it is likely to play a major part in the diagnostic evaluation of NSCLC and may ultimately supplant mediastinoscopy.
   8. **Bone marrow aspiration and biopsy.** Bone marrow examination remains a standard part of the evaluation for patients with apparently limited-stage SCLC because of the relatively high incidence of subclinical involvement. It is rarely indicated in NSCLC. Some believe that it is unnecessary if the patient has a normal lactate dehydrogenase level.
E. **Evaluation of the solitary pulmonary nodule** requires a diagnostic strategy that maximizes the chance of detecting cancer and minimizes the chance of performing a needless thoracotomy if the nodule is benign. *The diagnostic approach must be individualizec.* Facts that should be considered include the following:
   1. **Characteristics that define a solitary pulmonary nodule** are as follows:
      a. A *peripheral lung mass* measuring less than 6 cm in diameter
      b. The nodule is asymptomatic.
      c. Physical examination is normal.
      d. Complete blood count and liver function tests are normal.
   2. **Calcification** of the nodules has little bearing on the diagnostic approach. Calcified nodules are more likely to be malignant unless the pattern is circular, crescentic, or completely and densely calcified.
   3. **Risk that a solitary pulmonary nodule is malignant**

- a. **According to age**
  1. Younger than 35 years of age: less than 2%
  2. 35 to 45 years of age: 15%
  3. Older than 45 years of age: 30% to 50%
- b. **According to tumor volume doubling time** (DT)
  1. DT of 30 days or less: less than 1%
  2. DT of 30 to 400 days: 30% to 50%
  3. DT of greater than 400 days: less than 1%
- c. **According to smoking history.** The risk of a solitary nodule being cancerous in a smoker compared with a nonsmoker is not known. The incidence is generally higher for smokers in the older age group.
4. **Needle biopsies** of solitary nodules are falsely negative in 15% of cases. In a patient with a high likelihood of cancer (e.g., a smoker who is older than 40 years of age), who is also a good surgical candidate, proceeding directly to thoracotomy without a tissue diagnosis is reasonable.
5. **PET scanning** has recently demonstrated considerable value in the diagnostic evaluation of the solitary pulmonary nodules, with sensitivity and specificity exceeding all other diagnostic modalities short of thoracotomy.

IV. Staging system and prognostic factors
The TNM system is applied primarily to NSCLC (T, primary tumor; N, regional lymph nodes; M, distant metastases).

StageExtent

TX   Primary tumor cannot be assessed or tumor proved by the presence of malignant cells in sputum or bronchial washings but not visualized radiographically or bronchoscopically

T0   No evidence of primary tumor

Tis   Carcinoma *in situ*

T1   A tumor that is 3 cm or smaller in greatest dimension, surrounded by ung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy (i.e., not in the main bronchus)

T2   A tumor within a lobar bronchus at least 2 cm distal to the carina with any of the following features: larger than 3 cm in greatest dimension, invasion into visceral pleura, or associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3   A tumor of any size that directly invades chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or involves the main bronchus less than 2 cm distal to the carina but not the carina; or has associated atelectasis or obstructive pneumonitis of the entire lung

T4   A tumor of any size with invasion of the mediastinum, heart, great vessels, trachea, carina, esophagus, or vertebral body; or the presence of malignant pleural effusion. Satellite tumor nodules within the ipsilateral primary tumor lobe of the lung.

NX   Regional lymph nodes cannot be assessed.

N0   No demonstrable metastasis to regional lymph nodes

N1   Metastasis to ipsilateral or peribronchial ipsilateral hilar, including direct extension

N2   Metastasis to ipsilateral mediastinal or subcarinal lymph nodes

N3   Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes

M0   No (known) distant metastases

M1   Distant metastasis present

- A. **Stage Grouping**

  Ia   T1 N0 M0
  Ib   T2 N0 M0

  IIa T1 N1 M0
  IIb T2 N1 M0; T3 N0 M0

  IIIaT3 N1 M0; T1,2,3 N2 M0
  IIIbAny T N3 M0; T4, Any N, M0

  IV   Any T Any N M1

- B. **Performance status** (PS) has direct bearing on patient survival and should be accounted for in studies evaluating treatment modalities for lung cancer. Criteria for assessment of functional PS are described on the inside of the back cover. Patients who feel well and have few symptoms of disease (PS of 0 to 1) survive longer than ill patients (PS of 2 or more) and are more likely to respond to chemotherapy, independent of other prognostic factors.
- C. **Weight loss.** Involuntary weight loss of 5% or more is an independent and negative prognostic factor.
- D. **Tumor histology.** Survival is not greatly influenced by cell type if PS and extent of disease are taken into account. Patients with SCLC, however, have debility and extensive disease more often than those with the other cell types. A few patients with indolent but unresectable squamous lung cancer may live for several years.
- E. **Molecular prognostic factors.** Suppressor oncogene alterations are common in NSCLC and are associated with a poor prognosis; mutated p53 (17p) oncogene occurs in half of patients with NSCLC and in almost all with SCLC. Dominant oncogene overexpression (*c-myc, K-ras, erb-B2*) is associated with a poor prognosis.

V. Prevention and early detection

- A. **Prevention** is the best way to reduce the death rate from lung cancer. More than 90% of patients with lung cancer would not have developed the disease if they had not smoked. Every smoking patient should be advised of the enormous risks. Several ongoing studies are evaluating the role of retinoids and other compounds in preventing secondary tumors. Trials of vitamin A analog supplementation and beta-carotene have failed to demonstrate benefit.
- B. **Early detection** of lung cancer by screening high-risk populations with chest radiographs and sputum cytology has not been clearly demonstrated to improve survival rates. The role of chest radiography is being reevaluated. New antibody tests and fluorescent bronchoscopy are also under study. Data indicate that spiral CT scan may be an effective screening tool. Because the value of a screening test is dependent on the prevalence of a disease in a population, the determination that smokers with minimal degrees of obstructive disease are at substantially higher risk for lung cancer may improve the sensitivity and specificity of screening tests.

VI. Management

- A. **NSCLC.** The management of NSCLC has grown more complex. Surgery, the previous mainstay of management, is still the primary mode of therapy in stage I and II disease. Stage III disease (characterized by mediastinal nodal disease or involvement of major structures) is frequently resectable but almost invariably relapses, resulting in the patient's death within 5 years (90% to 95%), when managed by surgery alone. Therefore, multimodality therapy is increasingly employed in this large (about 40,000 patients per year) subset.

  After histologic proof of NSCLC is obtained, resectability is determined by the extent of the tumor and operability according to the overall medical condition of the patient. Age and mental illness *per se* are not factors in deciding operability. About half of patients with NSCLC are potentially operable. About half of tumors in operable patients are resectable (25% of all patients), and about half of patients with resectable tumors survive 5 years (12% of all patients, or 25% of operable patients). The following recommendations are consistent with those of the American Thoracic Society and European Respiratory Society.

  1. **Signs of unresectable NSCLC**
     - a. Distant metastases, including metastases to the opposite lung. If solitary adrenal, hepatic, or other masses are detected by scans, these areas should be evaluated by biopsy because there is a significant incidence of benign masses that masquerade as tumor. See also
     - b. Persistent pleural effusion, with malignant cells. Cytologic examination of 50 to 100 mL of fluid is positive for malignant cells in about 65% of patients.

Repeat thoracentesis may provide the diagnosis in most of the remaining patients. In the event of negative cytology and in the absence of other contraindications to surgery, thoracoscopy should be undertaken at the time of surgery. Pleural involvement with malignant cells would preclude surgery. Transudative and parapneumonic effusions that clear do not contraindicate surgery. Most exudative effusions in the absence of pneumonia are malignant, regardless of cytologic findings.

 c. Superior vena cava obstruction

 d. Involvement of the following structures:

  1. Supraclavicular or neck lymph nodes (proved histologically)

  2. Contralateral mediastinal lymph nodes (proved histologically)

  3. Recurrent laryngeal nerve

  4. Tracheal wall

  5. Main-stem bronchus less than 2 cm from the carina (resectable by sleeve resection technique)

 2. **Cardiac status.** The presence of uncontrolled cardiac failure, uncontrolled arrhythmia, or a recent myocardial infarction (within 6 months) makes the patient inoperable.

 3. **Pulmonary status.** The patient's ability to tolerate resection of part or all of a lung must be determined. The presence of pulmonary hypertension or inadequate pulmonary reserve makes the patient inoperable.

  a. **Routine pulmonary function tests** (PFT). Arterial blood gases and spirometry should be obtained in all patients before surgery. PFTs must be interpreted in the light of optimal medical management of pulmonary disease and patient cooperation. The patient with PFT abnormalities should receive a trial of bronchodilators, antibiotics, chest percussion, and postural drainage before inoperability is concluded. The following results suggest inoperability:

   1. A $Paco_2$ that is greater than 45 mm Hg (that cannot be corrected) or a Pao_2 that is less than 60 mm Hg, or

   2. Forced vital capacity (FVC) less than 40% of predicted value, or

   3. Forced expired volume at one second (FEV_1) less than or equal to 1 L. Patients with an FEV_1 of greater than 2 L or more than 60% of predicted value can tolerate pneumonectomy.

  b. **Special PFTs**

   1. **The quantitative perfusion lung scan** is done when patients with impaired pulmonary function are suspected of not being able to tolerate excision of lung tissue. The FEV_1 is measured before the scan. The percentage of blood flow to each lung is calculated from the results of the scan. The percentage of flow in the noncancerous lung is multiplied by the FEV_1, giving a measure of the anticipated postoperative FEV_1. Pneumonectomy is contraindicated if the calculated postoperative FEV_1 is less than 700 mL because the patient is likely to develop refractory cor pulmonale and respiratory insufficiency.

   2. **Exercise testing.** If maximal oxygen consumption is more than 20 mL/kg, perioperative morbidity is low; if it is less than 10 mL/kg, morbidity and mortality are high.

B. **NSCLC: management of operable disease**

 1. **Surgery.** Surgical resection of the primary tumor is the treatment of choice for patients who can tolerate surgery and who have stage I or II NSCLC. The selection of the operative procedure varies with the surgeon's criteria for patient selection, the extent of disease, and the patient's ventilatory function.

 Definition of nodal involvement during surgical resection is mandatory to determine prognosis and to evaluate the results of treatment; the anatomic boundaries of 13 nodal stations have been described. Although considered technically resectable, most patients with stage IIIa disease (predominantly N2 disease) do poorly (see section VI.C). An exception is the patient with malignant involvement of a single mediastinal nodal station.

 A multicenter study of contemporary operative mortality due to lung surgery documented the following death rates within 30 days of operation: pneumonectomy, 7.7%; lobectomy, 3.3%; and segmentectomy or wedge resection, 1.4%. Advanced age, weight loss, coexisting disease, reduced FEV_1, and more extensive resection are significant risk factors.

  a. **Incomplete resections** are rarely, if ever, indicated.

  b. **Lobectomy** is the procedure of choice in patients whose lung function permits it. Conservative resection (segmentectomy) has been associated with a significantly worse disease-free survival and an increased local recurrence rate.

  c. **Bilobectomy, sleeve lobectomy, or pneumonectomy** with or without lymph node dissection is used for other tumors.

  d. **Video-assisted thoracoscopic surgery** (VATS) is increasingly employed in thoracic surgery. Although of significant value in diagnostic evaluations and treatment of benign disease, the use of VATS in lung cancer resection remains investigational.

 2. **Pancoast's tumor.** RT has been employed as the preliminary treatment for Pancoast's tumors (T3 N0 M0, stage IIb) before surgical resection of the primary tumor and involved chest wall. Given the favorable results of combined chemotherapy and RT (chemoradiotherapy) as definitive treatment for locally advanced NSCLC or trimodality therapy (vide infra), the use of preoperative chemoradiotherapy is a reasonable approach. Preliminary results from a national intergroup trial using preoperative chemoradiotherapy in the treatment of this disease entity have been favorable.

 3. **Adjuvant therapy.** Most patients undergoing complete resections for NSCLC relapse and die within 2 years of resection. Trials from the 1970s demonstrated a prolongation in time to progression but no survival advantage and substantial toxicity with adjuvant chemotherapy. Alkylating agent-based adjuvant therapy available during that era is now considered suboptimal and even detrimental to long-term outcome. The issue of adjuvant chemotherapy is being addressed in the United States in two large cooperative group trials randomizing patients to chemotherapy or observation. Until the results of these trials are available, adjuvant chemotherapy should be considered investigational.

 Adjuvant RT has also been frequently employed in the treatment of resected stage I, II, and III disease. Its use clearly results in improved local control. As documented in a recent meta-analysis, however, improved local control may come at the expense of diminished survival. Hence, the use of adjuvant RT in completely resected NSCLC cannot be recommended.

C. **NSCLC: Management of inoperable disease**

 1. **Resectable but inoperable.** Definitive RT should be the primary treatment for medically inoperable but resectable patients. The overall survival rate at 5 years is about 20% (half the rate of that for a comparable group of patients treated surgically), depending on the size of the primary tumor. The sterilization rate for small tumors ranges from 25% to 50%. Chemoradiotherapy may also be considered for these patients, particularly those with N1 disease, for whom the outcome is very poor with RT alone.

 2. **Stages IIIa and IIIb**

  a. **Combined-modality therapy.** The standard treatment in the past for most of these patients was RT or surgery (see section VI.A) alone, with modest evidence of survival benefit over supportive care alone. Historical data suggest that RT results in a median survival of 9 months, a 2-year survival rate of 10% to 15%, and a 5-year survival rate of 5% (worse for stage IIIb).

  Data indicate a survival advantage at 1, 2, and 3 years with the use of chemoradiotherapy in this setting (with or without surgery); the 2-year survival rate has been reported to be 25% to 40%. Both sequential and concurrent chemotherapy and irradiation may be employed.

  Several drug combinations and approaches have been evaluated; the most mature data are with cisplatin plus vinblastine and cisplatin plus etoposide (PE). These combinations have been supplanted in some centers by newer regimens, such as carboplatin and paclitaxel, although the advantages of "newer" regimens in combined-modality therapy remain to be established and are the subject of ongoing randomized studies (see Table 8.1).

Table 8.1 Chemotherapy regimens for non–small cell lung cancer

 Most chemoradiotherapy trials entered patients with good PS, minimal weight loss, and little comorbid illness. The use of chemoradiotherapy is appropriate, however, in many poor-risk patients defined by weight loss and other medical problems. A multicenter study demonstrated a median survival of 13 months in these patients, comparable to that of more favorable patients. These sicker patients, not surprisingly, do not experience the same long-term survival.

  b. **Preoperative "neoadjuvant" chemotherapy** (with or without RT) for patients with locally advanced disease may down-stage the malignancy and make it

resectable. Whether surgical resection adds to survival compared with chemoradiotherapy alone in stage IIIa (N2) disease is unknown and is under evaluation in the current North American Intergroup trial.

   c. **Technical aspects of RT** are important, both as a single modality and in combination with chemotherapy. Issues of dose, schedule, and fields are crucial. Evidence indicates that hyperfractionated RT (twice-daily treatment) or hyperfractionated accelerated RT (three times a day) may be superior to conventional fractionation. Additionally, the use of three-dimensional conformal techniques may reduce or prevent toxicity to normal lung within the radiation field and allows dose escalation.

   d. **Specific management recommendations** should be individualized. In the absence of a clinical trial, patients with documented N2 or N3 disease should receive concurrent chemoradiotherapy. Two randomized controlled trials have demonstrated the superiority of concurrent chemotherapy over sequential therapy. A Japanese study utilized mitomycin, vindesine, and cisplatin concurrent with RT. A trial by the Radiation Therapy Oncology Group utilized cisplatin and vinblastine concurrent with 6100 cGy of RT administered over 6 weeks. Significant differences in median survival times (16 vs 13 months) and in survival at 2 and 3 years strongly favored concurrent treatment. Patients with T4 N0 disease may be considered for induction chemotherapy with or without RT followed by surgery.

   e. **Radiographic responses.** In all cases, patients treated with multimodality therapy may have variable radiographic responses. Except for those who demonstrate progressive disease (and consequently have a dire prognosis), there is no correlation between degree of radiographic response (complete response, partial response, or stable disease) and outcome. It is possible that PET scanning may improve the ability to assess these patients noninvasively.

3. **Stage IV**

   a. **Fully ambulatory patients** have modestly increased survival, and symptoms are often palliated by the use of platinum-containing (cisplatin or carboplatin) chemotherapy. A clear advantage for the use of chemotherapy has now been conclusively demonstrated in patients with stage IV disease and PS of 0 to 1. The median survival of such patients is 4 months, and the 1-year survival rate is 10% with "best supportive care"; with platinum-based chemotherapy (either as single agents or combined with etoposide, vinblastine, vindesine, or mitomycin), these survivals are improved to about 6 to 8 months and 20% to 25%, respectively.

   Newer regimens (carboplatin plus paclitaxel, cisplatin plus vinorelbine, cisplatin plus gemcitabine) have resulted in median survivals of 9 to 10 months and 1-year survival rates of 30% to 40% in large multicenter randomized trials. Several studies and metaanalyses have demonstrated improved quality of life for patients treated with chemotherapy as opposed to "best supportive care." Economic analysis has demonstrated that it is more cost-effective to treat patients with chemotherapy because of the reduced need for hospitalization, RT, and other interventions.

   b. **Patients who are less than fully ambulatory** (PS of 2 or more) tolerate combination chemotherapy poorly, particularly if cisplatin is a component of the regimen. Single-agent chemotherapy (vinorelbine or gemcitabine) or best supportive care can be considered as management options dependent on the presence of comorbid disease and the patient's wishes.

   c. **Patients who have progressed after initial chemotherapy** and who have good PS (0 to 1) may respond to second-line therapy with docetaxel. Two multicenter randomized trials have demonstrated an advantage for docetaxel in this setting (compared with best supportive care in one study and with either ifosfamide or vinorelbine in the other).

   d. **New chemotherapy agents and combinations** are undergoing evaluation. Many factors govern the response to and toxicity of these regimens. These include performance status, age, gender, degree of weight loss, and staging of the patients. Some phase II trials include patients with stage IIIb (nonpleural effusion) disease. Additionally, small numbers (25 to 50) of patients are accrued to such trials, as opposed to the hundreds of patients accrued to phase III trials. As a result, early reports of phase II data frequently overstate the activity and underestimate the toxicity of new regimens. Table 8.2 compares the phase I and II (toxicity and activity) versus phase III (activity against a standard regimen) trials of several accepted combinations. We recommend that in the nonprotocol setting, well-established regimens be used, with dose modifications employed at the time of the phase III trials.

Table 8.2 Phase II and phase III trial results in non–small cell lung cancer

   e. **The maximum number of cycles** of any specific regimen is eight. One study demonstrated equivalent response and survival when three cycles of a cisplatin-based regimen were compared with six cycles of the same regimen.

D. **SCLC: Management**

1. **Limited stage (I, II, III)** is confined to one hemithorax, including contralateral supraclavicular adenopathy. Less than 5% of patients with SCLC have stage I or II disease. About one third, however, have disease that is clinically confined to the hemithorax and draining regional nodes at presentation (stages IIIa and IIIb).

   a. **Combined-modality therapy.** The available data indicate that these patients should receive concurrent chemotherapy and thoracic RT. Sequential chemotherapy followed by RT results in inferior long-term survival and should be discouraged. At this time, the most accepted chemotherapy regimen is cisplatin and etoposide (Table 8.3). RT given twice daily (hyperfractionated) has been demonstrated to be superior to once-daily therapy (4500 cGy). It is unclear whether conventionally fractionated RT to a higher dose would be equal or superior to hyperfractionated 4500 cGy treatment. If given concurrently as induction, combined-modality therapy yields a median survival of 23 months and a 5-year survival rate of 25%.

Table 8.3 Regimens for small cell lung cancer

   b. **Prophylactic cranial irradiation** (PCI) decreases the rate of brain metastases. The use of PCI is controversial because the occurrence of synchronous metastases has made it difficult to demonstrate a survival advantage. The best evidence is that the use of PCI results in about a 5% improvement in survival. When PCI is administered in low dose fractions (200 cGy/day or less, to a dose of 3000 cGy), the incidence of neurocognitive dysfunction is not increased.

2. **Extensive stage.** Fully ambulatory patients with extensive disease have a good response to PE or cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV regimen), or alternation of PE and CAV regimens (Table 8.3). Only 15% to 20% of such patients achieve complete response. The median survival of fully ambulatory patients is about 1 year, and the 2-year survival rate is 20%. Survival for 5 years, however, is unusual. Topotecan has demonstrated activity as second-line therapy. Other agents (paclitaxel, gemcitabine, vinorelbine, and docetaxel) have activity in extensive-stage disease and are under evaluation.

Patients with SCLC who are less than fully ambulatory may still be appropriate candidates for chemotherapy. The period of benefit from "standard" regimens is generally only a few months; these patients should be considered for trials with new chemotherapeutic agents.

VII. Special clinical problems

A. **Positive sputum cytology with a negative chest radiograph** (TX N0 M0) and no other evidence of disease is an occasional problem, usually occurring in screening programs. Patients should be examined by CT scan of the chest and fiberoptic bronchoscopy with selective washings. Bronchial washings may not be helpful in localizing the malignancy because multiple sites may have tumors or suspected dysplastic change.

1. When these measures fail to identify a lesion, patients must be informed that they have a cancer too small to be detected is significant. Such patients should be followed with monthly chest radiographs and should be strongly advised to stop smoking. Repeated sputum cytology is not helpful if the original cytology findings were diagnostic of malignancy and laboratory errors were not suspected.

2. The cytologic discovery of an unequivocal small cell cancer in the absence of other findings should be confirmed by repeat sampling and solicitation of a second pathologist's opinion at another institution. After the diagnosis is confirmed, patients should be treated as described previously.

B. **Solitary metastatic disease.** Patients with NSCLC who present with a single site of metastatic disease, most commonly in the brain, can be treated with curative intent. There are two situations in which this occurs: patients who have received definitive therapy and relapse with a single CNS metastasis (and no other disease), and those who at initial presentation have chest disease and the CNS as the sole site of metastasis.

For the relapsed patients, resection of the CNS metastasis may lead to long-term survival. For patients with synchronous disease, resection of the primary chest tumor and resection or the use of radiosurgery for the CNS disease is appropriate. If the patient has locally advanced disease (stage IIIa or IIIb), one could

consider resection of the CNS disease followed by chemoradiotherapy with or without surgery for the chest disease in selected patients.

1. The use of postoperative whole-brain RT after surgical resection of a solitary metastasis has been recommended because of the frequency of occult micrometastases. However, the use of whole-brain RT in patients who have been treated either with surgery or radiosurgery has failed to demonstrate a survival advantage.
2. If brain metastasis is anatomically unresectable, stereotactic radiosurgery may be superior to whole-brain RT alone.

VIII. Follow-up

a. Although most cases of SCLC and NSCLC recur, there is little evidence that frequent laboratory or radiologic studies detect disease before the development of symptoms or that early detection improves outcome. In the nonprotocol setting, we recommend history and physical examination every 2 to 3 months and chest radiograph twice yearly for the first few years after resection.
b. Patients who undergo chemoradiotherapy frequently demonstrate scarring and infiltrates on radiologic studies, which may evolve with time. These abnormalities are frequently misinterpreted as progressive disease. Proper interpretation of these studies requires determination of RT ports and comparison of initial and follow-up studies.

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Chapter 9 Gastrointestinal Tract Cancers

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Cancers of the gastrointestinal (GI) tract account for 20% of all new visceral cancers and 23% of cancer deaths in the United States. The frequency and mortality of cancers of the various GI organs are shown in Table 9.1. In several other countries, GI cancers are an even more significant health problem.

Table 9.1 Occurrence of digestive tract cancers in the United States (1999)

Esophageal Cancer

I. Epidemiology and etiology

  A. **Epidemiology.** The incidence of esophageal cancer is noted in Table 9.1.
    1. Squamous cell esophageal cancer is the foremost malignancy in the Bantu of Africa. South Africa, Japan, China, Russia, Scotland, and the Caspian region of Iran also have relatively high incidence rates.
    2. Incidence rates of squamous cell esophageal cancer can vary 100- to 200-fold among different populations living in geographic adjacency.
  B. **Etiology**
    1. **Carcinogens**
      a. Long-term use of tobacco and alcohol increases the incidence of both squamous cell carcinoma and adenocarcinoma of the esophagus.
      b. Human papillomavirus (HPV) infection is associated with squamous cell carcinoma of the esophagus.
      c. Dietary carcinogens relevant to the development of squamous cell esophageal cancers include the following:
        1. Plants growing in soil deficient in molybdenum reduces their content of vitamin C and cause hyperplasia of esophageal mucosa, a precursor of

cancer.
2. Elevated nitrates in the drinking water and soup kettles that concentrate the nitrate
3. Food containing fungi: *Geotrichum candidum* (pickles, air-dried corn), *Fusarium* sp., and *Aspergillus* sp. (corn)
4. Bread that is baked once a week and eaten when moldy (*G. candidum*)
5. Dried persimmons, a rough food that injures the esophageal mucosa when eaten (China)
2. **Predisposing factors for squamous cell esophageal cancer**
   a. Howel-Evans syndrome or tylosis (hyperkeratosis of the palms and soles) is a rare genetic disease that is transmitted as a mendelian-dominant trait (nearly 40% develop esophageal cancer).
   b. Lye stricture (up to 30%)
   c. Esophageal achalasia (30%)
   d. Esophageal web (20%)
   e. Plummer-Vinson syndrome (iron-deficiency anemia, dysphagia from an esophageal web, and glossitis, 10%)
   f. Short esophagus (5%)
   g. Peptic esophagitis (1%)
   h. Other conditions associated with squamous cell esophageal cancer
      1. Patients with head and neck cancer (Field's cancerization theory)
      2. Patients with celiac disease
      3. Chronic esophagitis without Barrett's esophagus (see [section II.A](#))
      4. Thermal injury to the esophagus because of drinking boiling hot tea or coffee (Russia, China, and Middle East)
3. **Predisposing factors for adenocarcinoma of the esophagus**
   a. Barrett's esophagus is metaplastic replacement of squamous with intestinalized columnar epithelium.
      1. Adenocarcinomas associated with Barrett's esophagus constitute the cancer whose incidence is most rapidly increasing worldwide, but particularly in white men.
      2. In the United States, the incidence of adenocarcinoma of the esophagus has increased 6- to 7-fold since 1970. Patients with Barrett's esophagus have a 30- to 125-fold increased risk for esophageal adenocarcinoma compared with the average U.S. population.
   b. Obesity
   c. Reflux esophagitis

II. Pathology and natural history

A. **Histology.** Squamous cell tumors constitute 98% of esophageal cancers in the upper and middle esophagus; the remainder are adenocarcinomas and rare sarcomas, small cell carcinomas, or lymphomas. In the lower esophagus, adenocarcinoma is slightly more common and may arise from esophageal continuation of the gastric mucosa (Barrett's esophagus) or may represent extension of a gastric adenocarcinoma.
B. **Location of cancer in the esophagus**
   1. Cervical: 10%
   2. Upper thoracic: 40%
   3. Lower thoracic: 50%
C. **Clinical course.** Esophageal cancer is highly lethal; more than 90% of affected patients die from the disease. About 75% present initially with mediastinal nodal involvement or distant metastasis. Death is usually caused by local disease that results in malnutrition or aspiration pneumonia.

III. Diagnosis

A. **Symptoms and signs.** Dysphagia is the most common complaint. Patients become unable to swallow solid foods and eventually liquids. Symptoms rarely develop until the esophageal lumen is greatly narrowed and metastasis has occurred. Pain may or may not be present. Physical findings other than cachexia, palpable supraclavicular lymph nodes, or hepatomegaly are rare.
B. **Diagnostic studies**
   1. **Preliminary studies** include physical examination, complete blood count (CBC), liver function tests (LFTs), chest radiograph, esophagoscopy, and barium esophagogram. Brushings can be obtained and lesions can undergo biopsy using endoscopy.
   2. **Computed tomography** (CT) scan staging predicts invasion or metastases with an accuracy rate of more than 90% for the aorta, tracheobronchial tree, pericardium, liver, and adrenal glands; 85% for abdominal nodes; and 50% for paraesophageal nodes.
   3. **Endoscopic ultrasound** (EUS) is more accurate than CT in assessing tumor depth and paraesophageal nodes. Transesophageal biopsy to sample enlarged lymph nodes is possible under EUS guidance.
   4. **Laparoscopy** allows assessment of subdiaphragmatic, peritoneal, liver, and lymph node metastases. In patients who are getting chemotherapy and radiation, either preoperatively or in lieu of surgery, placement of a jejunostomy tube for enteral alimentation during laparoscopy is clinically useful. Thoracoscopy can allow patients who are noted to have intrathoracic dissemination to be spared radical resections.
   5. **Bronchoscopy** for tumors of the upper or middle esophagus can diagnose direct tumor extension into the tracheobroncheal tree and synchronous primary sites.

IV. Staging system and prognostic factors
A TNM staging classification is available. Patients with earlier disease stage, particularly N0 and M0, have a better prognosis. Readers should consult an up-to-date staging manual because of the frequent revisions of staging systems. Most patients die from their disease within 10 months of diagnosis. The 5-year survival rate is less than 10% despite all efforts at treatment.

V. Screening and early detection
In China, mass screening uses "the Chinese balloon" (a long, small-caliber stomach tube with a balloon covered with nylon netting on the distal end). This balloon is passed into the stomach, inflated, and then withdrawn the entire length of the esophagus; cells for cytologic study are trapped in the nylon net. In the United States, screening for esophageal cancer is not effective in the general population, but patients such as those with lye-induced strictures or Barrett's esophagus, who are at higher risk, should undergo periodic screening upper endoscopy.

VI. Management.
The aggressiveness of surgical treatment and radiation therapy (RT) is highly varied among institutions.

A. **Resection of primary tumor.** Results of surgical resection in cancer of the esophagus are poor. The operative mortality rate is about 5% to 10%. In the United States, the 5-year survival rate in patients undergoing tumor resection is less than 20%. Aggressive surgery, however, may be justified, particularly for some patients with lesions in the lower half of the esophagus.

In China, the 5-year survival rate is 85% for early cancer and 35% for moderately advanced disease. This high 5-year rate survival must be interpreted with caution because it likely is not a benchmark attainable in populations in the United States, where screening is seldom done.

B. **Palliating an obstructed esophagus** can be accomplished by several procedures and permits enteral nutrition.
   1. **Laser therapy** may relieve obstruction and bleeding. Endoscopic laser therapy has less than a 1% mortality rate but may require prior mechanical dilation. Although successful laser therapy may require multiple endoscopic sessions, it can be done on an outpatient basis, and its overall cost is still much lower than the cost of palliative surgery. Photosensitization of esophageal tumors using an injectable porphyrin derivative can increase the laser energy absorbed by the tumor with palliative benefit but is associated with generalized dermal photosensitivity to sunlight lasting 4 to 6 weeks.
   2. **Esophageal stenting.** At least 17 devices are available for esophageal intubation. About 15% of patients with malignant esophageal obstruction are candidates for tube placement. The tube may be introduced with a pusher tube, which is loaded either onto a bougie or over an endoscope and expands after placement. The latter method permits visualization of the obstructed lumen. The success rate is 90% to 97%.
      a. **Advantages** of tube placement are improved ability to swallow saliva, pleasure of oral alimentation, relief from pulmonary aspiration related to esophagopulmonary fistula, independence from physician or hospital for constant care, and ability to spend time with family and friends in relative comfort.
      b. **Contraindications** to placement of endoprosthesis are carcinoma less than 2 cm below the upper sphincter, limited life expectancy (less than 6 weeks), and uncooperativeness.
      c. **Complications** include perforation, dislocation, tumor overgrowth, reflux symptoms with stricturing, pressure necrosis, foreign-body impaction with obstruction, bleeding, and failure of intubation. The complication rate (early and late) is 10% to 25%.

3. **Feeding gastrostomy** is not advisable because it does not palliate dysphagia, which forces patients with complete or nearly complete esophageal obstruction to expectorate saliva and secretions, does not increase life expectancy, and has its own morbidity and mortality.
4. **Colonic interposition** to bypass the obstructed segment is recommended only for surgical candidates in whom a suitable gastric remnant cannot be fashioned because of prior gastric resection, extent of disease, or underlying esophageal disease.
5. **External-beam irradiation** or endoluminal brachytherapy can result in tumor regression with palliation in some cases. Up to 70% to 80% of patients with dysphagia may note improved swallowing after external-beam irradiation. Endoluminal brachytherapy can be useful in previously irradiated patients with local tumor regrowth causing dysphagia.

C. **Single-modality treatment**
1. **Radiotherapy alone.** Radiotherapy to a dose of 6000 cGy resulted in 1-, 2-, 3- and 5-year survival rates of 33%, 12%, 8%, and 7% of patients treated on the radiation arm of a randomized trial in which responding patients were permitted to go on to resection at physician discretion.
2. **Surgery alone.** The surgical procedures employed in esophagectomy depend on the location and preference of the surgeon and include principally transhiatal esophagectomy or the Ivor-Lewis procedure, which requires both thoracotomy and laparotomy. In the 25% to 30% of patients in whom complete resection is possible, 5-year survival rates of 15% to 30% are reported.
3. **Chemotherapy alone** is seldom an effective palliative modality in patients with esophageal cancer, and when chemotherapy is employed, it should be coupled with mechanical or radiotherapeutic approaches for palliation of dysphagia. Like in gastric cancer, multiagent chemotherapy-induced responses tend to be short lived.

D. **Combined-modality therapy**
1. **Preoperative or postoperative therapy** with radiation alone may reduce the local recurrence rate but has no apparent effect on median survival. Similarly, neither preoperative (as reported in six randomized trials) nor postoperative chemotherapy alone has improved outcomes in patients with esophageal cancer.
2. **Primary therapy without surgery.** In patients not planning to undergo esophageal surgery because of comorbid disease or patient or physician choice, combined chemotherapy and radiation can lead to long-term survival in some, as compared with surgery alone. In a prospective, randomized trial of patients with squamous cell or adenocarcinoma of the thoracic esophagus, combined-modality treatment (5-fluorouracil [5-FU] plus cisplatin plus 5000 cGy) resulted in improved median survival (9 months versus 12.5 months) when compared with RT alone (6400 cGy). The 2-year survival rate for patients randomized to combined chemotherapy and radiation was 38%, compared with 10% for those randomized to radiation alone. The patients receiving the combined-modality treatment experienced decreased local and distant recurrences but significantly more toxicity, much of which was serious or life-threatening. Only half of these patients received all the planned cycles of chemotherapy.
3. **Chemotherapy and surgery.** Response rate to multiagent neoadjuvant chemotherapy can be as high as 40% to 50%, and up to 25% of treated patients may have apparent pathologic complete remissions. Preoperative chemotherapy with cisplatin and 5-FU, however, did not improve overall survival when compared with surgery alone in a randomized trial of 440 patients with squamous esophageal cancer.
4. **Triple-modality therapy.** The combination of preoperative chemotherapy and radiation has led to an increase in the 3-year survival rates and prolonged median disease-free survival in two randomized studies compared with surgery alone. In one trial of stage I and II squamous cell cancers, the overall survival was not improved by triple-modality therapy. In the other trial in which both squamous and adenocarcinoma patients were entered, there was a statistically significant survival benefit for triple-modality treatment. This approach is being tested in a national intergroup trial in the United States. Patients with complete pathologic response at surgery have about a 50% likelihood of long-term survival.

E. **Advanced disease.** The responses using single chemotherapeutic agents (15% to 20%) are usually partial and of brief duration (2 to 5 months). Combination chemotherapy, usually including cisplatin with 5-FU, a taxane, or both, is associated with reported response rates ranging from 15% to 80%, a median duration of response of 7 months, and substantial toxicity. Higher response rates, however, do not necessarily translate into significant benefit for these patients, and the outcome remains poor.

Gastric Cancer

I. Epidemiology and etiology

A. **Incidence.** The prevalence and death rates of gastric carcinoma (particularly distal cancers) have been markedly and significantly decreasing in all regions of the world and in all age groups by about 2% to 7% per year. Deaths due to gastric cancer have decreased to 20% of that seen in the 1930s in the United States, although it remains the second leading cause of cancer death worldwide.

Dietary factors and improvement in food storage are believed to be the major factors causing this decline. Improvements include reduction in toxic methods of food preservation (such as smoking and pickling), a decline in salt consumption, greater use of refrigeration, and increased consumption of fruits and vegetables.

Mortality from gastric cancer is highest in Costa Rica (61 deaths per 100,000 population) and East Asia (Hong Kong, Japan, and Singapore) and lowest in the United States (5 deaths per 100,000). Of interest, the Nordic and Western European countries have incidence rates two to three times higher than the United States. The incidence remains high in Japan and is intermediate in Japanese immigrants to the United States; first-generation Japanese Americans have an incidence comparable to other Americans. The average age of onset is 55 years.

B. **Etiology.** Two gastric cancer entities can be distinguished by their risk factors and histology. *Diffuse gastric cancer* is associated with hereditary factors and a proximal location and does not appear to occur in the setting of intestinal metaplasia or dysplasia. *Intestinal-type gastric cancer* is more distal, occurs in younger patients, is more frequently endemic, and is associated with inflammatory changes and with *Helicobacter pylori* infection.
1. **Diet.** Gastric cancer has been linked to the ingestion of red meats, cabbage, spices, fish, salt-preserved or smoked foods, a high-carbohydrate diet, and low consumption of fat, protein, and vitamins A, C, and E. Selenium dietary intake may be inversely proportioned to the risks of gastric cancer but not of colorectal cancer.
2. *H. pylori* **infection** is associated with an increased risk for gastric adenocarcinoma and may be a cofactor in the pathogenesis of noncardiac gastric cancer. The *H. pylori* organism was identified in 89% of patients with intestinal-type cancer in the malignant and nearby inflammatory tissue, whereas it was present in 32% of tissues taken from patients with diffuse-type cancers. This raises the possibility now under investigation in prospective randomized trials that eradicating *H. pylori* through antibiotic treatment and bismuth administration may be preventive of both atrophic gastritis and intestinal-type gastric cancer.
3. **Heredity and race.** African, Asian, and Hispanic Americans have a higher risk for gastric cancer than whites. The diffuse histologic pattern is the predominant pathologic type seen in families with multiple affected members.
4. **Pernicious anemia, achlorhydria, and atrophic gastritis.** Pernicious anemia carries an increased relative risk for gastric cancer said to be 3 to 18 times that of the general population based on retrospective studies. Although some controversy surrounds this finding, follow-up endoscopy is generally suggested for patients known to have pernicious anemia.
5. **Previous gastric resection.** Gastric stump adenocarcinomas, which occur with a latency period of 15 to 20 years, are more common in patients after surgical treatment for benign peptic ulcer disease, particularly those who have hypochlorhydria and reflux of alkaline bile. These cancers are associated with dysplasia of gastric mucosa, elevated gastrin levels, and a poor prognosis. Two meta-analyses have supported this increased risk. Some population-based studies do not support this finding.
6. **Mucosal dysplasia** is graded from I to III, with grade III showing marked loss in cell differentiation and increased mitosis. The finding of high-grade dysplasia by experienced pathologists in two separate sets of endoscopic biopsies is considered to be a marker for future gastric cancer. Intestinal metaplasia, replacement of gastric glandular epithelium with intestinal mucosa, is associated with intestinal-type gastric cancer. The risk for cancer appears to be proportional to the extent of metaplastic mucosa.
7. **Gastric polyps.** As many as half of adenomatous polyps show carcinomatous changes in some series. Hyperplastic polyps (more than 75% of all gastric polyps) do not appear to have malignant potential. Patients with familial adenomatous polyposis (FAP) have a higher incidence of gastric cancer. Patients with adenomatous polyps or FAP should have endoscopic surveillance.
8. **Chronic gastritis.** In chronic atrophic gastritis of the corpus or antrum, *H. pylori* infection and environmental and autoimmune (as in pernicious anemia) causes are thought to be associated with an increased risk for gastric cancer. In Ménétrier's disease (hypertrophic gastritis), an increase in the incidence of gastric cancer is also observed.
9. **Other risk factors.** Gastric cancer is more common in men older than 50 years of age and in people with blood group A. Gastric cancer is consistently seen more commonly among those of lower socioeconomic class across the world.

II. Pathology and natural history

A. **Histology and classification.** About 95% of gastric cancers are adenocarcinomas; 5% are leiomyosarcomas, lymphomas, carcinoids, squamous cancers, or other rare types.

1. **Useful characteristics of gastric cancer**
   a. **Histologic classification (Lauren):** Diffuse (scattered solitary or small clusters of small cells in the submucosa), intestinal (polarized columnar large cells with inflammatory infiltrates localized in areas of atrophic gastritis or intestinal metaplasia), and mixed types. This classification has proved to be the most useful for adenocarcinomas because the two major types (diffuse and intestinal) represent groups of patients with differing ages, sex ratios, survival rates, epidemiology, and apparent origin. Studies have shown that "diffuse" histology affects younger patients, with slight predominance among women. Diffuse histology occurred in 50% of all cases and in 55% of unresectable cases. Intestinal type predominates in high-risk regions of the world and among older people and affects more men than women.
   b. **Clinical classification (gross anatomy).** Superficial (superficial spreading), focal (polypoid, fungate, or ulcerative), and infiltrative (linitis plastica) types
   c. **Japanese Endoscopic Society (JES) classification.** Type I (polypoid or masslike), type II (flat, minimally elevated, or depressed), and type III (cancer associated with true ulcer)
2. **Location of cancers**
   a. Distal location: 40%
   b. Proximal: 35%
   c. Body: 25%
B. **Clinical course.** About 18% of gastric cancer patients are long-term survivors in the United States. Gastric carcinoma spreads by the lymphatic system and blood vessels, by direct extension, and by seeding of peritoneal surfaces. The ulcerative and polypoid types spread through the gastric wall and involve the serosa and draining lymph nodes. The scirrhous type spreads through the submucosa and muscularis, encasing the stomach, and in some instances spreading to the entire bowel. Often, the physical examination is normal.

Widespread metastatic disease may affect any organ, especially the liver (40%), lung (may be lymphangitic, 40%), peritoneum (10%), supraclavicular lymph nodes (Virchow's node), left axillary lymph nodes (Irish's node), and umbilicus (Sister Joseph nodule). Sclerotic bone metastases, carcinomatous meningitis, and metastasis to the ovary in women (Krukenberg's tumor) or rectal shelf in men (Blumer's shelf) may also occur.

C. **Associated paraneoplastic syndromes**
   1. Acanthosis nigricans (55% of cases that occur in malignancy are associated with gastric carcinoma)
   2. Polymyositis, dermatomyositis
   3. Circinate erythemas, pemphigoid
   4. Dementia, cerebellar ataxia
   5. Idiopathic venous thrombosis
   6. Ectopic Cushing's syndrome or carcinoid syndrome (rare)
   7. Leser-Trélat sign

III. Diagnosis

A. **Symptoms and signs.** Gastric cancer often progresses to an advanced stage before symptoms and signs develop. Symptoms of advanced disease include anorexia, early satiety, distaste for meat, weakness, and dysphagia. Abdominal pain is present in about 60% of patients, weight loss in 50%, nausea and vomiting in 40%, anemia in 40%, and a palpable abdominal mass in 30%. The abdominal pain is similar to ulcer pain, is gnawing in nature, and may respond initially to antacid treatment but remains unremitting. Hematemesis or melena occurs in 25% and, when present, is seen more often with gastric sarcomas.
B. **Diagnostic studies**
   1. **Preliminary studies** include CBC, LFTs, esophagogastroduodenoscopy (EGD) or upper GI barium studies, and chest radiographs.
   2. **CT of the abdomen** is useful for assessing the extent of disease. At laparotomy, however, half of patients are found to have more extensive disease than predicted by CT. Laparoscopy can identify patients with regionally advanced or disseminated disease who are not candidates for immediate potentially curative surgical intervention.
   3. **EUS** is up to six times more accurate in staging the primary gastric tumors than CT, but differentiation between benign and malignant changes in the wall is often difficult. EUS is useful in imaging the cardia, which may be difficult to evaluate by CT. Lymph node biopsy can also be obtained by EUS guidance.
   4. **Endoscopy.** The combination of flexible upper GI endoscopy with biopsy of visible lesions, exfoliative cytology, and brush biopsy is able to detect more than 95% of gastric cancers. Biopsy of a stomach lesion alone is accurate in only 80% of cases. Positive gastric cytology with no endoscopic or radiographic abnormalities indicates superficial spreading gastric cancer.
C. **Differential diagnosis and gastric polyps.** The differential diagnosis of gastric cancer includes peptic gastric polyps, ulcer, leiomyoma, leiomyoblastoma, glomus tumor, malignant lymphoma (and pseudolymphoma), granulocytic sarcoma, carcinoid tumors, lipoma, fibrous histiocytoma, and metastatic carcinoma. Gastric polyps rarely undergo malignant transformation (3% after 7 years), but many contain independent carcinoma.
   1. **Inflammatory gastric polyps** are not true neoplasms. They are usually located in the pyloroantrum and are associated with hypochlorhydria but not with carcinoma.
   2. **Hyperplastic gastric polyps** (Ménétrier's polyadenome polypeux) are the most common polyps (75%). Randomly distributed throughout the stomach, these polyps are usually small and multiple. Coexisting carcinoma is present in 8% of cases.
   3. **Adenomatous polyps** are usually located in the antrum of the stomach and are frequently single and large. Coexisting carcinoma is present in 40% to 60% of patients.
   4. **Villous adenomas** rarely occur in the stomach but are more often malignant.
   5. **Polyposis syndromes**
      a. **Familial gastric polyposis** presents with multiple gastric polyps but no skin or bone tumors. The gastric wall is usually invaded with atypical carcinoma.
      b. **Familial adenomatous polyposis** (FAP) is associated with gastric involvement in more than half of patients. The gastric polyps are adenomatous, hyperplastic, or of the fundic gland hyperplasia type. Gastric carcinoma and carcinoid tumor may occur.

IV. Staging and prognostic factors

A. **Staging system.** A TNM system has been developed for gastric cancer that accounts for degree of penetration into the stomach wall, the presence of lymph involvement (whether adjacent or distant), and distant metastases. Readers should consult an up-to-date staging manual because of frequent revisions of staging systems. The current TNM system does not take into account the location of the tumor within the stomach, the number of lymph nodes rather than their location relative to the stomach, the histologic type (Lauren's classification), the pattern of growth (linitis plastica), or whether all disease could be resected (and if so, the type of resection).
B. **Prognostic factors.** Previously, data using three grave prognostic signs (serosal involvement, nodal involvement, and tumor at the line of resection) have shown that if none of these signs is present, the 5-year survival rate is 60%, and if all are present, the 5-year survival rate is less than 5%.
   1. **Stage.** Multivariate analysis indicated that stage, invasion, and lymph node involvement are the most significant prognostic factors. The most important prognostic determinant appears to be the number of positive lymph nodes. Interestingly, patients with one to three lymph nodes involved with metastasis have as good a prognosis as those without nodal involvement.
   2. **Clinical classification.** Survival is better with superficial than with focal cancer and worst with infiltrative types of cancer.
   3. **JES classification.** Survival is better with type II (flat) than with type III (associated with ulcer) tumors and worst with type I (polypoid) tumors.
   4. **Grade.** Tumors with high histologic grade have a poor prognosis.
   5. **Flow cytometry.** The median disease-free survival is 18 months for patients with diploid tumors and 5 months for those with aneuploid tumors. Aneuploid tumors constitute 96% of gastroesophageal junction–cardia carcinomas and only 48% of body–antrum tumors. Women are more likely to have diploid tumors.
   6. **Nature and extent of resection.** Survival is better with curative resection (a resection with uninvolved margins, or R-2 resection) versus palliative resection, distal gastrectomy versus proximal gastrectomy, and subtotal gastrectomy versus total gastrectomy.

V. Screening and early detection
Early detection of gastric cancers is clearly improved with relentless investigation of persistent upper GI symptoms. In Japan, mobile screening stations equipped with video gastrocameras have resulted in early detection of gastric cancer. Gastric cancer, which was detected in 0.3% of those screened, was associated with a 95% 5-year survival rate (50% of the patients had involvement of mucosa and submucosa only). Despite such screening programs, gastric cancer remains the most common cause of cancer death in Japan. Screening of populations with routine risk factors for gastric cancer is not recommended, however, in the United States.

VI. Management

A. **Surgery**
  1. **Curative resection.** Subtotal gastrectomy with adequate margins of grossly uninvolved stomach (3 to 4 cm) and regional lymph node dissection is the treatment of choice and is generally considered the only potentially curative approach for patients with gastric cancer. Total gastrectomy is not superior to subtotal gastrectomy for achieving cures and should be used only when indicated by the local extent of the disease. More extensive lymphatic dissection, known as D-2 resections (e.g., of the celiac lymph nodes), omentectomy, and splenectomy are no longer advisable.
  2. **Palliative resections** are performed to rid patients of infected, bleeding, obstructed, necrotic, or ulcerated polypoid gastric lesions. For these purposes, a limited gastric resection may suffice. Palliative resections succeed in ameliorating symptoms about half the time.
  3. **Vitamin B_{12} deficiency** develops in all patients who undergo total gastrectomy within 6 years and in 20% of patients who undergo subtotal gastrectomy within 10 years unless parenteral B_{12} injections are administered.
B. **Chemotherapy**
  1. **Neoadjuvant chemotherapy.** Patients with potentially resectable disease treated in phase II studies with preoperative chemotherapy, RT, or both have shown a high response rate, and some have had pathologically negative resection specimens. There have not been any randomized trials published to help discern whether response translates into a resectability, time to progression, or survival advantage over no neoadjuvant therapy.
     a. **Systemic adjuvant chemotherapy.** Nearly all trials involving 5-FU in combination with other agents (doxorubicin, epirubicin, mitomycin, or cytarabine) as adjuvant therapy have failed to show any benefit. A recent meta-analysis of data from 14 trials published since 1980 on adjuvant chemotherapy after resection of gastric cancer versus surgery alone concluded that postoperative chemotherapy cannot be considered standard treatment. Chemotherapy plus radiation showed promise in one of two randomized trials, but more data need to be generated before this can be routinely considered. An intergroup trial in which 660 patients were randomized to no treatment versus chemotherapy and radiation completed accrual in 1998 and has not yet been analyzed.
     b. **Intraperitoneal adjuvant therapy.** Because the resection site is the most common place for recurrence of gastric cancer, intraperitoneal chemotherapy is being advocated in certain centers.
        1. **Perioperatively.** Intraperitoneal mitomycin (50 mg) given in one trial from Japan was associated with significantly higher patient survival than was noted in untreated patients. Side effects were mild and well tolerated.
        2. **Postoperatively.** Intraperitoneal cisplatin and 5-FU followed by systemic 5-FU or 5-FU and mitomycin is being evaluated. Side effects are mainly neutropenia and sclerosing encapsulating peritonitis (late toxicity).
  2. **Chemotherapy for advanced disease.** Single agents produce low response rates. Combination regimens produce higher response rates but are more toxic and more costly. Cisplatin has been increasingly used in new combinations that also yield higher response rates, but the incidence of important toxic events exceeds 10%. The reported response rates are about 20% for 5-FU alone and 10% to 50% for combination chemotherapy; the median survival times range from 5 to 11 months. After nearly two decades of using combination chemotherapy, including mitomycin, doxorubicin, epidoxorubicin, etoposide, methotrexate, nitrosoureas, irinotecan, or cisplatin, there is no regimen considered standard in the setting of advanced disease.
C. **RT**
  1. **Localized disease.** RT alone has not proved useful for treating gastric cancer. RT (4000 cGy in 4 weeks) in combination with 5-FU (15 mg/kg IV on the first 3 days of RT), however, appears to improve survival over RT alone in patients with localized but unresectable cancers. Intraoperative radiation (IORT) allows high doses of radiation to the tumor bed or residual disease while permitting the exclusion of mobile radiosensitive normal tissues from the area irradiated. Trials are limited to single institutional experiences; therefore, generalizing from such trials is difficult. Selected patients may benefit from IORT, particularly when combined with supplemental external-beam radiation and chemotherapy. Long-term survival has been reported in some patients treated in this fashion for residual disease after surgery.
  2. **Advanced disease.** Gastric adenocarcinoma is relatively radioresistant and requires high doses of radiation with attendant toxic effects to surrounding organs. RT may be useful for palliating pain, vomiting due to obstruction, gastric hemorrhage, and metastases to bone and brain.

Colorectal Cancer

I. Epidemiology and etiology

A. **Incidence.** Colorectal cancer is the second most common cause of cancer mortality after lung cancer in the United States and ranks third in frequency among primary sites of cancer in both men and women. Nearly 600,000 cases are diagnosed annually worldwide, accounting for 9% of human cancers. Peak incidence rates are observed in the United States, Australia, and New Zealand. The lowest incidence rates are noted in India and South America and among Arab Israelis. A 10-fold variability is noted from highest to lowest incidence rates.

Both the incidence and the mortality rates have declined since they peaked in 1985. Studies of migrant populations have discerned that the incidence of colorectal cancer reflects current geographic location and not the country of origin. This suggests that environmental influences outweigh genetic trends for populations in which the experiences of those people with inherited special risk are pooled with those of lesser risk. Rural dwellers have a lower incidence of colorectal cancer than do urbanites. In the United States, cancer of the colorectum is more common in the East than the West and in the North than the South.

The risk for colorectal cancer increases with age, but 3% of colorectal cancers occur in patients younger than 40 years of age. The incidence is 19 per 100,000 population for those younger than 65 years of age and 337 per 100,000 among those older than 65 years of age. In 1999, it is estimated that in the United States, 131,000 new cases of colorectal cancer will develop and an estimated 47,000 persons will die from the disease. In the United States, a person of average risk has a 5% lifetime risk for developing colorectal cancer.

B. **Etiology.** Multiple forces drive the transformation of colorectal mucosa to cancer. Inheritance and environmental factors, including diet, are both crucial, but the extent of their interdependence as causative variables remains unknown.
  1. **Polyps.** The main importance of polyps is the well-recognized potential of a subset to evolve into colorectal cancer. The evolution to cancer is a multistage process that proceeds through mucosal cell hyperplasia, adenoma formation, and growth and dysplasia, to malignant transformation and invasive cancer. Environmental carcinogens may result in the development of cancer regardless of a patient's genetic background, but patients with genetically susceptible mucosa inherit a predisposition to abnormal cellular proliferation. Oncogene activation and chromosomal deletion lead to adenoma formation, growth with increasing dysplasia, and invasive carcinoma.
     a. **Types of polyps.** Histologically, polyps are classified as neoplastic or nonneoplastic. Nonneoplastic polyps have no malignant potential and include hyperplastic polyps, mucous retention polyps, hamartomas (juvenile polyps), lymphoid aggregates, and inflammatory polyps. Neoplastic polyps (or adenomatous polyps) have malignant potential and are classified according to the World Health Organization system as tubular (microscopically characterized by networks of complex branching glands), tubulovillous (mixed histology), or villous (microscopically characterized by relatively short, straight glandular structures) adenomas depending on the presence and volume of villous tissue. Polyps larger than 1 cm in diameter, those with high-grade dysplasia, and those with predominantly villous histology are associated with higher risk for colorectal cancer. Colonoscopic polypectomy and subsequent surveillance can reduce the incidence of colon cancer by 90%, compared with that observed in unscreened controls.
     b. **Frequency of polyp types.** About 70% of polyps removed at colonoscopy are adenomatous, 75% to 85% of which are tubular (no or minimal villous tissue), 10% to 25% are tubulovillous (less than 75% villous tissue), and fewer than 5% are villous (more than 75% villous tissue).
     c. **Dysplasia** may be classified as mild, moderate, or severe. However, it is preferable to classify dysplasia into only two grades: low and high. About 6% of adenomatous polyps exhibit severe dysplasia, and 4% contain invasive carcinoma at the time of diagnosis.
     d. **The malignant potential of adenomas correlates** with increasing size, the presence and the degree of dysplasia in a villous component, and the patient's age. Small colorectal polyps (smaller than 1 cm) are not associated with increased occurrence of colorectal cancer; the incidence of cancer, however, is increased 2.5- to 4-fold if the polyp is large (larger than 1 cm) and 5- to 7-fold in patients who initially have multiple polyps. The study of the natural history of untreated polyps larger than 1 cm showed that the risk for progression to cancer is 2.5% at 5 years, 8% at 10 years, and 24% at 20 years. The time to malignant progression depends on the severity of dysplasia: 3.5 years for severe dysplasia and 11.5 years for mild atypia.
     e. **Management of polyps.** Because of the adenoma–cancer relationship and the evidence that resecting adenomas prevents cancer, newly detected polyps should be excised and additional polyps should be sought through colonoscopy. The sensitivity of colonoscopic examinations, particularly for detection of polyps less than 1 cm in diameter, exceeds that of barium enema. Additionally, with colonoscopy, therapeutic polypectomy can be accomplished during the diagnostic examination. The incidence of synchronous adenomas in patients with one known adenoma is 40% to 50%. The 1993 recommendations of the American College of Gastroenterology for the management of colorectal polyps are discussed by Bond and colleagues (see Suggested Reading).
     f. **Intestinal polyposis syndromes.** Table 9.2 summarizes familial polyposis syndromes and their histology distribution, malignant potential, and management (see section V.B.3 for discussion of the potential benefit of anti-inflammatory drugs).

Table 9.2 Polyp syndromes and colorectal cancer

2. **Diet.** Populations with high intake of fat, higher caloric intakes, and low intake of fiber (fruits, vegetables, and grains) tend to have increased risk for colorectal cancer in most but not all studies. Higher calcium intake, calcium supplementation, and regular aspirin use are associated with a lower risk for colorectal cancer in some studies. Increased intake of vitamins C and E and beta-carotene do not appear to decrease the risk for polyp formation. The higher incidence of rectal and sigmoid cancer in men may be related to their greater consumption of alcohol. Postmenopausal women who have taken estrogen replacement therapy appear to have a lower risk for colorectal cancer than those who have not.
3. **Inflammatory bowel disease**
   a. **Ulcerative colitis** is a clear risk factor for colon cancer. About 1% of colorectal cancer patients have a history of chronic ulcerative colitis. The risk for the development of cancer in these patients varies inversely with the age of onset of the colitis and directly with the extent of colonic involvement and duration of active disease. The cumulative risk is 3% at 15 years, 5% at 20 years, and 9% at 25 years.

   The recommended approach to the increased risk for colorectal cancer in ulcerative colitis has been annual colonoscopy to determine the need for total proctocolectomy in patients with extensive colitis of more than 8 years' duration. This strategy is based on the assumption that dysplastic lesions can be detected before invasive cancer has developed. An analysis of prospective studies concluded that immediate colectomy is essential for all patients diagnosed with dysplasia (high grade or low grade). Most important, the analysis demonstrated that the diagnosis of dysplasia does not preclude the presence of invasive cancer. The diagnosis of dysplasia has inherent problems with sampling of specimens and with variation in agreement among observers (as low as 60%, even with experts in the field).

   b. **Crohn's disease.** Patients with colorectal Crohn's disease are at increased risk for colorectal cancer, but the risk is less than that of those with ulcerative colitis. The risk is increased about 1.5 to 2 times.
4. **Genetic factors**
   a. **Family history** may signify either a genetic abnormality or shared environmental factors or a combination of these factors. About 15% of all colorectal cancers occur in patients with a history of colorectal cancer in first-degree relatives.
   b. **Gene changes.** Specific inherited (adenomatous polyposis coli [*APC*] gene) and acquired genetic abnormalities (*ras* gene point mutation; *c-myc* gene amplification; allele deletion at specific sites of chromosomes 5, 17, and 18) appear to be capable of mediating steps in the progression from normal to malignant colonic mucosa. About half of all carcinomas and large adenomas have associated point mutations, most often in the *K-ras* gene. Such mutations are rarely present in adenomas smaller than 1 cm. Allelic deletions of 17p– are demonstrated in three-quarters of all colorectal carcinomas, and deletions of 5q– are demonstrated in more than one-third of colonic carcinoma and large adenomas.

   Two major syndromes and several variants of these syndromes of inherited predisposition to colorectal cancer have been characterized. The two syndromes, which predispose to colorectal cancer by different mechanisms, are FAP and hereditary nonpolyposis colorectal cancer syndrome (HNPCC).

   1. **FAP.** The genes responsible for FAP, *APC* genes, are located in the 5q21 chromosome region. Inheritance of defective *APC* tumor-suppressor gene leads to a virtually 100% likelihood of developing colon cancer by 55 years of age. Screening for polyps should begin during early teenage years. The FAP syndrome is associated with the development of gastric and ampullary polyps, desmoid tumors, osteomas, abnormal dentition, and abnormal retinal pigmentation. Variants of FAP include Gardner's and Turcot's syndromes.
   2. **HNPCC.** The autosomal-dominant pattern of HNPCC includes Lynch's syndromes I and II, both of which are associated with an increased incidence of predominantly right-sided colon cancer. This genetic abnormality in the mismatch repair mechanism leads to defective excision of abnormal repeating sequences of DNA known as *microsatellites* ("microsatellite instability"). Retention of these sequences leads to expression of a mutator phenotype characterized by frequent DNA replication errors (*RER+* phenotype), which predispose affected people to a multitude of primary malignancies, including endometrial, gastric, ovarian, bladder, and ureteral cancers and biliary tract cancers. Specific mutated genes on chromosomes 2 and 3, known as *hMSH2, hMLH1, hPMS1,* and *hPMS2,* have been linked to HNPCC.

   Patients with HNPCC have a tendency to develop colon cancer at an early age, and screening should begin by 20 years of age for relatives of HNPCC patients. The median age of HNPCC patients with colon cancer at diagnosis was 44 years, versus 68 years for control patients in one study. The prognosis for HNPCC patients appears to be better than for those patients with sporadic colon cancer; the death rate from colon cancer for HNPCC patients is two thirds that for sporadic cases over 10 years.

   c. **Tumor location.** Proximal tumors appear to represent a more genetically stable form of the disease and may arise through the same mechanisms that underlie inherited nonpolyposis colon cancer. Distal tumors show evidence of greater genetic instability and may develop through the same mechanisms that underlie polyposis-associated colorectal cancer.
5. **Smoking.** Men and women smoking during the previous 20 years have three times the relative risk for small adenomas (less than 1 cm) but not for larger ones. Smoking for more than 20 years was associated with a 2.5 relative risk for larger adenomas.
6. **Other factors.** Personal or family history of cancer in other anatomic sites (such as breast, endometrium, and ovary) is associated with increased risk for colorectal cancer. Exposure to asbestos (e.g., in brake mechanics) increases the incidence of colorectal cancer to 1.5 to 2 times that of the average population. Other than this association, there appears to be little relationship between occupational exposures and the incidence of colon cancer. Data indicate that HPV infection of the columnar mucosa of the colon may cause benign and malignant neoplasia.

II. Pathology and natural history

A. **Histology.** Ninety-eight percent of colorectal cancers above the anal verge are adenocarcinomas. Cancers of the anal verge are most often squamous cell or basaloid carcinomas. Carcinoid tumors cluster around the rectum and cecum and spare the rest of the colon.
B. **Location.** Two thirds of colorectal cancers occur in the left colon and one third in the right colon. About 20% of colorectal cancers develop in the rectum. Rectal tumors are detected by digital rectal examination in 75% of cases. Nearly 3% of colorectal adenocarcinomas are multicentric, and 2% of patients develop a second primary tumor in the colon.
C. **Clinical presentation.** The common clinical complaints of patients with colorectal cancer relate to the size and location of the tumor. Right-sided colonic lesions most often result in dull and ill-defined abdominal pain, bleeding, and symptomatic anemia causing weakness, fatigue, and weight loss, rather than in colonic obstruction. Left-sided lesions lead commonly to changes in bowel habits, bleeding, gas pain, decrease in stool caliber, constipation, increased use of laxatives, and colonic obstruction.
D. **Clinical course.** Metastases to the regional lymph nodes are found in 40% to 70% of cases at the time of resection. Venous invasion is found in up to 60% of cases. Metastases occur most frequently in the liver, peritoneal cavity, and lung, followed by the adrenals, ovaries, and bone. Metastases to the brain are rare. Rectal cancers are three times more likely to reoccur locally than are proximal colonic tumors, in part because the anatomic confines of the rectum preclude wide resection margins and in part because the rectum lacks an outer serosal layer through most of its course. Because of the venous and lymphatic drainage of the rectum into the inferior vena cava (as opposed to the venous drainage of the colon into the portal vein and variable lymphatic drainage), rectal cancer often reoccurs first in the lungs. Colon cancer more frequently reoccurs first in the liver.

III. Diagnosis

A. **Diagnostic studies.** About 85% of patients diagnosed with colorectal cancer can undergo surgical resection. Patients with incurable cancer may benefit from palliative resection to prevent obstruction, perforation, bleeding, and invasion to adjacent structures. After the clinical diagnosis of colorectal cancer is made, several diagnostic and evaluation steps should be taken.
1. **Biopsy confirmation** of malignancy is important. If an obstructing lesion cannot undergo biopsy, brush cytology may be feasible.
2. **General evaluation** includes a complete physical examination with digital rectal examination, CBC, LFTs, and chest radiograph.
3. **Carcinoembryonic antigen (CEA) screening** is favored by some physicians as a means of identifying early recurrence despite the limited specificity and sensitivity of this test. A preoperative CEA can be useful as a prognostic factor and to determine if the primary tumor is associated with CEA elevation. Preoperative CEA elevation implies that CEA may aid in early identification of of metastases because metastatic tumor cells are more likely to result in CEA

elevation in this circumstance.

4. **CT or magnetic resonance imaging** (MRI) with contrast of the abdomen and pelvis may identify liver or intraperitoneal metastases.
5. **Endoscopy or barium enema** is indicated to assess the entire colonic mucosa because about 3% of patients have synchronous colorectal cancers and a larger percentile have additional premalignant polyps.
6. **EUS** significantly improves the preoperative assessment of the depth of invasion of large bowel tumors, especially rectal tumors. The accuracy rate is 95% for EUS, 70% for CT, and 60% for digital rectal examination. In rectal cancer, the combination of EUS to assess tumor extent and digital rectal examination to determine mobility should enable both precise planning of surgical treatment and definition of those patients who may benefit from preoperative chemoradiation. Transrectal biopsy of perirectal lymph nodes can often be accomplished under EUS direction.

B. **Biologic markers**
1. **CEA** is the best known marker for monitoring colorectal cancer disease status and for detection of early recurrence and liver metastases. CEA is too insensitive and nonspecific to be valuable for screening of colorectal cancer (see Chapter 1, section III.B.3.b). Elevation of serum CEA levels, however, does correlate with a number of parameters. Higher CEA levels are associated with histologic grade 1 or 2 tumors, more advanced stages of the disease, and the presence of visceral metastases. Although serum CEA concentration is an independent prognostic factor, its putative value lies in serial monitoring after surgical resection.
2. **New markers,** such as CA 19-9, may be of value in monitoring recurrences and complement CEA. Monoclonal antibodies (anti-CEA, anti– TAG-72) may also be useful in immunohistologic chemical staining of tissues. The presence of an abnormal number of chromosomes in the tumor cells (aneuploidy) confers a worse prognosis than is observed in patients with diploid tumors. Light microscopic features and stage, however, remain the most reliable prognostic measures.

IV. Staging and prognostic factors

A. **Staging system.** Staging using the TNM system has been recommended over the Astler-Coller modification of the Dukes system. Readers should consult an up-to-date staging manual because of frequent revisions of staging systems. The current staging system is delineated here.

Stage Description

Tis   Carcinoma *in situ:* intraepithelial or invasion of the lamina propria
T1   Invasion of the submucosa
T2   Invasion of the muscularis propria
T3   Invasion through the muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissues
T4   Perforation of visceral peritoneum or direct invasion into adjacent organs or tissues
N0   No regional lymph node metastases
N1   Metastases in one to three pericolic or perirectal lymph nodes
N2   Metastases in 4 or more lymph nodes
N3   Metastases in lymph nodes along a named vascular trunk node, tumor invasion of adjacent organs

M0   No distant metastasis
M1   Distant metastatic disease

Stage	TNM grouping	5-year Survival (%)	Dukes' grouping
0	Tis N0 M0	100	
I	T1 N0 M0	95	A
	T2 N0 M0	90	A
II	T3 N0 M0	80	B
	T4 N0 M0	75	B
III	Any T N1 M0	72	C
	Any T N2 M0	60	C
	Any T N3 M0	40	C
IV	Any T Any N M1	5	D

B. **Prognostic factors**
1. **Stage** is the most important prognostic factor (see section IV.A)
2. **Histologic grade** significantly influences survival regardless of stage. Patients with well-differentiated carcinomas (grades 1 and 2) have a better 5-year survival than those with poorly differentiated carcinomas (grades 3 and 4).
3. **The anatomic location of the tumor** appears to be an independent prognostic factor. For equal stages, patients with rectal lesions have a worse prognosis than than those with colon lesions, and transverse and descending colon lesions result in poorer outcomes than ascending or rectosigmoid lesions.
4. **Clinical presentation.** Patients who present with bowel obstruction or perforation have a worse prognosis than patients who present with neither of these problems.
5. **Chromosome 18.** The prognosis of patients with an allele loss of chromosome 18q is significantly worse than that of patients with no allelic loss. The survival of patients with stage B disease is the same as that for stage A when there is no allelic loss and the same as for stage C when there is allelic loss. Other abnormalities that have been identified and that are of potential value for determining prognosis are located on chromosomes 1, 5, 8, 17, and 22. Identification of these genes or their products is possible using gel electrophoresis or immunohistochemical probes. These observations may ultimately prove to be helpful in selecting patients with stage II disease for adjuvant therapy or stage III patients with better than average prognoses who can avoid the potential toxicity and expense of adjuvant therapy.

V. Screening and prevention

A. **Screening.** The National Cancer Institute (NCI), the American College of Surgeons, the American College of Physicians, and the American Cancer Society (ACS) recommend that asymptomatic patients who are 50 years of age and older have a sigmoidoscopic examination (preferably flexible) every 3 to 5 years. An annual digital rectal and fecal occult blood (FOB) test examination is recommended by the ACS and NCI for people 50 years of age and older, but the arguments for this practice are not strongly substantiated. Screening colonoscopy of patients with family history of colorectal cancer in first-degree relatives but no clear evidence of FAP or HNPCC should begin at 40 years of age.

The value of testing FOB for screening remains controversial. Three large randomized trials in which patients were tested for FOB or followed according to the usual patterns of care have been reported. In the largest trial and the only one conducted in the United States, annual testing of a rehydrated fecal smear was associated with a 33.4% decrease in risk for death from colorectal cancer in 46,551 adults older than 50 years of age. Better markers for colorectal cancer are being sought because of the high false-positive and false-negative rates associated with FOB.

B. **Prevention.** The management of patients with ulcerative colitis is discussed in section I.B.3.a.
1. **Periodic sigmoidoscopy** identifies and removes precancerous lesions (polyps) and reduces the incidence of colorectal cancer in patients who undergo colonoscopic polypectomy. The presence of even small rectosigmoid polyps is associated with polyps beyond the reach of the sigmoidoscope, and their presence should lead to full colonoscopy.
2. **Diets** that are high in fiber and low in fat or contain calcium supplements or both may deter polyp progression to cancer.
3. **Nonsteroidal anti-inflammatory drugs** (NSAIDs). In a randomized, double-blind, placebo-controlled study of patients with familial polyposis, the NSAID sulindac at a dose of 150 mg b.i.d. significantly decreased the mean number and mean diameter of polyps as compared with those in patients given placebo. The size and number of the polyps, however, increased 3 months after the treatment was stopped but remained significantly lower than at baseline. Data further suggest that the use of NSAIDs (aspirin or sulindac) reduces the formation, number, and size of colorectal polyps and reduces the incidence of colorectal cancer, whether familial or nonfamilial. These protective effects require continuous exposure to at least 650 mg of aspirin per day for years.

VI. Management

A. **Surgery** is the only universally accepted potentially curative treatment for colorectal cancer. Curative surgery should excise the tumor with wide margins and

maximize regional lymphadenectomy while preserving function when possible. For lesions above the rectum, resection of the tumor with a minimum 5-cm margin of grossly negative colon is considered adequate, although the ligation of vascular trunks required to perform an adequate lymphadenectomy may necessitate larger bowel resections. Laparoscopic colectomy approaches have been developed and are being compared with open surgical techniques in a randomized trial. Subtotal colectomy and ileoproctostomy may be advisable for patients with potentially curable colon cancer and with adenomas scattered in the colon or for patients with a personal history of prior colorectal cancer or a family history of colorectal cancer in first-degree relatives.

1. **Arterial supply.** Excision of a tumor in the right colon should include the right branch of the middle colic artery as well as the entire ileocolic and right colic artery. Excision of a tumor at the hepatic or splenic flexure should include the entire distribution of the middle colic artery.
2. **Avoidance of permanent colostomy** in middle and low rectal cancers has been encouraged by the emergence of new surgical stapling techniques.
3. **Rectal tumors** may be treatable by primary resection and more distal anastomosis, usually without even a temporary (anastomosis protective) colostomy, if the lower edge is above 5 cm from the anal verge. Treatment options for rectal tumors include the following:
   a. **Middle and upper rectum** (6 to 15 cm): anterior resection of rectum
   b. **Lower rectum** (0 to 5 cm): coloanal anastomosis, with or without a pouch, transanal excision, transsphincteric and parasacral approaches, diathermy, primary radiation therapy, or abdominoperineal (AP) resection
4. **Obstructing tumors** in the right colon are usually managed by primary resection and primary anastomosis. Obstructing tumors in the left colon may be managed with initial decompression (proximal colostomy) followed by resection of the tumor and deferred closure of the colostomy. Recent trends, however, favor extending resection and primary anastomosis to include obstructing tumors in the transverse, descending, and even sigmoid colon.
5. **Perforated colon cancer** requires initial excision of the primary tumor and a proximal colostomy, followed later by reanastomosis and closure of the colostomy.

B. **Adjuvant therapy**
1. **Adjuvant chemotherapy for stage III colon cancer** (lymph node involvement) with 5-FU plus levamisole or 5-FU plus leucovorin has reduced the incidence of recurrence by 41% ($p < 0.001$) in a number of large prospective, randomized trials. One year of therapy with 5-FU plus levamisole improves the 5-year survival rate from 50% to 62% and reduces cancer-related deaths by 33%. More recent trials, however, have shown that 6 months of therapy with 5-FU plus leucovorin is at least as effective and requires half the time to administer. As a consequence, the standard treatment for stage III colon cancer is now 5-FU plus leucovorin.
   a. **5-FU and leucovorin** are begun simultaneously 3 to 5 weeks after surgery. Two regimens commonly employed in the United States are as follows:
      1. **Dosage, Mayo Clinic regimen:** leucovorin, 20 mg/m^2 by 30-minute IV infusion, followed by 5-FU, 425 mg/m^2 by rapid IV injection, daily for 5 consecutive days for two 4-week cycles and then every 5 weeks thereafter
      2. **Dosage, Roswell Park Memorial Institute (RPMI) regimen:** leucovorin, 500 mg/m^2 by 30-minute IV infusion, followed by 5-FU 500 mg/m^2 by rapid IV injection weekly for 6 of every 8 weeks
      3. **The side effects of the Mayo and RPMI regimens** are similar. Toxicity of grade III or more is based on the NCI common toxicity criteria (NCI-CTC; see Appendix B-2). The principal difference in toxicity between the two regimens relates to rates of severe stomatitis and diarrhea. The Mayo regimen is associated with more grade III stomatitis and the RPMI regimen, with a higher rate of grade III diarrhea. Hematologic toxicity seen with both regimens is mainly neutropenia. Grade III or greater neutropenia afflicts about one third of patients at some time during the course of therapy. Nausea and vomiting are generally not severe. Dermatologic side effects are generally limited to erythema and desquamation of sun-damaged skin. Less than 1% of the U.S. population has a deficiency of dihydropyrimidine dehydrogenase (DPD), which is the rate-limiting enzyme in the breakdown of 5-FU. Such patients have severe toxicity and often die after exposure to standard doses because of profound and prolonged neutropenia and mucositis. Cerebellar toxicity occurs relatively commonly in DPD-deficient patients.
   b. **Other regimens** that have been investigated as adjuvant therapy include MOF (methyl-CCNU + vincristine (Oncovin) + 5-FU), 5-FU plus leucovorin + interferon, 5-FU plus levamisole, 5-FU plus leucovorin plus levamisole, portal vein infusion of 5-FU, and infusional 5-FU with levamisole. None of these regimens has been judged superior to the Mayo or RPMI regimens described previously. A regimen using five monthly infusions of a monoclonal antibody to a protein present on the surface of many colorectal cancers led to a survival advantage of similar magnitude to that seen with 5-FU plus leucovorin chemotherapy in the hands of an international group of European investigators. Confirmatory trials are underway in the United States.
2. **Adjuvant chemotherapy for stage II colon cancer** (no lymph node involvement) is controversial. Investigators from the National Surgical Adjuvant Breast Project (NSABP) advocate for adjuvant therapy in this setting because it has produced a small but consistent benefit in patients with stage II disease in serial NSABP trials. Conversely, a meta-analysis of five trials involving about 1000 patients showed a statistically insignificant difference in 5-year survival rates of 82% versus 80% for treated versus untreated patients with stage II disease. Intense efforts have focused on differentiating stage II patients with higher risk for recurrence from those with lower risk through examination of tumor ploidy (number of chromosomes), p53 status, levels of thymidylate synthesis, presence or absence of individual chromosomal mutations, and other parameters. Although none of these is accepted as a standard prognostic determinant, patients with aneuploid tumors had a 5-year survival rate of 54%, compared with patients with diploid tumors, who had a 74% 5-year survival in one trial.
3. **Adjuvant therapy for rectal cancer.** Because of the anatomic confines of the pelvic bones and sacrum, surgeons often cannot achieve wide, tumor-free margins during the resection of rectal cancer. Almost half of recurrences in rectal cancer are in the pelvis.
   a. **Variations** in the use of RT alone or combined with chemotherapy and in surgical technique have been investigated in attempts to improve local control rates. Numerous randomized, controlled studies of both preoperative and postoperative RT alone have demonstrated no improvement in survival; at best, there has been a small decrease in the rate of local recurrence. A number of European surgeons have advocated surgical excision of the rectal mesentery (*total mesorectal excision* [TME]). The advocates of TME claim a low local recurrence rate but have also noted that rectal stump devascularization results in a higher rate of postoperative anastomotic site leakage.
   b. **The most effective adjuvant approach,** which has become standard practice in the United States, employs combined 5-FU chemotherapy and RT. This approach has significantly reduced the rates of local recurrence, distant metastasis, and cancer-related deaths among patients with stage II and III rectal cancer. The addition to RT of 5-FU (given either by rapid injection or by continuous intravenous infusion throughout the period of radiation) apparently was crucial to the marked reduction in the local recurrence of rectal cancer. **The current standard therapy** for stage II and III rectal cancer is 5-FU bolus, 500 mg/m^2/day for 5 days each month for 2 months both before and after RT. During RT (5040 cGy), 5-FU is given as a radiosensitizer at a dose of 225 mg/m^2/day by continuous IV infusion. The addition of a nitrosourea, levamisole, or leucovorin to the regimen did not improve the results.

C. **Follow-up.** About 85% of all recurrences that are destined to occur in colorectal cancer are evident within 3 years after surgical resection. High preoperative CEA levels usually revert to normal within 6 weeks after complete resection.
1. **Clinical evaluation.** After curative surgical resection, patients with stage II and III colon or rectal cancer are commonly seen more frequently during the first two postoperative years and less frequently thereafter. After 5 years, follow-up is mainly targeted at detection of new primary tumors. The primary goal of follow-up is to detect metastatic disease early. Some patients with colorectal cancer develop a single or a few metastatic sites (known as oligometastases) in the liver, in the lungs, or at the anastomotic site from which the primary bowel cancer was removed that can be resected with curative intent (see section E).
2. **Chest radiographs** appear to be as good as CT scans for detecting recurrence. They are advocated annually or semiannually by those who believe in follow-up testing.
3. **Colonoscopy.** Patients who presented with obstructing colon lesions that preclude preoperative imaging of the colon should have colonoscopy 3 to 6 weeks after surgery to ensure the absence of a concurrent neoplastic lesion in the remaining colon. The purpose of endoscopy done thereafter is to detect a metachronous tumor, suture line recurrence, or colorectal adenoma. In the absence of obstruction, colonoscopy is performed annually for 1 to 3 years after surgery and, if negative, at 2- to 3-year intervals thereafter.
4. **Rising CEA levels** call for further studies to identify the site of recurrence and are most often helpful in identifying hepatic recurrences. An elevated CEA calls for further testing using CT of the abdomen, pelvis, and chest as well as other studies as dictated by symptoms. If pelvic recurrence of a rectal cancer is suspected, MRI may be more helpful than CT. The use of hepatic imaging by CT, ultrasound, or MRI at regular intervals is advocated by some oncologists.

D. **CEA-based "second-look" laparotomies** have not been evaluated in prospective, randomized trials. Retrospective studies of patients undergoing laparotomy for asymptomatic elevations of CEA levels have shown that 60% of cases were judged to be potentially resectable based on preoperative imaging. About 55% of those cases were actually resectable with curative intent, and about 60% of the latter developed recurrence. Only about 10% of patients undergoing laparotomy as a result of preoperative imaging suggesting resectable recurrence remained alive and disease free. This small percentage of success must be viewed against the 10% of patients in whom tumor could not be identified at the CEA-directed second-look operation.

E. **Management of isolated recurrence.** Early detection and surgical resection of isolated intrahepatic or pulmonary recurrence may be curative or result in improved survival. Those patients most likely to do well have a single lesion in a single site and a disease-free interval of 3 or more years between the primary diagnosis and evidence of metastatic disease. Resection of isolated hepatic metastasis that involves one lobe of the liver may result in a 30% 5-year survival rate. Resection of isolated pulmonary metastasis may result in 5- and 10-year survival rates of 40% and 20%, respectively.

F. **Management of advanced colorectal cancer**
1. **Chemotherapy.** The most commonly used chemotherapeutic agents are 5-FU or floxuridine (FUDR), alone or in combination with leucovorin, and irinotecan (CPT-11).
   a. **Biochemical modulation of 5-FU with leucovorin.** The combination of 5-FU and leucovorin increases the activity as well as the toxicity of 5-FU, results in significant improvement in regression rate, and according to some studies, culminates in improved survival. The partial response rate is about 35%. The dose-limiting toxicities are diarrhea, mucositis, and hematosuppression. Regimens being used with essentially the same response rate involve low-dose or high-dose leucovorin given weekly or for 5 days every 4 to 5 weeks.

b. **Continuous intravenous infusion of 5-FU** changes the toxicity profile from hematologic to predominantly mucositis and dermatologic (hand–foot syndrome) when compared with bolus administration. Three randomized trials, however, have shown that continuous infusion of 5-FU using an ambulatory infusion pump, as compared with rapid injection, does not result in improved survival. In Europe, it is common practice to administer 5-FU as a 24- to 48-hour short-term infusion. Such regimens have been shown to improve the response rate but have not convincingly extended median survival times as compared with those achieved with bolus therapy.

c. **Hepatic arterial infusion** takes advantage of the dual nature of hepatic blood supply. Metastases in the liver derive their blood supply predominantly from the hepatic artery, whereas hepatocytes derive blood principally from the hepatic vein. The installation of FUDR into the hepatic artery has been advocated and appears to improve the response rate over 5-FU administered systemically. Problems with this approach include variable anatomy, which makes placement of a single catheter impossible; catheter migration; biliary sclerosis; and gastric ulceration. Progression of extrahepatic disease is a common pattern of failure with this modality. Randomized trials of systemic versus intrahepatic therapy are in progress.

d. **Second-line therapy with CPT-11** has been shown to improve survival and quality of life. In patients with recurrent disease refractory to at least one 5-FU regimen, the survival at 1 year of patients treated with supportive care alone or with 5-FU was about 15%, compared with 36% when patients were treated with CPT-11. In the United States, a commonly used regimen for CPT-11 is 125 mg/m^2 weekly for 4 of every 6 weeks. In Europe, the most common regimen for CPT-11 is 350 mg/m^2 every 3 weeks.

e. **Oxaliplatin** is a diaminocyclohexane-containing platinum agent with broad activity in cisplatin-resistant human tumor xenografts. It is in use in Europe and in clinical trials in the United States. It is generally administered in combination with 5-FU and leucovorin.

2. **RT** may be used as the primary and only treatment modality for small, mobile rectal tumors or in combination with chemotherapy after resection of rectal tumors (see earlier). RT in palliative doses relieves pain, obstruction, bleeding, and tenesmus in about 80% of cases. In selected cases with locally advanced disease, the use of IORT may provide an advantage. No randomized trials of external-beam versus IORT or IORT plus external-beam therapy have been reported, however.

Anal Cancer

I. Epidemiology and etiology

A. **Incidence.** Anal cancers constitute 1% to 2% of large bowel cancers, and 2500 new cases are diagnosed annually in the United States. Anal canal cancer most commonly develops in patients 50 to 60 years of age and is more frequent in women than in men (female-to-male ratio, 2:1). Cancer of the anal margin is more frequent in men. During the 1990s, however, the incidence of anal canal cancer in men younger than 35 years of age increased, and the gender ratio is reversed in this age group. Anal cancer more frequently afflicts urban than rural populations.

B. **Etiology.** In most patients with carcinoma of the anus, HPV appears to play a causal role.

1. **Infectious agents.** HPV, particularly types 16 and 18, is a prime suspect as a causative agent for anal cancer (see Chapter 36, <u>section IV.D.2</u>). More than 70% of tumor tissues show HPV DNA by polymerase chain reaction techniques. An HPV-produced protein, E6, inactivates the tumor-suppressor gene *p53*. The presence of genital warts increases the relative risk by a factor of 30.

   Although human immunodeficiency virus (HIV) has been suggested as a causative agent, anal tumors are extremely rare in intravenous drug abusers. The relative risk for homosexuals with acquired immunodeficiency syndrome (AIDS) is 84 and for heterosexuals with AIDS is 38. Other associated infections include herpes simplex virus type 2, *Chlamydia trachomatis* infection in women, and gonorrhea in men.

2. **Diseases associated with anal cancer** include AIDS, prior irradiation, anal fistulas, fissures, chronic local inflammation, hemorrhoids, Crohn's disease, lymphogranuloma venereum, condylomata acuminata, carcinoma of cervix, and carcinoma of the vulva. The relative risk for anal cancer development after a diagnosis of AIDS is 63. Sexual activity, particularly with multiple partners, is associated with an increased risk for anal canal cancer.

3. **Immune suppression.** Kidney transplant recipients have a 100-fold increase in anogenital tumors.

4. **Cigarette smoking** is associated with an eight-fold increase in the risk for anal cancer.

5. **Anal-receptive intercourse in men** but not in women is strongly associated with anal cancer at a risk ratio of 33. Studies have shown that the incidence of anal cancer (squamous and transitional cell carcinomas) is six times greater in single men than in married men. Single women are not at an increased risk.

II. Pathology and natural history

A. **Anatomy.** The anal canal is a tubular structure 3 to 4 cm in length. The junction between the anal canal and perineal skin is known as the anal verge (Hilton's line). The pectinate (or dentate) line is located at the center of the anal canal. The lining of the anal canal is composed of columnar epithelium in its upper portion and keratinized and nonkeratinized squamous epithelium in its lower portion. Intermediate epithelium (also known as *transitional* or *cloacogenic* epithelium, which resembles bladder epithelium) lines a middle zone (0.5 to 1 cm in length) that corresponds to the pectinate line. Anal tumors appear to originate near the mucocutaneous junction and grow either upward into the rectum and surrounding tissue or downward into the perineal tissue.

B. **Lymphatics.** Some of the upper lymphatics of the anus communicate with those of the rectal ampulla that lead to the sacral, upper mesocolic, and para-aortic lymph nodes. The lower lymphatics communicate with those of the perineum that lead to the superficial inguinal lymph nodes. Of patients undergoing AP resection, 25% to 35% manifest pelvic lymph node metastases.

C. **Histology.** Squamous cell carcinoma accounts for 63% of cases; transitional cell (cloacogenic) carcinoma, 23%; and mucinous adenocarcinoma, 7% (often with multiple fistulous tracts). Basal cell carcinoma (2%) is curable either by local excision or irradiation. Paget's disease (2%) is a malignant neoplasm of the intraepidermal portion of the apocrine glands. Malignant melanoma (2%) usually begins at the pectinate line and progresses as single or multiple polypoid masses; the prognosis is poor and depends on tumor size and depth of invasion. Other forms include small cell carcinoma (rare but extremely aggressive), verrucous carcinoma (a polypoid neoplasm closely related to giant condyloma acuminata), Bowen's disease, embryonal rhabdomyosarcoma (infants and children), and malignant lymphoma (in patients with AIDS).

III. Diagnosis

A. **Symptoms.** Bleeding occurs in 50% of patients, pain in 40%, sensation of a mass in 25%, and pruritus in 15%. About 25% of patients do not have symptoms.

B. **Physical examination** should include digital anorectal examination, anoscopy, proctoscopy, and palpation of inguinal lymph nodes. Anorectal examination may have to be performed under sedation or general anesthesia in patients with severe pain and anal spasm.

C. **Biopsy.** An incisional biopsy is necessary and preferable to confirm the diagnosis. Excisional biopsy should be avoided. Suspicious inguinal lymph nodes should undergo biopsy to differentiate inflammatory from metastatic disease. Needle aspiration of these nodes may establish the diagnosis; if aspiration is negative, surgical biopsy should be performed.

D. **Staging evaluation** should include physical examination, chest radiograph, and LFTs. Pelvic CT and EUS of the anal canal may be useful. HIV testing is appropriate when warranted by individual patient risk factors.

IV. Staging and prognostic factors

A. **Staging system.** The TNM staging system may be used. Readers should consult an up-to-date staging manual because of frequent revisions of staging systems. Anal margin tumors are staged as for skin cancer. The T stage of anal canal tumors is determined by size and by invasion into adjacent organs, as follows:

TX Primary tumor cannot be assessed
Tis Carcinoma *in situ*
T1 Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but 5 cm or smaller in greatest dimension
T3 Tumor larger than 5 cm in greatest dimension
T4 Tumor of any size that invades adjacent organ or organs (e.g., vagina, urethra, bladder [involvement of sphincter muscle alone is not classified as T4])

B. **Prognostic factors**

1. **TNM stage.** Patients with T1 cancer (lesions smaller than 2 cm in diameter) have a significantly better prognosis than those with larger lesions. Five-year survival rates are more than 80% for patients with T1 and T2 cancers and less than 20% for those with T3 and T4 cancers. The survival is poor even with aggressive therapy for lesions larger than 6 to 10 cm in diameter. In a multivariate analysis, T stage was the only significant independent prognostic factor for

anal cancers. Metastasis to lymph nodes also results in a poor outcome. Anal canal cancers tend to remain regionally localized, with distant metastases noted in less than 10% of cases.

2. **Other factors**
   a. **Histology.** The histologic type (i.e., cloacogenic versus epidermoid) has not been found to be prognostically relevant. Keratinizing carcinoma is associated with a better outcome than nonkeratinizing cancers. Patients with mucoepidermoid carcinoma and small cell anaplastic carcinoma have a worse prognosis.
   b. **Symptoms.** Patients without symptoms do better than those with symptoms. Symptoms are usually directly related to the size of the tumor.
   c. **Tumor grade.** Patients with low-grade tumors have a better 5-year survival rate than patients with high-grade tumors (75% versus 25%, respectively). DNA ploidy may or may not have prognostic significance.

V. Prevention and early detection Early detection depends on the patient's and physician's awareness of the disease, the presence of risk factors, and the histologic examination of all surgical specimens, even those removed from minor anorectal surgery. Yearly anoscopy may be indicated in high-risk patients. Anal examination should be performed routinely in patients with cervical and vulvar cancer.

VI. Management. Small tumors of the anal verge or the anal canal (less than 2 cm) can be cured in 80% of cases by simple excision with 1-cm margins, and cure by repeat local excision may be possible after local recurrence. Combined chemotherapy and RT are the primary therapeutic modalities for more advanced anal verge or anal canal carcinoma. AP resection is now used as salvage treatment for chemoradiation-resistant disease (i.e., patients who fail to respond or who relapse after a complete response) and for patients who have fecal incontinence at presentation. Considering the rarity of anal canal cancer, randomized trials have led to considerable advances, shifting the standard of therapy from surgery, in which colostomy was routinely necessary as a first approach, to combined-modality chemoradiotherapy, leaving surgery as a last resort.

A. **Combined chemoradiation therapy** is the primary treatment of choice for anal carcinoma. This combination resulted in higher rates of both local control and survival (82%) and preserved anal function when compared with surgery. The administration of high-dose RT reduced the incidence of persistent carcinoma and eliminated the need for surgical lymphadenectomy. The radiation dose, the number of chemotherapy cycles required to improve the local control rate, and the role (if any) of invasive restaging after completion of therapy remain controversial.

1. **Primary therapy.** External-beam RT appears to be superior to interstitial implants. RT doses of greater than 5000 cGy do not appear to be necessary. Using mitomycin C plus 5-FU with RT is superior to using 5-FU alone with RT at 4 years of median follow-up with respect to colostomy-free survival (71% versus 59%), locoregional control (82% versus 64%), and disease-free survival (73% versus 51%). The combination of these two drugs when administered concurrently with RT is superior to RT alone. RT regimens vary among institutions; 5-FU is given by continuous intravenous infusion in each case. Two useful regimens are as follows:
   a. **Radiation Therapy Oncology Group (RTOG)**

   Mitomycin C: 10 mg/m^2 IV bolus (day 2)
   5-FU: 1000 mg/m^2/24 hours by continuous IV infusion (days 2 to 4 and days 28 to 32)
   RT: 170 cGy/day between days 1 and 28
   Total RT dose: 4500 to 5000 cGy

   b. **National Tumor Institute (Milan)**

   Mitomycin C: 15 mg/m^2 IV bolus (day 1)
   5-FU: 750 mg/m^2/24 hours by continuous IV infusion (days 1 to 5)
   RT: 180 cGy/day for 4 weeks with a 2-week rest
   Total RT dose: 5400 cGy (in patients with locally advanced disease, the boost dose is increased but the total dose does not exceed 6000 cGy)

2. **Follow-up therapy.** Additional 6-week cycles of chemotherapy with mitomycin C and 5-FU are given depending on tumor control or treatment toxicity. Full-thickness biopsy at the original tumor site is performed 6 to 8 weeks after the completion of therapy. Patients are examined at 3-month intervals for the first year and at 6-month intervals thereafter. AP resection is performed for biopsy-proven carcinoma during the follow-up period. Second-line chemotherapy with 5-FU plus cisplatin and AP resection are potentially curative salvage approaches after relapse.

B. **Surgery alone.** Wide, full-thickness excision is sufficient treatment for discrete, superficial, anal margin tumors and results in an 80% 5-year survival rate unless the tumor is large and deep. AP resection of the anorectum as the exclusive treatment for anal canal tumors and large anal margin tumors results in only a 55% 5-year survival rate.

C. **Follow-up** of patients with anal cancer every 3 months with digital rectal examination, anoscopy or proctoscopy, and biopsy of suspicious lesions is especially important during the first 3 years after initial treatment because salvage therapy may be curative.

Pancreatic Cancer

I. Epidemiology and etiology

A. **Incidence.** In the United States, the incidence of pancreatic cancer is 9 cases per 100,000 population and has not changed since 1973. Blacks are more frequently affected, with an incidence of 15 per 100,000. There are 28,000 new cases diagnosed annually in the United States and 25,000 deaths from pancreatic cancer, making it the fifth leading cause of U.S. cancer deaths. The disease has a male-to-female ratio of 1:1 and is rare before the age of 45 years; the peak incidence occurs between the ages of 65 and 79 years.

In India, Kuwait, and Singapore, the rate is less than 2 per 100,000 population. In Japan, the incidence has risen sharply from 2 to 5 per 100,000 since the early 1980s.

B. **Etiology and risk factors.** The cause of pancreatic adenocarcinoma remains unknown, but several factors show a modest association with its occurrence.
   1. **Cigarette smoking** is a consistently noted risk factor for pancreatic cancer, with a relative risk of at least 1.5. The risk increases with increasing duration and amount of cigarette smoking. The excess risk levels off 10 to 15 years after cessation of smoking. The risk is ascribed to tobacco-specific nitrosamines.
   2. **Diet.** A high intake of fat, meat, or both is associated with increased risk, whereas the intake of fresh fruits and vegetables appears to have a protective effect.
   3. **Partial gastrectomy** appears to correlate with a two to five times higher than expected incidence of pancreatic cancer 15 to 20 years later. The increased formation of N-nitroso compounds by bacteria that produce nitrate reductase and proliferate in the hypoacidic stomach has been proposed to account for the increased occurrence of gastric and pancreatic cancer after partial gastrectomy.
   4. **Cholecystokinin** is the primary hormone that causes growth of exocrine pancreatic cells; others include epidermal growth factor and insulin-like growth factors. Pancreatic cancer has been induced experimentally by long-term duodenogastric reflux, which is associated with increased cholecystokinin levels. Some clinical evidence suggests that cholecystectomy, which also increases the circulating cholecystokinin, may increase the risk for pancreatic cancer.
   5. **Diabetes mellitus** may be an early manifestation of pancreatic cancer or a predisposing factor. It is found in 13% of patients with pancreatic cancer and in only 2% of controls. Diabetes mellitus that occurs in patients with pancreatic cancer may be characterized by marked insulin resistance, which moderates after tumor resection. Islet amyloid polypeptide, a hormonal factor secreted by pancreatic b cells, reduces insulin sensitivity *in vivc* and glycogen synthesis *in vitrc* and may be present in elevated concentrations in patients with pancreatic cancer who have diabetes.
   6. **Chronic and hereditary pancreatitis** are associated with pancreatic cancer. Chronic pancreatitis is associated with a 15-fold increase in the risk for pancreatic cancer.
   7. **Toxic substances.** Occupational exposure to 2-naphthylamine, benzidine, and gasoline derivatives is associated with a five-fold increased risk for pancreatic cancer. Prolonged exposure to DDT and two DDT derivatives (ethylan and DDD) is associated with a four-fold to seven-fold increased risk for pancreatic cancer.
   8. **Socioeconomic status.** Pancreatic cancer occurs in a slightly higher frequency in populations of lower socioeconomic status.
   9. **Coffee.** Analysis of 30 epidemiologic studies showed that only one case-control study and none of the prospective studies confirmed a statistically significant association between coffee consumption and pancreatic cancer.
   10. **Idiopathic deep-vein thrombosis** is statistically correlated with the subsequent development of mucinous carcinomas (including pancreatic cancer),

especially among patients in whom venous thrombosis recurs during follow-up.

11. **Dermatomyositis and polymyositis** are paraneoplastic syndromes associated with pancreatic cancer and other cancers.
12. **Tonsillectomy** has been shown to be a protective factor against the development of pancreatic cancer, an observation that has been described for other cancers as well.
13. **Familial pancreatic cancer.** It is estimated that 3% of pancreatic cancers are linked to inherited predisposition to the disease.

II. Pathology

A. **Primary malignant tumors** of the pancreas involve either the exocrine parenchyma or the endocrine islet cells (the latter are discussed in Chapter 15, section VI). Nonepithelial tumors (sarcomas and lymphomas) are rare. Ductal adenocarcinoma makes up 75% to 90% of malignant pancreatic neoplasms: 57% occur in the head of the pancreas, 9% in the body, 8% in the tail, 6% in overlapping sites, and 20% in unknown anatomic subsites. Uncommon but reasonably distinctive variants of pancreatic cancer include adenosquamous, oncocytic, clear cell, giant cell, signet ring, mucinous, and anaplastic carcinoma. Anaplastic carcinomas often involve the body and tail rather than the head of pancreas. Reported cases of pure epidermoid carcinoma (a variant of adenosquamous carcinoma) probably are associated with hypercalcemia. Cystadenocarcinomas have an indolent course and may remain localized for many years. Ampullary cancer (which carries a significantly better prognosis), duodenal cancer, and distal bile duct cancer may be difficult to distinguish from pancreatic adenocarcinoma.
B. **Metastatic tumors.** Autopsy studies show that for every primary tumor of the pancreas, four metastatic tumors are found. The most common tumors of origin are the breast, lung, cutaneous melanoma, and non-Hodgkin's lymphoma.
C. **Genetic abnormalities.** Mutant *c-K-ras* genes have been found in most specimens of human pancreatic carcinoma and their metastases.

III. Diagnosis

A. **Symptoms.** Most patients with pancreatic cancer have symptoms at the time of diagnosis. Predominant initial symptoms include abdominal pain (80%); anorexia (65%); weight loss (60%); early satiety (60%); xerostomia and sleep problems (55%); jaundice (50%); easy fatigability (45%); weakness, nausea, or constipation (40%); depression (40%); dyspepsia (35%); vomiting (30%); hoarseness (25%); taste change, bloating, or belching (25%); dyspnea, dizziness, or edema (20%); cough, diarrhea because of fat malabsorption, hiccup, or itching (15%); and dysphagia (5%).
B. **Clinical findings.** At presentation, patients with pancreatic cancer have cachexia (44%), serum albumin concentration of less than 3.5 g/dL (35%), palpable abdominal mass (35%), ascites (25%), or supraclavicular adenopathy (5%). Metastases are present to at least one major organ in 65% of patients, to the liver in 45%, to the lungs in 30%, and to the bones in 3%. Carcinomas of the distal pancreas do not produce jaundice until they metastasize and may remain painless until the disease is advanced. Occasionally, acute pancreatitis is the first manifestation of pancreatic cancer.
C. **Paraneoplastic syndromes.** Panniculitis-arthritis-eosinophilia syndrome that occurs with pancreatic cancer appears to be caused by the release of lipase from the tumor. Dermatomyositis, polymyositis, recurrent Trousseau's syndrome or idiopathic deep-vein thrombosis, and Cushing's syndrome have been reported to be associated with cancer of the pancreas.
D. **Diagnostic studies**
   1. **Ultrasonography.** Abdominal ultrasound is technically adequate in 60% to 90% of patients and is noninvasive, safe, and inexpensive. Ultrasound can detect pancreatic masses as small as 2 cm, dilation of the pancreatic and bile ducts, hepatic metastases, and extrapancreatic spread. Intraoperative ultrasound facilitates surgical biopsy and may detect unsuspected liver metastases in 50% of patients.
   2. **CT** is less operator dependent than ultrasound and is not limited by air-containing abdominal organs, as is ultrasound. CT is favored over ultrasound because of its superior ability to demonstrate retroperitoneal invasion and lymphadenopathy. A pancreatic tumor must be at least 2 cm in diameter to become visible. *Dynamic CT* with continuous infusion of intravenous contrast is the best test for assessing the size of the tumor and its extension. At least 20% of pancreatic tumors believed to be resectable may not be detectable by CT.
   3. **MRI** has no demonstrated advantage over CT in the diagnosis and staging of pancreatic cancer.
   4. **Endoscopic retrograde cholangiography** (ERCP) is the mainstay in the differential diagnosis of the tumors of the pancreatobiliary junction, 85% of which originate in the pancreas (about 5% each in the distal common bile duct, ampulla, and duodenum). Ampullary and duodenal carcinoma can usually be visualized and biopsy performed with ERCP. The pancreatogram typically shows the pancreatic duct to be encased or obstructed by carcinoma in 97% of cases.

      It may be difficult to distinguish between pancreatic cancer and chronic pancreatitis because both diseases share clinical and radiologic characteristics. Pancreatic duct stricture usually does not exceed 5 mm in chronic pancreatitis; strictures longer than 10 mm (especially if irregular) indicate pancreatic cancer. Cytologic examination of cells in samples of pancreatic juice obtained during ERCP with secretin stimulation has been reported to be highly specific for the diagnosis of carcinoma and 85% sensitive. Brush biopsy of the pancreatic stricture (when possible) increases the diagnostic yield.

   5. **EUS.** Prospective studies showed that EUS is more accurate than standard ultrasound, CT, and ERCP for diagnosis, staging, and predicting resectability of pancreatic tumors. EUS detected 100% of malignant lesions smaller than 3 cm, whereas angiography, CT, and ultrasound were of limited value for these small lesions. EUS can detect tumors smaller than 2 cm; ERCP cannot. The additional information obtained from EUS has been reported to result in a major change in the clinical management in one third of patients and to aid in the clinical decision in three fourths of patients.

      The present limitations of EUS include a short optimal focal range of only 4 cm, inability to differentiate focal chronic pancreatitis from carcinoma reliably, and inability to differentiate chronic lymphadenitis from metastatic lymph node involvement. The ability to biopsy lymph nodes using EUS does allow assessment of lymph nodes for malignancy in some cases.

   6. **Percutaneous fine-needle aspiration cytology** is safe and reliable, with a reported sensitivity of 55% to 95% and no false-positive results for the diagnosis of pancreatic cancer. This procedure should be performed for histologic confirmation on all patients with unresectable or metastatic disease unless a palliative surgical procedure is planned. Needle aspiration cytology distinguishes adenocarcinoma from islet cell tumors, lymphomas, and cystic neoplasms of the pancreas, permitting therapy to be tailored to the specific diagnosis in each case.

      The drawbacks to percutaneous aspiration biopsy include potential tumor seeding along the needle tract, potential to enhance intraperitoneal spread, and negative biopsy results that do not exclude the diagnosis of malignancy. Furthermore, the diagnosis of early and smaller tumors is most likely to be missed by this technique.

   7. **Angiography** is excellent for assessing major vascular involvement but is not useful in determining the size and location of tumor (pancreatic cancer is hypovascular). In most cases, spiral CT scanning with proper administration of intravenous contrast allows resectability to be judged preoperatively.
   8. **Laparoscopy** can demonstrate extrapancreatic involvement in 40% of patients without demonstrable lesions on CT.
   9. **Tumor markers.** No available serum marker is sufficiently sensitive or specific to be considered reliable for screening of pancreatic cancer.
      a. **CA 19-9** is widely used for the diagnosis and follow-up of patients with pancreatic cancer but is not specific for pancreatic cancer.
      b. **CEA** is of minimal value in pancreatic cancer.

IV. Staging and prognostic factors

A. **Staging system.** The TNM system is most commonly used. Readers should consult an up-to-date staging manual because of frequent revisions of staging systems. T1 and T2 tumors are potentially resectable tumors. T1 tumors are localized to the pancreas, and T1a tumors are less than 2 cm in diameter. T2 indicates that there is a limited direct extension into the duodenum, bile duct, or stomach. T3 indicates advanced direct extension that is incompatible with surgical resection.
B. **Preoperative evaluation.** Identifying patients with unresectable pancreatic tumor or with metastasis or vessel involvement would spare many patients a major operation. Operative mortality and morbidity for pancreatic surgery remain high, except in specialized centers. Modern diagnostic methods have reduced unnecessary laparotomies from 30% to 5% and have increased the resectability rate on patients judged to be potentially resectable on the basis of preoperative imaging from 5% to 20%. Accuracy in determining resectability before exploration has become even more important because of the availability of effective decompression of biliary obstruction endoscopically for palliation of obstructive jaundice without the need for laparotomy.

CT, angiography, and laparoscopy assess different aspects of resectability and are complementary. In general, if one of these studies indicates vascular invasion or local or regional spread, the resectability rate is about 5%, whereas if all are negative, the resectability rate is 78%. Gross nodal involvement is usually

associated with other signs of unresectability and may be identified by CT or EUS.

C. **Prognostic factors.** Fewer than 20% of patients with adenocarcinoma of the pancreas survive the first year, and only 3% are alive 5 years after the diagnosis.
   1. **Resectable disease.** The 5-year survival rate of patients whose tumors were resected is poor; the reported range is 3% to 25%. The 5-year survival is 30% for patients with small tumors (2 cm or less in diameter), 35% for patients with no residual tumor or for patients in whom the tumor did not require dissection from major vessels, and 55% for patients without lymph node metastasis.
   2. **Nonresectable or metastatic disease.** The median survival of patients with such disease is 2 to 6 months. Performance status and the presence of four symptoms (dyspnea, anorexia, weight loss, and xerostomia) appear to influence survival; patients with the higher performance status and the least number of these symptoms lived the longest.

V. Management

A. **Surgery.** Only 5% to 20% of patients with pancreatic cancer have resectable tumors at the time of presentation.
   1. **Surgical procedures**
      a. **Pancreaticoduodenal resection** (Whipple's procedure or a modification) is the standard operation. This implies that only cancer involving the head of the pancreas is resectable.
      b. **A pylorus-preserving variation of Whipple's procedure** is a commonly used operation in the United States, in part because it has resulted in a significant reduction of postgastrectomy syndrome with no decrease in survival.
      c. **An extended Whipple's procedure,** with a more extensive lymph node dissection, is used commonly in Japan but has not been widely accepted in the United States because of higher morbidity and lack of data from randomized trials to suggest that the procedure results in better survival.
      d. **Regional pancreatectomy** confers no survival advantage over conventional Whipple's procedure.
      e. **Total pancreatectomy** produces exocrine insufficiency and brittle diabetes mellitus and should be performed only when necessary to achieve clear surgical margins.
   2. **Surgical mortality and morbidity.** The perioperative mortality rate from pancreatic resection is less than 5% when the operation is performed by expert surgeons. Nationally, however, the surgical mortality rate is about 18%. The major complication rate is 20% to 35% and includes sepsis, abscess formation, hemorrhage, and pancreatic and biliary fistulae.
   3. **Relief of obstructive jaundice by surgical biliary bypass** (cholecystojejunostomy or choledochojejunostomy) is effective, but the average survival time is 5 months, and the postoperative mortality rate in large collected series is 20%. Jaundice can be relieved endoscopically by the placement of stents with a success rate of up to 85%, a procedure-related mortality rate of 1% to 2%, and significant reduction in the length of hospitalization and recovery compared with palliative surgery. Randomized trials showed no difference in survival between endoscopic stent placement and surgical bypass, but patients treated with stents had more frequent readmissions for stent obstruction, recurrent jaundice, and cholangitis.

B. **Adjuvant therapy** appears to be a reasonable approach to the patient who has undergone curative resection. There is one prospective randomized study of 43 patients (completed by the Gastrointestinal Study Group in the 1980s) that showed that adjuvant RT and 5-FU after a curative Whipple's procedure improved survival. In that study, the median survival was 20 months for patients treated, and 3 of 21 patients survived 5 years or more. For patients not treated, the median survival was 11 months, and only 1 of 22 patients survived 5 years. The 5-year survival rate was 40% for patients with no lymph node involvement and less than 5% for patients with lymph node metastasis.

C. **Therapy for locally advanced disease**
   1. **External-beam RT combined with 5-FU** (15 mg/kg IV on the first 3 and last 3 days of RT) significantly improves survival as compared with RT alone (10 months versus 5.5 months, respectively). Some favor the use of continuous infusion 5-FU during irradiation, although there are no randomized trials to suggest incremental benefit to infusion over bolus 5-FU in pancreatic cancer.
   2. **Intraoperative electron-beam RT** delivered to a surgically exposed tumor from which radiosensitive bowel has been excluded by insertion of a field-limiting cone increased the median survival compared with historical controls in selected patients to 13 months, with excellent local control (5% of patients have lived 3 to 8 years). Intraoperative RT relieves pain in 50% to 90% of patients.

D. **Chemotherapy for metastatic disease.** 5-FU has a response rate of 20% in pancreatic cancer. Gemcitabine has been shown to have activity and provide palliative benefit exceeding that of 5-FU in a randomized trial of 126 patients with advanced disease. The median survivals times were 5.65 versus 4.41 months ($p = 0.002$) for gemcitabine versus 5-FU. Gemcitabine is a potent radiation sensitizer that is under investigation for use in locally advanced and resected tumors. Other drugs with reported activity include mitomycin, streptozocin, doxorubicin, and ifosfamide. The administration of multiagent chemotherapy has not resulted in better outcomes than single-agent therapy.

E. **Neuroablation for pain control.** The boring, relentless, posterior abdominal and back pain caused when the celiac nerve plexus becomes invaded by pancreatic cancer can be extremely distressing and frequently requires the use of large doses of narcotics, particularly sustained-release morphine. Chemical splanchnicectomy (celiac axis nerve block) should be performed at the time of operation in nonresectable cases. Either 6% phenol or 50% alcohol (25 mL is injected on each side of the celiac axis) is used. This procedure results in relief of pancreatic cancer-related pain in more than 80% of patients. Percutaneous chemical neurolysis of the celiac ganglion, which may be attempted in patients who did not have an intraoperative splanchnicectomy or were not explored, is reported to be equally effective. Transient postural hypotension may occur. Celiac plexus block may be repeated if initially unsuccessful or if pain reoccurs.

F. **Other supportive measures.** Appetite suppression, decreased caloric intake, and malabsorption can all lead to cancer cachexia in patients with pancreatic cancer. Megestrol acetate (Megace) suspension in doses up to 800 mg/day can be an effective appetite stimulant for treatment of anorexia. Calorie supplements are also potentially valuable. Fat malabsorption resulting from loss of the exocrine function of the pancreas responds to pancreatic enzyme replacement. Ascites can be managed with diuretics when possible and paracentesis when necessary. Removal of protein-rich ascitic fluid, however, can become an additional contributor to the negative protein balance in these all ready malnourished patients.

Liver Cancer

I. Epidemiology and etiology

A. **Incidence.** Liver cancer is among the most common neoplasms and causes of cancer death in the world, occurring most commonly in Africa and Asia. Up to 1 million deaths due to hepatocellular carcinoma (HCC) occur each year worldwide. In the United States, 16,000 new cases of cancer of the liver and biliary passages develop annually. Incidence throughout the world varies dramatically with 115 cases per 100,000 people noted in China and Thailand, compared with 1 to 2 cases per 100,000 in Britain. In countries with high incidence rates, there are often subpopulations with high incidence rates living nearby lower-risk subpopulations. For example, the incidence rates in black South Africans and Alaskan natives far exceeds those of nearby white populations. HCC is 4 to 9 times more common in men than in women.

B. **Conditions predisposing to HCC**
   1. **Hepatitis B virus** (HBV). High titers of hepatitis B surface antigen (HBsAg) and core antibody (HBcAb) are frequently found in patients with HCC. HBsAg was found in the serum of 50% to 60% of patients with HCC and in 5% to 10% of the general population. In the United States, HCC is increased by 140-fold in HBsAg carriers. Anti-HBcAb was found in 90% of black South African and 75% of Japanese patients with HCC, as compared with 35% and 30% of matched controls, respectively. When HCC develops, the patient usually has had chronic HBV infection for three to four decades. The risk factors for the development of HCC in HBsAg carriers are the presence of cirrhosis; family history of HCC; increasing age; male sex; Asian or African race; cofactors (such as alcohol, aflatoxin, and perhaps smoking); and the duration of the carrier state. In Asia, HBV is transmitted vertically from mother to infant in the first few months of life; in Africa, HBV is transmitted horizontally.
   2. **Cirrhosis.** HCC often develops in a cirrhotic liver. Autopsy studies showed that 60% to 90% of HBsAg-positive subjects have associated cirrhosis and 20% to 40% of patients with cirrhosis have HCC. Studies show that in Taiwan, the annual estimated incidence of HCC is 0.005% in HBsAg-negative patients, 0.25% in HBsAg-positive patients, and 2.5% in HBsAg-positive patients with liver cirrhosis (500 times higher than in HBsAg-negative patients). In France, the development of HCC in the presence of alcoholic cirrhosis was nearly always associated with HBV infection, and alcoholism was thought to hasten the development of HCC. In Italy, the prevalence of HCC in patients with cirrhosis was nearly 7%, with a yearly crude incidence of 3%; hepatitis C virus (HCV) chronic infection was the cause of cirrhosis in 45% of these patients. A clear association between alcohol-induced cirrhosis and HCC exists; associations between alcohol and HCC in the absence of cirrhosis are less clear.
   3. **HCV infection** is a risk factor for the development of HCC. Apparently, HCV induces cirrhosis and to a lesser extent increases the risks for HCC in patients with cirrhosis. HCV infection acts independently of HBV infection, alcohol abuse, age, and gender. The ratios for HCC risk factors in patients with chronic liver disease, adjusted for age, sex, and other factors, are as follows:
      a. Risk ratio six- to seven-fold: age, 60 to 69 years; HBsAg positive
      b. Risk ratio four-fold: high-titer anti-HBcAb, anti-HCV positivity
      c. Risk ratio two-fold: presence of liver cirrhosis, currently smoking

4. **Aflatoxins** are produced by the ubiquitous fungi *Aspergillus flavus* or *Aspergillus parasiticus,* which commonly colonize peanuts, corn, and cassava in all except extremely cold climates. Aflatoxin B1 has been proved to be a potent hepatocarcinogen in experimental animals, and the amount of exposure is correlated with increased HCC risk in humans. For example, the daily intake of aflatoxin in Mozambique is four times greater than in Kenya, and the incidence of HCC is eight times greater.

5. **Mutations of tumor-suppressor gene *p53*** have been reported in half of patients with HCC. These mutations, specifically of 249 ser *p53,* are correlated both with geographic areas where the ingestion of aflatoxin is common and with the prevalence of HBV infection.

6. **Sex hormones.** The risk for liver cell adenomas and HCC is increased in women who have used oral contraceptives for eight or more years. Although liver cell adenomas regress with discontinuation of oral contraceptives in most cases, adenomas must be considered premalignant. Close and prolonged follow-up is necessary for women with adenomas who continue to use oral contraceptives. HCC has also been observed in people with a history of anabolic steroid use.

7. **Cigarette smoking, alcohol intake, diabetes, and insulin intake.** A study performed in Los Angeles showed that in non-Asian populations that have a low risk for HCC, cigarette smoking, heavy alcohol consumption, and diabetes mellitus, especially with insulin administration, appear to be significant risk factors for HCC.

8. **Other factors.** A relatively small number of HCCs develop in patients with various other diseases. The most common of these are a_1-antitrypsin deficiency, tyrosinemia, and hemochromatosis. Phlebotomy therapy can deplete hepatic iron and induce regression of hepatic fibrosis but does not prevent the development of HCC in hemochromatosis. Clonorchiasis, vinyl chloride exposure, and administration of thorium dioxide (an x-ray contrast agent used between 1930 and 1955) or methotrexate are also associated with the development of HCC.

II. Pathology and natural history

A. **Pathology**

1. **Liver cell adenoma** has low malignant potential. True adenomas of the liver are rare and occur mostly in women taking oral contraceptives. Most adenomas are solitary; occasionally multiple (10 or more) tumors develop in a condition known as *liver cell adenomatosis.* These tumors are smooth encapsulated masses and do not contain Kupffer's cells. Patients usually have symptoms; hemoperitoneum occurs in 25% of cases.

2. **Focal nodular hyperplasia** (FNH) has no malignant potential. FNH occurs with a female-to-male ratio of 2:1. The relationship of oral contraceptives to FNH is not as clear as for hepatic adenoma; only half of patients with FNH take oral contraceptives. FNH tumors are nodular, are not encapsulated, but do contain Kupffer's cells. Patients usually do not have symptoms; hemoperitoneum rarely occurs.

3. **HCC** may present grossly as a single mass, multiple nodules, or as diffuse liver involvement; these are referred to as *massive, nodular,* and *diffuse* forms. The growth pattern microscopically is trabecular, solid, or tubular, and the stroma, in contrast to bile duct carcinoma, is scanty. A rare sclerosing or fibrosing form has been associated with hypercalcemia. Fibrolamellar carcinoma, another variant, occurs predominantly in young patients without cirrhosis, has a favorable prognosis, and is not associated with elevation of serum a-fetoprotein (a-FP) levels. In the United States, almost half of HCCs in patients younger than 35 years of age are fibrolamellar, and more than half of them are resectable.

4. **Bile duct adenomas** are solitary in 80% of cases and may grossly resemble metastatic carcinoma. Most are less than 1 cm in diameter and are located under the capsule.

5. **Biliary cystadenoma and cystadenocarcinoma.** Benign and malignant cystic tumors of biliary origin arise in the liver more frequently than in the extrahepatic biliary system.

6. **Bile duct carcinoma** (cholangiocarcinoma; see Extrahepatic Bile Duct Cancer, later). Malignant tumors of intrahepatic bile ducts are less common than HCC and have no relation to cirrhosis. Mixed hepatic tumors with elements of both HCC and cholangiocarcinoma do occur; most of these cases are actually HCC with focal ductal differentiation. Table 9.3 depicts the clinical and pathologic differences between HCC, bile duct carcinoma, and metastatic adenocarcinoma. Appendix C-3.V shows immunohistochemical phenotypes of HCC and bile duct carcinomas as well as other adenocarcinomas.

Table 9.3 Differential diagnosis of hepatocellular carcinoma (HCC) versus adenocarcinoma

B. **Natural history.** Most patients die from hepatic failure and not from distant metastases. The disease is contained within the liver in only 20% of cases. HCC invades the portal vein in 35% of cases, hepatic vein in 15%, contiguous abdominal organs in 15%, and vena cava and right atrium in 5%. HCC metastasizes to the lung in 35% of cases, abdominal lymph nodes in 20%, thoracic or cervical lymph nodes in 5%, vertebrae in 5%, and kidney or adrenal gland in 5%.

C. **Associated paraneoplastic syndromes** include fever, erythrocytosis, hypercholesterolemia, gynecomastia, hypercalcemia, hypoglycemia, and virilization (precocious puberty).

III. Diagnosis

A. **Symptoms and signs.** Pain in the right subcostal area or on top of the shoulder from phrenic irritation is common (95%). Severe symptoms of fatigue (31%), anorexia (27%), and weight loss (35%) and unexplained fever (30% to 40%) are not uncommon. Many patients have vague abdominal pain, fever, and anorexia for up to 2 years before the diagnosis of carcinoma is made. Hemorrhage into the peritoneal cavity is often seen in patients with HCC and may be fatal. Ascites or the presence of an upper abdominal mass noticeable by the patient are ominous prognostic signs. Any sudden deterioration in a patient with known liver disease or with positive HbsAg or hepatitis C serology should raise the suspicion of HCC. Physical findings include hepatomegaly (90%), splenomegaly (65%), ascites (52%), fever (38%), jaundice (41%), hepatic bruit (28%), and cachexia (15%).

B. **Diagnostic studies**

1. **LFTs** may be normal or elevated and are affected by liver cirrhosis. Elevated serum bilirubin and lactate dehydrogenase values and lowered serum albumin are associated with a poor survival. Serum g-glutamyl transferase (GGT) isoenzyme II (out of 11 isoenzymes) was positive in 90% of patients with HCC. GGT-II was negative in most patients with acute and chronic viral hepatitis or extrahepatic tumors, in pregnant women, and in healthy controls. GGT-II was found to be valuable for the detection of small or subclinical HCC.

2. **Biopsy of liver nodules.** Some authors believe that percutaneous liver biopsy carries a high risk and has little or no role in the workup of liver tumors, whereas others believe that it can be performed without any significant risk. Nevertheless, liver biopsy is needed to establish the diagnosis and may be obtained either at operation or percutaneously.

3. **Serum tumor markers.** Serum a-FP is often elevated in patients with HCC but can also be elevated in patients with benign chronic liver disease (see Chapter 1, section III.B.3.a). In patients with liver cirrhosis and no HCC, serum a-FP may be normal or elevated, with values ranging from 30 to 460 ng/mL (median, 30 to 70 ng/mL). In patients with HCC, the serum a-FP concentrations may range from 30 to 7000 ng/mL (median, 275 ng/mL). Measurement of a-FP fractions L3, P4, and P5 (different sugar-chain structures) may allow the differentiation of HCC from cirrhosis in some cases. It may also be predictive for the development of HCC during follow-up of patients with cirrhosis. Serum ferritin levels are also frequently elevated in patients with HCC.

4. **Radiologic studies**

a. **Ultrasound.** HCC is usually well circumscribed, hyperechogenic, and associated with diffuse distortion of the normal hepatic parenchyma. Metastatic deposits are usually hyperechogenic but may be hypoechogenic.

b. **CT.** HCC typically appears as an area of low attenuation on CT. Lesions may occasionally be isodense with normal hepatic parenchyma, however. Metastatic tumors with low attenuation (close to the density of water) include mucin-producing tumors of the ovary, pancreas, colon, and stomach and tumors with necrotic centers, such as sarcomas. Mucin-producing metastases may have nearly normal attenuation values because of diffuse microscopic calcifications within the tumor.

c. **MRI** has been reported to be superior to CT scanning and ultrasound for the detection of liver tumors.

d. **Selective hepatic, celiac, and superior mesenteric angiography** can confirm portal vein involvement, define the arterial supply, and identify vascular lesions that are as small as 3 mm in diameter. Intraarterial epinephrine injection can differentiate normal hepatic arteries from tumor vessels, which do not constrict because of the absence of smooth muscles in their walls.

e. **Radionuclide scans**

1. **Liver-spleen scan.** All primary and metastatic liver tumors, except for FNH and regenerating nodules, are devoid of Kupffer's cells and appear as "cold" areas in liver scans. However, the liver-spleen scan has now been replaced by MRI, ultrasound, and CT.

2. **Gallium scan** of liver may be able to differentiate primary hepatic tumors from metastatic carcinoma because gallium is taken up by the HCC.

IV. Staging and prognostic factors

A. **Staging.** The initial step is to establish whether the HCC is resectable. Indications of unresectability may be determined either at exploratory laparotomy, by

laparoscopy, or by CT, MRI, or angiography. Unresectable disease includes bilobar or four-segment hepatic parenchymal involvement, portal vein thrombus, and vena caval involvement with tumor or tumor thrombus. Metastatic disease includes involvement of regional lymph nodes, which is proved by biopsy at surgery. Liver failure or portal hypertension alone does not contraindicate surgery. Readers should consult an up-to-date staging manual because of frequent revisions of staging systems.

B. **Prognostic factors.** The number of liver lesions and the presence of vascular involvement are the most significant prognostic determinants in patients with disease limited to the liver. Neither the presence nor the degree of a-FP elevation has any prognostic importance. The prognostic factors that relate to survival in patients with resectable HCC are as follows:

1. **Number, size, and location of liver lesions.** The 5-year survival rate for patients with a solitary tumor is 45%, and it is 15% to 25% for those with multiple liver lesions. The 5-year survival rate is 40% to 45% for patients with small tumors (2 to 5 cm) and 10% for patients with tumors larger than 5 cm. Patients without cirrhosis with tumors located in the left lobe of the liver or in the right inferior segments (anteriorly or posteriorly) have the best prognosis.

2. **Vein involvement.** All patients with gross tumor thrombi involving the portal vein or hepatic vein die within 3 years, whereas the 5-year survival rate for patients with no vascular involvement of any kind is 30%.

3. **Extent and type of resection.** The 5-year survival rate for patients undergoing curative resection is 55%, compared with 5% for those undergoing noncurative resections. The 5-year survival rate is 85% for hepatic lobectomy, 50% for subsegmentectomy, and 20% for wedge enucleation. In patients with resected HCC, the liver is the site of disease recurrence in 90% of cases.

4. **Hepatic reserve.** Patients who have better hepatic reserve, as determined by retention rate of indocyanine green dye at 15 minutes, have better survival.

V. Prevention and early detection

A. **Prevention.** Avoidance of the risk factors for HCC is difficult in those parts of the world where socioeconomic conditions are poor and where HBV infection is endemic. The widespread use of HBV vaccine may affect the incidence of HCC, but with a considerable lag time.

1. Almost 4 billion people (75% of the world population) live in areas of intermediate or higher prevalence of HBV. Infections with HBV and HCV can be treated with interferons, although prevention of initial infection is preferable. Protection against HBV, if attempted, is best done in infancy. In the United States, vaccination with recombinant HBsAg is recommended for health workers in contact with blood, for people residing for more than 6 months in areas that are highly endemic for HBV, and for all others at risk. Interferon- a treatment of patients with chronic active hepatitis and cirrhosis lowered the rate of progression to hepatocellular carcinoma two-fold in one trial.

2. Steps should be taken to reduce the high levels of aflatoxin food contaminations that exist in many areas of Asia and southern Africa, as has been done in the Western world.

B. **Early detection.** Two recent reports describe attempts for early detection of HCC in patients with liver cirrhosis. A study from Italy shows that patients with persistently elevated serum a-FP have a higher incidence of HCC (3% per year) than those with fluctuating levels. This screening program did not appreciably increase the rate of detection of potentially curable liver tumors, however. In a study from Japan, higher percentages of a-FP L3, P4, and P5 fractions allowed the differentiation of HCC in some cases.

VI. Management

A. **Liver anatomy.** The liver is anatomically divided into four lobes: a larger right lobe, which is separated from a smaller left lobe by the attachment of the falciform ligament, and two small lobes (the quadrate lobe on the anterior inferior aspect and the caudate lobe). Practical surgical anatomy divides the liver into nearly equal halves, and each half is divided into two segments. The right half is divided into anterior (ventrocranial) and posterior (dorsocaudal) segments. The left half is divided into medial and lateral segments by a visible left sagittal accessory fissure. Each of the four segments is subdivided into superior and inferior subsegments. The French literature labels the eight liver subsegments with Roman numerals.

B. **Localized and resectable HCC.** Only 10% of HCCs are resectable with solitary or unilobar hepatic lesions at the time of diagnosis. The survival in resectable lesions depends on the prognostic factors discussed in section IV.B. In the United States, the median survival after surgical resection is about 22 months for patients with cirrhotic livers and 32 months for patients with normal livers (range, 2 months to 15 years). The perioperative morbidity is minimal and is slightly higher in the cirrhotic group. Morbidity includes subphrenic abscess, subhepatic abscess, pneumothorax, and wound infection. Total hepatectomy with orthotopic liver transplantation may be of benefit in patients with unresectable nonmetastatic fibrolamellar HCC, intrahepatic bile duct cancers, or hemangiosarcoma and is under investigation as a strategy for patients with poor underlying hepatic function or bilobar disease limited to the liver.

C. **Localized and nonresectable disease**

1. **Preoperative multimodality treatment followed by surgery.** At Johns Hopkins University, preoperative external-beam radiation therapy (2100 cGy in 300 cGy fractions) and chemotherapy (both 15 mg/m^2 of doxorubicin and 500 mg/m^2 of 5-FU given on days 1, 3, 5, and 7 of RT) resulted in greater than 50% tumor reduction in all patients. Most patients also received radiolabeled polyclonal antiferritin immunoglobulin conjugate with ^{131}I. The actuarial 5-year survival, the types of operative procedures performed, and the complication rates for patients with initially unresectable tumors who received preoperative chemoradiation therapy were similar to the 5-year survival rates of patients with initially resectable tumors.

2. **Chemoradiation therapy.** Conformal (three-dimensional) radiation therapy and intraarterial fluorodeoxyuridine appear to produce a durable response rate and good median survival (19 months) in patients with nondiffuse HCC.

3. **Transcatheter arterial embolization** (TAE) of unresectable HCC using a mixture of Gelfoam powder, Lipiodol, and contrast media with or without chemotherapeutic drugs has been used with some success. TAE may also be used preoperatively to reduce intraoperative bleeding or as a palliative measure in patients with far advanced HCC. Reports of delayed formation of gallstones after TAE suggest that elective cholecystectomy may be advisable at the time of partial hepatectomy.

4. **Other treatments.** Percutaneous intralesional installation of absolute ethanol under ultrasound guidance has resulted in a reported 5-year survival rate of nearly 80% in highly selected patients, particularly those with small tumors who are not surgical candidates. Groups of Japanese investigators have found that this technique yields a better survival than surgery, even for resectable lesions. Cryosurgery has been reported to have similar efficacy in highly selected patients.

D. **Nonresectable and metastatic disease**

1. **Tamoxifen.** About 40% of patients with HCC have estrogen receptor protein in the cell cytosol. Large tumors are commonly estrogen receptor negative. In a prospective, randomized study of tamoxifen (40 mg/ day) plus best supportive care versus best supportive care alone, there was no difference in median survival (16 versus 15 months).

2. **Recombinant interferon-**a**2a,** 50 million IU/m^2 IM three times a week, resulted in a significant improvement in median survival and more objective tumor regression as compared with the no-treatment group in a recent randomized, placebo-controlled study from China. These large doses of interferon result in substantial toxicity, however.

3. **Systemic chemotherapy** has a response rate of 20% and does not affect median survival (3 to 6 months). Doxorubicin as a single agent or in combination with other drugs has been used. Mitoxantrone is as effective as doxorubicin but is associated with less toxicity. 5-FU intravenously and FUDR intraarterially have also been used with similar results.

Gallbladder Cancer

I. Epidemiology and etiology

A. **Incidence.** Primary gallbladder carcinoma (GBC) is the most common malignant tumor of the biliary tract and the fifth most common cancer of the digestive tract. There are 6000 to 7000 cases annually in the United States. GBCs were found in 1% to 2% of operations on the biliary tract.

B. **Risk factors.** The cause of GBC remains unknown. Reported risk factors include the following:

1. **Sex.** The female-to-male ratio is 3:1 to 4:1. Acalculous carcinoma is also more common in women.

2. **Race.** The incidence of GBC is doubled in Southwest American Indians, who also have a two- to three-fold greater incidence of cholelithiasis. The incidence of GBC is also high in Peru and Ecuador among populations with native American genealogy.

3. **Older age.** The mean age for the occurrence of GBC is 65 years; the disease is rare before 40 years of age.

4. **Chronic cholecystitis and cholelithiasis** are associated with the development of GBC in 50% and 75% of cases, respectively. Latency periods are lengthy; 1% of patients known to have gallstones for more than 20 years develop GBC. Those with larger stones are more prone to GBC than those with stones smaller than 1 cm. The incidence of GBC is decreasing among populations in the world where cholecystectomy is becoming more common. Calcification of the wall of the gallbladder (porcelain gallbladder) increases the risk for GBC by 10% to 60%. Cholecystitis associated with liver flukes and in chronic typhoid carriers is linked to the increased incidence of GBC.

5. **Benign neoplasms.** Both inflammatory and cholesterol polyps are associated with appreciable risk. Papillary and nonpapillary adenomas of the gallbladder may contain carcinoma *in situ.* Malignant transformation is rare, however.

6. **Ulcerative colitis** increases the risk for extrahepatic biliary cancer by a factor of 5 to 10; 15% of these cancers occur in the gallbladder.
7. **Carcinogens.** Rubber-industry employees have a higher incidence and earlier onset of GBC.

II. Pathology and natural history

A. **Pathology.** Most GBCs are adenocarcinomas (80%) showing varying degrees of differentiation. The mucus secreted by this cancer is typically of the sialomucin type, in contrast to the sulfomucin type secreted by the normal or inflamed mucus-secreting glands. Other types of GBC include adenoacanthoma, adenosquamous carcinoma, and undifferentiated (anaplastic, pleomorphic, sarcomatoid) carcinomas. Some adenocarcinomas have choriocarcinoma-like elements, and others have morphology equivalent to small cell carcinoma.

B. **Natural history.** GBC has a propensity to involve the liver, stomach, and duodenum by direct extension. The common sites of metastasis are the liver (60%), adjacent organs (55%), regional lymph nodes (35%), peritoneum (25%), and distant visceral organs (30%).

C. **Clinical presentation.** GBC may present as one of the following clinical syndromes:
1. **Acute cholecystitis** (15% of patients). These patients appear to have less advanced carcinoma, a higher rate of resectability, and longer survival.
2. **Chronic cholecystitis** (45%)
3. **Symptoms suggestive of malignant disease** (e.g., jaundice, weight loss, generalized weakness, anorexia, or persistent right upper quadrant pain; 35%)
4. **Benign nonbiliary manifestations** (e.g., GI bleeding or obstruction; 5%)

III. Diagnosis

A. **Symptoms.** The lack of specific symptoms prevents detection of GBC at an early stage. Consequently, the diagnosis is usually made unexpectedly at the time of surgery because the clinical signs commonly mimic benign gallbladder disease. Pain is present in 79% of patients; jaundice, anorexia, or nausea and vomiting in 45% to 55%; weight loss or fatigue in 30%; and pruritus or abdominal mass in 15%.

B. **Physical examination.** Certain combinations of symptoms and signs may suggest the diagnosis, such as an elderly woman with a history of chronic biliary symptoms that have changed in frequency or severity. A right upper quadrant mass or hepatomegaly and constitutional symptoms suggest GBC.

C. **Laboratory examination.** Elevated serum alkaline phosphatase is present in 65% of patients, anemia in 55%, elevated bilirubin in 40%, leukocytosis in 40%, and leukemoid reaction in 1% of patients with GBC. The association of elevated alkaline phosphatase without elevated bilirubin is consistent with GBC; about 40% of these patients have resectable lesions.

D. **Radiologic examination**
1. **Abdominal ultrasound** is abnormal in about 98% of patients. Cholelithiasis, thickened gallbladder wall, a mass in the gallbladder, or a combination of these constitutes the most common finding. Ultrasound is diagnostic of GBC in only 20% of cases, however.
2. **CT of the abdomen** may be diagnostic in half of patients.
3. **MRI** can differentiate gallbladder tumors from adjacent liver. Use of magnetic resonance cholangiography can help determine whether biliary tract encasement is present, and vascular enhancement techniques often permit preoperative diagnosis of portal vein involvement.
4. **Percutaneous transhepatic cholangiography** (PTHC) is abnormal in 80% of cases and diagnostic in 40%.
5. **ERCP** is abnormal in about 75% of cases and yields a tissue diagnosis in 25%.
6. **Laparoscopic exploration** may allow assessment of the peritoneal surfaces, liver, and tissues adjacent to the gallbladder to determine potential resectability.

IV. Staging and prognostic factors

A. **Staging.** There are two commonly used staging systems: the American Joint Commission on Cancer Staging (AJCC) system (stages 0 to IV) and Nevin system (stages 1 to 5). Readers should consult an up-to-date staging manual because of frequent revisions of staging systems.

Stage I: An intramuscular lesion or muscular invasion unrecognized at operation and later discovered by the pathologist
Stage II: Transmural invasion
Stage III: Lymph node involvement
Stage IV: Involvement of two or more adjacent organs, or more than 2 cm invasion of liver, or distant metastasis

B. **Prognostic factors.** The overall median survival of patients with GBC is 6 months. After surgical resection, only 27% are alive at 1 year, 19% at 3 years, and 13% at 5 years. Disease stage is the most significant prognostic factor. The 5-year survival rate after surgical resection is 65% to 100% for stage I, 30% for stage II, 15% for stage III, and 0% for stage IV disease. Poorly differentiated (higher-grade) tumors and the presence of jaundice are associated with poorer survival. Ploidy patterns do not correlate with survival.

V. Prevention. Cholecystectomy has been recommended to prevent GBC. For every 100 gallbladders removed, there is one patient with GBC. However, the overall mortality rate of cholecystectomy is also about 1% (including patients with diabetes and gangrenous gallbladder as well as patients with cholangitis or gallstone pancreatitis).

VI. Management. Despite the improvement of diagnostic capabilities, better perioperative care, and more aggressive surgical approach, GBC remains a fatal illness in most patients.

A. **Cholecystectomy** is the only effective treatment. The best chance for long-term survival is the serendipitous discovery of an early cancer at the time of cholecystectomy. Radical cholecystectomy or resection of adjacent structure has not resulted in better survival.

B. **RT** appears to have no added benefit in the adjuvant setting, although the only reports of such therapy have been small retrospective series. Intraoperative RT has been reported to be of benefit in several small series of highly selected patients. RT may be useful as a primary treatment (without surgical resection) using either external-beam RT alone or external-beam RT plus ^{192}Ir implants. RT may relieve pain in a small number of patients.

C. **Chemotherapy.** The data on adjuvant systemic chemotherapy are anecdotal. 5-FU–based combinations are most commonly used, but the response rates are poor. Anecdotal reports of hepatic arterial infusion of chemotherapy have also claimed benefit in highly selected patients.

Extrahepatic Bile Duct Cancer

I. Epidemiology and etiology

A. **Epidemiology.** Bile duct carcinomas (BDCs, cholangiocarcinomas) are rare and occur with equal frequency in men and women at the average age of 60 years. In American Indians, Israelis, and Japanese, the incidence of BDC is 6 to 7 per 100,000 population, compared with 1 per 100,000 among the U.S. population. Tumors arising from the intrahepatic bile ducts are discussed with liver cancers. BDC accounts for less than one third of biliary tract cancers; GBC is the most common type. Half of patients with BDC have undergone cholecystectomy for cholelithiasis.

B. **Etiology and risk factors.** An increased incidence of BDC has been reported in patients with Crohn's disease, choledocholithiasis, cystic fibrosis, chronic long-term ulcerative colitis, sclerosing cholangitis, and *Clonorchis sinensis* infestation. The incidence is also reportedly increased in patients with congenital anomalies of the intrahepatic and extrahepatic bile ducts (e.g., cysts, congenital dilation of the bile ducts, choledochal cyst, Caroli's disease [congenital cystic dilation of multiple sections of the biliary tree], congenital hepatic fibrosis, polycystic disease, abnormal pancreaticocholedochal junction). Conditions that cause chronic bile duct stasis and infection are linked to increased risk for BDC. A history of exposure to the outmoded contrast agent Thorotrast has also been associated with BDC.

II. Pathology

A. **Histology.** Malignant tumors of the bile ducts are adenocarcinoma in 95% of cases. Microscopically, BDCs generally extend to 1 to 4 cm beyond the gross margin of the tumor. Multiple foci of carcinoma *in situ* may be noted. Other malignant tumors that involve the bile ducts include anaplastic and squamous carcinomas, cystadenocarcinomas, primary malignant melanoma, leiomyosarcoma, carcinosarcoma, and metastatic tumors (particularly breast cancer, myelomas, and lymphomas). See Liver Cancer, section II.A.4, section II.A.5 and section II.A.6.

B. **Location.** BDCs are divided anatomically into those that arise from the intrahepatic upper third of the biliary tract, including the hilum (50% to 70% of all tumors); the middle third (10% to 25%); the lower third (10% to 20%); and the cystic duct (less than 1%). Tumors found near the junction of the right and left hepatic duct (Klatskin's tumors) are usually small and may be inconspicuous at laparotomy. Adenocarcinomas located in the right and left hepatic ducts or common hepatic duct are frequently scirrhous, constricting, diffusely infiltrating, or nodular and may mimic sclerosing cholangitis or stricture. Adenocarcinomas of the common bile duct or cystic duct are more often fungating and may have a better prognosis. Carcinoma of the cystic duct is rare, and distention of the gallbladder occurs before jaundice becomes apparent.

III. Diagnosis

A. **Symptoms.** Jaundice is present in 90% of patients. Abdominal pain, weight loss, fever, malaise, or hepatomegaly occurs in half of cases. Patients with proximal tumors in the upper third of the biliary tract usually have symptoms for twice as long as those with tumors in the lower third. Ascites, spider angiomas, and splenomegaly are seen in less than 3% of patients.

B. **Laboratory studies**
1. **Serum chemistries.** Serum bilirubin levels greater than or equal to 7.5 mg/dL are found in 60% of cases, alkaline phosphatase greater than twice normal in 80%, and elevation of transaminase and prothrombin time in 25%.
2. **Tumor marker.** Serum CA 19-9 is elevated in 90% of patients.
3. **Radiologic examination**
   a. **Abdominal ultrasound** shows dilation of the common bile duct or intrahepatic biliary ducts.
   b. **CT or MRI** may reveal a mass and suggest the site or origin of carcinoma.
   c. **PTHC** is the most specific test for proximal bile duct lesions.
   d. **ERCP** is the best diagnostic test for distal bile duct tumors.
   e. **Angiography and portovenography** are useful in determining the extent of the disease for the preoperative evaluation of resectability.

IV. Staging and prognostic factors

A. **Staging.** Readers should consult an up-to-date staging manual because of frequent revisions of staging systems. All patients should be initially staged so that those with unresectable tumors are not subjected to needless surgery. If PTHC shows that the tumor extends into the parenchyma of both the right and left lobes of the liver, the tumor is unresectable, and no surgery is performed. If angiography shows encasement of the main portal vein or hepatic artery, the tumor is also unresectable. If, however, the tumor extends into only one lobe, or if there is involvement of one branch of the portal vein or hepatic artery, surgical exploration is considered with the possibility of adding hepatic lobectomy to the hepatic duct resection. The criteria (Blumgart's) for unresectability are as follows:
1. Bilateral intrahepatic duct involvement
2. Entrapment of the main trunk of the portal vein
3. Bilateral invasion of the branches of the portal vein or hepatic artery
4. Ductal involvement in the contralateral lobe

B. **Prognostic factors.** The poor prognostic variables with statistical significance are mass lesion, cachexia, poor performance status, serum bilirubin greater than or equal to 9 mg/dL, multicentric disease, hilar or proximal sites, high tumor grade, sclerotic histology, liver invasion, lymph node involvement, and advanced stage.

V. Management

A. **Surgical resection** is the only treatment that may result in long-term survival. In specialized medical centers, about 45% of patients who are explored undergo complete resection with no gross tumor left behind, 10% undergo incomplete resection, and 45% have tumors that are not resectable. Tumors in the middle and distal ducts have a higher resectability rate than tumors in the proximal ducts, which have a maximal resectability rate of 20%. The median survival of patients whose tumors are resected for cure is 11 to 33 months, and the 5-year survival rate is about 12%. The 30-day operative mortality rate may be as high as 25%. The high postoperative complication rate includes wound infection, cholangitis, liver abscess, subphrenic abscess, pancreatitis, and biliary fistulas. Orthotopic liver transplantation has been attempted and can result in long-term survival in up to 20% of highly selected patients with disease limited to the liver.

B. **Adjuvant therapy** has been advocated to reduce the high incidence of local recurrence (up to 100%), but it does not appear to improve survival after curative resection. The role of adjuvant RT remains unclear. Cholangiocarcinoma is radiosensitive, but bile duct tolerance to radiation is limited. The complications of RT include biliary and duodenal stenosis. The results of small series of selected patients treated with 5-FU combined with RT have led some authors to advocate this as an adjuvant to surgery or in cases with locally advanced and unresectable disease.

C. **Biliary tract bypass**
1. **Surgical biliary tract bypass** is carried out predominantly in those patients whose tumors are found to be unresectable at operation. Biliary-enteric anastomosis is usually performed using a Roux-en-Y jejunal loop. The operative mortality rate ranges from 0% to 30%, and the median survival varies from 11 to 16 months. The theoretical advantage of operative drainage is the decreased potential for recurrent cholangitis.
2. **Surgical stenting.** T-tube or U-tube catheters can be passed through the obstruction. A T-tube is hard to replace when it becomes clogged. The advantage of a U-tube is that both of its ends are externalized separately, easing replacement when the tube becomes obstructed. The 30-day mortality rate for operative stenting varies from 10% to 20%.
3. **Endoscopic stenting** has two advantages: a decreased morbidity and no creation of external fistulization. This method is more successful with distal bile duct tumors and is associated with a 30-day mortality rate of 10% to 20%.
4. **Percutaneous stenting** to provide drainage, either as externalized stent or an endoprosthesis, is associated with a 30-day mortality rate of 15% to 35%.

D. **Other methods of treatment**
1. **Liver transplantation** is not considered appropriate because of the high incidence of local recurrence.
2. **RT** appears to have some effect on the tumor size and may relieve jaundice in patients without biliary stenting. RT may be used (usually with biliary stenting) either as primary treatment or as adjuvant therapy. Conventional external-beam RT has the advantage of giving a moderately high dose of radiation (5000 to 6000 cGy) to a relatively large volume of tissue and is more effective in treating bulky tumor masses. Implantation with ^{192}Ir seeds (effective radius of 1 cm from the seeds) delivers high-dose RT to localized residual disease after surgical resection or may provide palliation to patients with bile ducts obstructed by tumor. The typical dose with ^{192}Ir seeds is 2000 cGy.
3. **Chemotherapy** is of little benefit. 5-FU has a response rate of 15%. Other agents with some efficacy include mitomycin C and doxorubicin. Combinations of 5-FU with nitrosoureas showed no better responses than are observed with single-agent treatment.

Cancer of the Ampulla of Vater

I. Pathology. Carcinoma of the ampulla of Vater is a papillary neoplasm arising in the last part of the common bile duct where it passes through the duodenum. Distinction between true ampullary tumor and periampullary tumors originating in the duodenal mucosa or pancreatic ducts is important because the periampullary cancers have a poor prognosis compared with ampullary cancers. The differentiation may be made by examination of the mucins they produce. Ampullary cancer produces sialomucins, whereas periampullary cancers produce sulfated mucins.

II. Staging system and prognostic factors The TNM staging system is used to stage ampullary cancer. The prognosis of patients with ampullary carcinoma is better than that of patients with cancer arising in any other site in the biliary tree. Pancreatic invasion and lymph node metastasis are the two most important prognostic factors. The 5-year survival rate is in excess of 50% when no nodal metastasis and no invasion of the pancreas have occurred. Nodal metastasis occurs much more frequently in patients with tumors larger than 2.5 cm.

III. Management. Surgery is the only curative treatment modality for ampullary carcinoma. Pancreaticoduodenal resection (Whipple's procedure or a modification) is the surgical procedure of choice. The 5-year survival rate ranges from 5% to 55% depending on lymph node involvement, invasion of the pancreas, and histologic differentiation. Ampullectomy (local ampullary excision) performed on poor-risk patients with apparently localized disease is associated with a 10% 5-year survival rate.

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Chapter 10 Breast Cancer

Charles M. Haskell and Dennis A. Casciato

I. Epidemiology and etiology

A. **Incidence**
   1. Breast cancer is the most common lethal neoplasm in women. The American Cancer Society (ACS) has estimated that breast cancer will constitute 29% of all new malignant neoplasms and 16% of deaths from cancer in women. The annual incidence of breast cancer in the United States increases dramatically with age (5 per 100,000 population at 25 years of age, rising to 150 per 100,000 at 50 years of age and to more than 200 per 100,000 at 75 years of age).
   2. The incidence of male breast cancer is about 2.5 per 100,000 population. Fewer than 1% of all breast cancer cases occur in men.
B. **Etiology.** Breast cancer is the result of mutations in one or more **critical genes**. Two genes in women on chromosome 17 have been implicated. The most important gene is called *BRCA-1* (at 17q21); the other is the *p53* gene (at 17p13). A third gene is the *BRCA-2* gene on chromosome 13. A fourth gene implicated in the etiology of breast cancer is the androgen-receptor gene, found on the Y chromosome. Mutations of the latter gene have been associated with several cases of male breast cancer but not female breast cancer.

The best established etiologic agent in breast cancer is exposure to **radiation**. A viral cause has also been postulated but never proved in humans. Complex experimental and epidemiologic evidence points strongly to the influence of **hormones** and **diet** in the pathogenesis of breast cancer. The variation of incidence of breast cancer in different populations is highly correlated with consumption of dietary fat, dietary sugar, or parity in 75% of cases affecting postmenopausal women and in about 50% of cases affecting premenopausal women.

   1. **Diet.** Diets in Western countries typically have a high content of fat and sugar. The dietary contents of both fat and total calories independently are strongly correlated with the incidence of breast cancer. Women from Western countries have about six times the risk for breast cancer as do women from Asian or underdeveloped countries. The low breast cancer rate in Asian women may also relate to the higher oral intake of phytoestrogens in Asia than in the United States and Europe.

   The risk for breast cancer increases progressively with age except in countries with low-fat diets, where the risk is stabilized or decreased in older women. The risk changes accordingly when populations move from a low-risk country to a high-risk country and adopt the dietary habits of the new country. It is likely, however, that the effect of diet on breast cancer incidence occurs at an early age, such as in childhood or adolescence. No data in humans prove that changing from a high-fat diet to a low-fat diet later in life reduces the risk for breast cancer.

   2. **Hormones.** There is ample evidence implicating hormones in the cause of breast cancer, but the role of individual hormones is uncertain. High prolactin levels are clearly related to the development of breast cancer in animal models, but epidemiologic evidence is conflicting, and a causative relationship between prolactin and breast cancer has not been proved in humans. Estrogens, either alone or in combination with progestins in various oral contraceptive preparations, are also of concern. Short-term studies have shown no increased risk for breast cancer from oral contraceptives, whereas other studies suggest that long-term use may increase the risk for breast cancer in young women.
   3. **Links between diet and hormones.** Differences in estrogen and prolactin levels in female populations correlate with differences in dietary fat; that is, high-fat diets are associated with increased hormone secretion. Furthermore, obesity is associated with increased adrenal production of androstenedione, which is converted to estrogens in adipose tissue; this source of production and conversion continues after menopause. Finally, tumor-promoting steroid hormones are also fat soluble and likewise may be accumulated in breast tissue.
   4. **Hereditary breast cancer.** Familial aggregations of breast cancer occur in about 18% of cases, but only about 5% of cases can be considered truly familial based on extended pedigree analysis. Most of these are due to mutations in the *BRCA-1* and *BRCA-2* genes. The disease tends to occur at an earlier age and to be bilateral in patients with familial breast cancer. It can also be associated with carcinomas developing in other organs (especially the colon, ovary, or uterus) or with other rare cancers (sarcomas, brain, leukemia, adrenal glands) as part of the Li-Fraumeni syndrome associated with mutations in the *p53* gene. Familial transmission can occur through either the maternal or paternal germ line as an autosomal dominant trait. In such families, the lifetime risk of women developing breast cancer is at least 50%. Features in the history of a patient that increase the liklihood of having *BRCA* mutations include the following:
      a. Multiple cases of early onset breat cancer in the family
      b. Ovarian cancer with family history of breast or ovarian cancer
      c. Breast and ovarian cancer in the same woman
      d. Bilateral breast cancer
      e. Ashkenazi Jewish heritage
      f. Male breast cancer
C. **Risk factors for breast cancer**
   1. **High-risk factors** (three-fold or more increase)
      a. **Age** (older than 40 years of age)
      b. **Previous cancer in one breast,** especially if it occurred before menopause
      c. **Breast cancer in the family.** Increased occurrence of breast cancer is seen in mothers, daughters, and sisters particularly, but also in aunts, cousins, and grandmothers. Mothers, daughters, and sisters of women who develop bilateral or unilateral breast cancer before menopause are at higher risk for developing breast cancer.
      d. **Hyperplasia with atypia.** Most forms of benign breast disease do not predispose patients to the subsequent development of breast cancer. This is especially true of "fibrocystic disease." Women with proliferative disease of the breast with atypical hyperplasia (atypia) are at increased risk for developing breast cancer (five-fold increase), however. The risk for atypia is greater in patients with a strong family history of breast cancer (11-fold increase).
      e. **Parity.** Women who are nulliparous or who were first pregnant after the age of 31 years are three to four times more likely to develop breast cancer than those who complete the first pregnancy before the age of 18 years.
      f. **Lobular carcinoma** *in situ* carries a 30% risk of invasive cancer.
      g. **Risk factors in men.** Klinefelter's syndrome, gynecomastia, and family history of male breast cancer
   2. **Intermediate risk factors** (1.2- to 1.5-fold increase)
      a. Menstruation history:
         1. Early menarche
         2. Late menopause
      b. Oral estrogens (see) in women
      c. History of cancer of the ovary, uterine fundus, or colon
      d. Diabetes mellitus
      e. Use of alcoholic beverages
   3. **Factors known to decrease risk**
      a. Asian ancestry
      b. Term pregnancy before age 18 years of age
      c. Early menopause

d. Surgical castration before the age of 37 years
4. **Factors having no effect on risk** (previously thought to be risk factors): multiparity, lactation, and breast feeding

II. Pathology and natural history

A. **Histology** may influence treatment decisions, but the stage of disease is usually more important. Poorly differentiated tumors (high-grade) have a worse prognosis than well-differentiated (low-grade) tumors. Inflammatory carcinoma has a poor prognosis, irrespective of stage. For patients with negative nodes, a group of "special tumor types" is associated with a better prognosis (typical medullary, mucinous, papillary, and pure tubular types). For early disease without lymph node involvement (stage I), the 5-year survival rate is about 80% for invasive ductal carcinomas and 90% to 95% for invasive lobular, comedocarcinomas, and colloid carcinomas.
   1. **Ductal adenocarcinoma** (78%) tends to be unilateral. Invasive ductal carcinoma can occur with and without scirrhous components; nearly all male breast cancer is of this type. Noninvasive ductal adenocarcinoma (also called *ductal carcinoma* in situ or *intraductal carcinoma*) usually occurs without forming a mass because there is no scirrhous component.
   2. **Lobular carcinoma** (9%). About half of the cases of lobular carcinoma are found *in situ* without any sign of local invasion (this disease is considered premalignant by some authorities and has been termed *lobular neoplasia*). Lobular carcinoma is associated with an increased risk for bilateral breast cancer (about one third of cases). The classic form of the disease (including the alveolar and mixed variants) is frequently bilateral, but otherwise it has a somewhat better prognosis than infiltrating ductal carcinomas. The solid and signet-ring cell variants have a worse prognosis than infiltrating ductal carcinoma because of a high propensity to metastasize as a diffuse or finely nodular infiltrate in the retroperitoneum with prominent desmoplastic (fibrotic) reaction. Taking all forms of invasive lobular carcinoma as a group, the overall prognosis is about the same as for infiltrating ductal carcinoma.
   3. **Special types with a good prognosis** (10%). Pure papillary, tubular, mucinous, and typical medullary carcinomas. Adenocystic carcinomas may qualify as well, but they are sufficiently rare for this to be uncertain.
   4. **Comedocarcinoma** (5%). Ducts packed with small cell tumor and central debris
   5. **Medullary carcinoma** (4%). Undifferentiated cells with a heavy lymphocytic infiltrate
   6. **Colloid carcinoma** (3%). Duct is blocked with inspissated carcinoma cells, and proximal cysts develop.
   7. **Inflammatory carcinoma** (1%). Poorest prognosis. Lymphatics become packed with tumor, leading to breast and skin changes that mimic infection.
   8. **Paget's disease of the breast.** Unilateral eczema of the nipple; always associated with ductal carcinoma in women. Prognosis is good if detected before a mass is present.
B. **Mode of spread.** Breast cancers spread by contiguity, lymphatic channels, and blood-borne metastases. The most common organs involved with symptomatic metastases are regional lymph nodes, skin, bone, liver, lung, and brain.
C. **Lymph node metastases**
   1. Axillary lymph node metastases are present in 55% to 70% of patients at the time of diagnosis when not detected by screening mammography. Clinically normal axillae have histologic evidence of metastases in 40% of patients.
   2. Axillary dissections lead to removal of an average of 15 to 20 lymph nodes (range, 0 to 80). The prognosis depends on the number of histologically positive nodes found and is independent of the number of nodes removed.
   3. The number of nodes found to contain tumor increases by up to 30% with meticulous serial sectioning. The use of immunohistochemical techniques may result in finding an even larger number of nodes with "micrometastases."
   4. Tumors that grow fast are more likely to metastasize to lymph nodes than tumors that grow slowly.
   5. Tumor size is closely associated with the presence of axillary metastases.

Tumor size (cm)	Patients with four or more positive lymph nodes (%)
<1	25
1–2	35
2–3	50
>3	55–65

   6. Internal mammary nodes have evidence of tumor in 26% of patients with inner quadrant lesions and 15% with outer quadrant lesions. Mammary node metastases rarely occur in the absence of axillary node involvement.
D. **Natural history.** *Breast cancer is a heterogeneous disease, which grows at very different rates in different patients and is often a systemic disease at the time of initial diagnosis.* Evidence for this statement is as follows:
   1. **The tumor doubling time (TDT) of breast cancer.** A 1-cm breast tumor contains about 10^9 cells and has undergone 30 of the 40 doublings that will occur before the patient dies. The TDT of primary breast cancer varies from 25 to 200 days for early lesions, but in advanced disease, the TDT may exceed 500 days. Thus, a 1-cm tumor may have been present for 2 to 17 years before diagnosis.
   2. **Prognosis is influenced by biochemical markers**
      a. Endocrine tissues contain receptors for critical hormones. Receptors for estrogen (ER) and progesterone (PgR) should be routinely assessed in breast cancer specimens because they are useful in choosing therapy (see section VI.B.1) and their presence predicts a better prognosis.
      b. Measurements of aneuploidy and rapid cell division (e.g., high S phase on flow cytometry) appear to predict for early recurrence and early death.
      c. Numerous biochemical changes in breast cancer tissue have been proposed to influence prognosis, including HER-2/ *neu,* cathepsin D, heat-shock protein, and *p53.* None has been firmly established as an independent prognostic factor, but this area continues to undergo investigation.
   3. **Local measures have only a limited effect on survival.** Untreated patients have a median survival of 2.5 years. Patients treated with mastectomy or RT have an improved survival expectancy over untreated patients. However, they continue to die at a faster rate than age-matched controls for the first 20 years after treatment. Whatever the cause of death, 75% to 85% of patients with a history of breast cancer have evidence of the tumor at autopsy.
   4. **Removal of a primary tumor does not substantially alter the risk of metastases.**
      a. Distant metastases are present in two thirds of breast cancer patients at the time of diagnosis.
      b. Variation in local therapies (radical, modified radical, or simple mastectomies with or without RT) does not alter survival results.
      c. Patients with axillary lymph node metastases have a high rate of relapse with distant metastases despite complete removal of all local tumor.
      d. Breast cancer that recurs locally is associated with distant metastases in 90% of cases.
   5. **Regional lymph nodes are harbingers of systemic disease and not barriers to tumor spread.**
      a. Removal of axillary nodes at surgery does not affect the frequency of recurrence, the development of distant metastases, or survival rates.
      b. Half of all patients with four or more positive axillary nodes have clinical evidence of metastatic disease within 18 months.
      c. The 10-year survival rate is about 65% for patients without axillary node metastases, 40% with one to three positive nodes, and 15% with four or more positive nodes.
E. **Associated paraneoplastic, metabolic, and neoplastic problems**
   1. **Nonmalignant conditions** that may be associated with breast cancer
      a. Dermatomyositis (breast cancer is the most commonly associated malignancy, and treatment of the cancer has been associated with resolution of dermatomyositis)
      b. Acanthosis nigricans
      c. Cushing's syndrome (rare)
      d. Paraneoplastic neuromuscular disorders
      e. Hypercalcemia (only in the presence of metastases)
      f. Hemostatic abnormalities (rare)
   2. **Second malignancies** in patients with breast cancer
      a. Ovarian cancer, especially in familial breast cancer
      b. Colorectal carcinoma

III. Diagnosis

A. **Physical findings and differential diagnosis**
   1. **Breast lumps** are detectable in 90% of patients with breast cancer and constitute the most common sign on history and physical examination. The typical breast cancer mass has a **dominant character** and tends to be solitary, unilateral, solid, hard, irregular, nonmobile, and nontender.
   2. **Spontaneous nipple discharge** through a mammary duct is the second most common sign of breast cancer. Nipple discharge develops in about 3% of women and 20% of men with breast cancer but is a manifestation of benign disease in 90% of patients. Discharge in patients older than 50 years of age is more likely to represent cancerous rather than benign conditions. The character of nipple discharge is helpful in establishing a diagnosis (Table 10.1).

Table 10.1 Nipple discharges

a. **Discharges treated medically.** Milky discharges are galactorrhea, purulent discharges are due to infection, and multicolored or sticky discharges represent duct ectasia. These types of discharge are rarely associated with cancer. Duct ectasia (comedomastitis) appears as burning, itching, and pain associated with palpable subareolar, tortuous, tubular swellings.

b. **Discharges treated surgically.** Serous, serosanguineous, bloody, or watery discharges may represent intraductal papilloma (usually characterized by nipple discharge without a mass), cysts, or cancer; surgical exploration is imperative.

3. **Other presenting manifestations** include skin changes, axillary lymphadenopathy, or signs of locally advanced or disseminated disease. A painful breast is a common symptom but is usually a result of something other than the cancer. Paget's carcinoma appears as unilateral eczema of the nipple. Inflammatory carcinoma appears as skin erythema, edema, and underlying induration in the absence of infection.

4. **Benign lesions resembling breast carcinoma**
   a. **Lumps.** Fibrous tumors, lymphadenitis, calcified fibroadenomas, myoblastomas, posttraumatic fat necrosis, residual inflammatory masses, complex cysts, plasma cell mastitis (sequelae of duct ectasia)
   b. **Nipple discharges** (see section III.A.2)
   c. **Skin and nipple changes.** Inflammatory diseases, superficial thrombophlebitis (Mondor's disease)

B. **Evaluation after discovery of a suspected mass**
   1. **Biopsy.** Any new or previously unevaluated breast mass in any woman of any age that has a "dominant" character must undergo biopsy without delay.
      a. **Fine-needle aspiration cytology** may be performed if both technical and cytopathologic expertise are available. The method is easy, quick, and safe. "Seeding tumor cells along the needle track" is not a consideration in breast cancer. The sensitivity in diagnosing malignancy has been reported to be 90% to 95%, with almost no false-positive results (98% specificity).
      b. **Ultrasound or stereotactic core biopsy.** These techniques are increasingly used as an alternative to excisional biopsy by a surgeon.
      c. **Excisional biopsy.** The National Institutes of Health Consensus Development Program recognizes a two-step procedure as the standard practice. A diagnostic biopsy specimen should be studied with permanent histologic sections before definitive treatment alternatives are discussed with the patient. The exception to this practice would be for a patient who insists on mastectomy immediately; these patients should undergo complete staging procedures before the biopsy is undertaken.
         1. Patients should be informed that most breast lumps are benign, but the possibility of cancer is real.
         2. The biopsy should excise the tumor if it is small.
         3. Fresh tissue should be sent for ER, PgR, and histologic evaluation.
   2. **Cyst aspiration.** Patients with a soft, rounded, movable mass are likely to have a cyst that can be managed with aspiration. Local anesthetics may distort the ability to feel if a mass has resolved after aspiration and should therefore be avoided. After aspiration has been attempted, it is necessary to obtain a biopsy specimen under the following circumstances:
      a. No fluid can be aspirated.
      b. Fluid is aspirated, but a mass remains palpable.
      c. The fluid is bloody.
      d. The mass recurs at a 2-week follow-up examination.
      e. The cytology examination of the fluid (if obtained) reveals malignancy; these patients require definitive cancer treatment.
   3. **Mammography** detects 85% of breast cancers. A distinction must be made between diagnostic mammography and screening mammography (as discussed in section V.B.3). Although 15% of breast cancers cannot be visualized with mammography, 45% of breast cancers can be seen on mammography before they are palpable. A normal mammographic result must not dissuade the physician from obtaining a biopsy of a suspicious mass.
      a. **Clear indications for mammography**
         1. Evaluation of suspected benign or malignant breast disease, including an assessment of apparently normal breast tissue in patients with a dominant mass
         2. Evaluation of the contralateral breast in patients with documented breast cancer
         3. Follow-up of patients with prior breast cancer
         4. Follow-up of patients with premalignant breast disease (gross cystic disease, multiple papillomatosis, lobular neoplasia, and severe atypia)
      b. **Other possible indications for mammography**
         1. Evaluation of breasts that are difficult to examine
         2. Workup of metastatic adenocarcinoma from an unknown primary
         3. Evaluation of patients at high risk for breast cancer (especially patients with prior breast augmentation with silicone and patients with a strong family history of breast cancer)
         4. Screening for breast cancer (see section V.B).
      c. **Mammographic signs of malignancy** (sensitivity is about 75% and specificity almost 90%)
         1. Calcium deposits, unless in a mulberry (fibroadenoma) or curvilinear (cystic disease) pattern
         2. Mammary duct distortion or asymmetry
         3. Skin or nipple thickening
         4. Breast mass

C. **Pretreatment staging procedures**
   1. Complete blood count, liver function tests, calcium and phosphorous levels
   2. Chest radiograph, mammography
   3. Liver scan (usually by computed tomography) and bone scan with plain film correlation are performed routinely for clinical stage II, III, and IV disease but are not usually indicated for patients with clinical stage I disease unless symptoms, signs, or biochemical tests suggest an abnormality.
   4. Bone marrow aspiration if there is unexplained cytopenia or leukoerythroblastic blood smear

D. **Tumor markers.** The blood CEA and CA 27.29 (CA 15-3) levels may be useful to follow response to treatment in advanced disease.

IV. Staging system and prognostic factors

A. **Staging system.** The standard staging system for breast cancer is the TNM system (Table 10.2). Regional disease (stage III) is now separated into operable (IIIA) and inoperable disease (IIIB). "Relative survival" rates for each of the stage groupings are also shown in Table 10.2.

Table 10.2 Postoperative-pathologic TNM staging system for breast cancer

B. **Prognostic factors and approximate survival**
   1. **Clinical stage**

Clinical stage	Five years (%)	Ten years (%)
0	>90	90
I	80	65
II	60	45
IIIA	50	40
IIIB	35	20
IV and inflammatory breast cancer	10	5

   2. **Histologic involvement of axillary lymph nodes** (survival rates shown are for those not treated with adjuvant chemotherapy)

Axillary lymph nodes	Five years (%)	Ten years (%)
None positive	80	65
1–3 positive nodes	65	40
>3 positive nodes	30	15

   3. **Tumor size**

Size of tumor (cm)	Ten years (%)
<1	80

3–4	55
5–7.5	45

4. **Histology.** Patients with poorly differentiated, metaplastic, or high-grade malignancies have a poorer prognosis than those with tumors that are well differentiated or of low grade. See also section II.A.
5. **Hormone receptors.** Patients with ER-positive tumors have longer survival times than patients with ER-negative tumors.

V. Screening and early detection

A. **Prophylactic mastectomy** can be considered only for very high-risk groups. Even "total mastectomy" can leave breast tissue behind; hence, there is no guarantee that breast cancer will truly be prevented by mastectomy.
   1. **Prophylactic simple mastectomy and reconstructive surgery** can be considered for the following patients:
      a. **Patients with benign breast disease and a family history of bilateral, premenopausal breast cancer** (see section I.C.1.c). These patients need to have biopsies done frequently on suspected masses, but the results usually are benign. The morbidity of repeated biopsies may be offset by a definitive procedure. The patient must be informed that even a "total" mastectomy leaves residual breast tissue *in situ* and thus does not guarantee prevention of later breast cancer.
      b. **Patients with a previous history of breast cancer and fibrocystic disease in the remaining breast**
      c. **Patients with lobular carcinoma** *in situ*
   2. **Age for prophylactic mastectomy.** The appropriate age is not well defined. Such patients should be apprised of the risks involved, followed carefully, and be prepared to consider prophylactic mastectomy after they reach 30 years of age.
B. **Screening** women for breast cancer is controversial because the long-term survival advantage of detecting small lesions early is not established. The most aggressive recommendations for screening are those of the American Cancer Society (ACS). They are briefly summarized here for reference.
   1. **Monthly self-examination** for all women older than than 20 years of age. Premenopausal women should perform the examination 5 days after the end of the menstrual cycle; postmenopausal women should examine themselves on the same day each month.
   2. **Physical examination** by a physician every 3 years for women between 20 and 40 years of age and annually for women older than 40 years of age.
   3. **Mammography.** Current mammographic techniques using dedicated film screen equipment expose the breast to 0.02 cGy for a two-view study; xeromammography increases this dose two- to three-fold. An exposure of 1 cGy is expected to increase the risk for breast cancer by six cases per 1 million population.
      a. Annual mammograms have been demonstrated to reduce breast cancer mortality in women older than 50 years of age.
      b. The ACS recommends a mammogram as a baseline for women 35 to 39 years old, mammograms every 1 to 2 years for women 40 to 49 years old, and mammograms yearly for women 50 years of age and older.
      c. The National Cancer Institute makes no recommendations for mammographic screening before 50 years of age but does recommend annual mammography after 50 years of age.

VI. Management: disseminated disease (stage IV)

The responses of metastasized breast cancer to systemic therapy provide the foundation for adjuvant therapy of earlier stages of disease. Thus, the management of advanced disease is presented first in this chapter. For most patients, either chemotherapy or endocrine therapy is given as initial treatment for documented disseminated breast cancer. A flow diagram for the selection of systemic therapy is shown in Fig. 10.1.

Figure 10.1 Flow diagram for the management of advanced breast cancer.

A. **Predictive factors for response to therapy.** ER and PgR activities are the most predictive factors for response to hormonal therapies for primary and metastatic breast cancer. There are no validated predictive factors for response to chemotherapy, although tumor expression of HER-2/*neu* may be the first exception. Patients whose tumors have a low or undetectable level of HER-2/*neu* appear to derive considerable benefit from regimens containing cyclophosphamide, methotrexate, and 5-fluorouracil (CMF regimen). Conversely, patients whose tumors overexpress HER-2/*neu* appear not to derive benefit from CMF, are less likely to respond to hormone therapy even if they are ER positive, but appear to achieve a significantly improved clinical outcome when treated with regimens that contain doxorubicin (Adriamycin).
B. **Endocrine therapy** is used for patients whose life is not in immediate danger from advancing cancer. Patients who develop recurrent disease within 1 year of primary treatment usually have rapidly growing tumors and have a poor response to endocrine treatments.
   1. **The hormone receptor status** of the tumor should be positive or unknown before embarking on endocrine manipulations. The response rate varies directly with which receptors are positive and the amount of ER and PgR activity that is present (Table 10.3). Patients with receptor-negative tumors usually should not be treated initially by endocrine manipulation because response is unlikely (less than 10%).

Table 10.3 Response rates of metastatic breast cancer to hormonal treatment are related to activities of estrogen receptor (ER) and progesterone receptor (PgR) in the tumor specimen

   2. **Anti-estrogens.** Tamoxifen citrate (Nolvadex) is basically an antiestrogen and the first endocrine therapy used in patients with ER-positive or ER-unknown tumors, regardless of the patient's age. Tamoxifen (20 mg PO once daily) is given continuously until relapse occurs. Toremifene appears to be similar to tamoxifen but has a much smaller experience in treatment. Raloxifene is inferior to tamoxifen in clinical trials but is approved for use in the treatment of osteoporosis.
   3. **Aromatase inhibitors** block the conversion of androgens to estrogens. Anastrozole (Arimidex, 1 mg PO once daily) and letrozole (Femara, 2.5 mg PO once daily) are alternative second-line endocrine agents to megestrol acetate for the treatment of breast cancer. Other similar agents are undergoing study. The spectrum of side effects from these agents is similar to that of tamoxifen, but side effects are usually less frequent with the former drugs than is the case with tamoxifen. Aminoglutethimide is a nonselective inhibitor and has been largely replaced by the newer agents.
   4. **Megestrol acetate** (Megace, 40 mg PO four times daily) is a progestin and an excellent second- or third-line choice of endocrine therapy for eligible patients.
   5. **Fourth-line endocrine agents.** An androgen (fluoxymesterone, 10 mg four times daily) or estrogen (diethylstilbestrol, 5 mg three times daily) can be used in patients who respond to and then fail to respond to treatment with tamoxifen, an aromatase inhibitor, and megestrol acetate but who show metastatic disease that still mandates endocrine therapy.
   6. **Ovarian ablation** is still used by some practitioners to treat premenopausal women with relapsed breast cancer who are ER positive. Sterilization can be accomplished by surgery or radiation therapy (RT), although if the latter modality is used, the lapse of time until response occurs is longer, and the response may be incomplete. Medical castration with a luteinizing hormone–releasing hormone agonist (leuprolide or goserelin) may also be considered in premenopausal women.
   7. **Adrenalectomy or hypophysectomy** can cause difficult problems in medical management. Other therapeutic choices are preferable.
   8. **Hypercalcemic crises or worsening bone pain after hormonal therapy** can occur. This "endocrine flare" is evidence of a hormonally responsive cancer. It is usually worthwhile to continue the treatment with hormones while treating the hypercalcemia. If hypercalcemia is refractory to treatment, the endocrine therapy should be discontinued and cytotoxic chemotherapy undertaken.
   9. **A worsening bone scan in a clinically improving patient** may follow endocrine therapy of any type. The worsening probably reflects healing of diseased bone associated with increased or new uptake of isotopic tracers. This situation commonly indicates successful therapy, which should be continued.
C. **Chemotherapy**
   1. **Indications**
      a. Patients who are ER-negative
      b. Patients who are ER-positive and who fail endocrine therapy
      c. Patients with life-threatening disease: lymphangitic dissemination in the lungs, liver metastases, or rapidly advancing cancer in any site
   2. **Choice of cytotoxic agents.** Many cytotoxic agents used singly are effective in achieving partial (rarely complete) response in 20% to 35% of cases. Remission commonly lasts 4 to 6 months. The most effective single agents are doxorubicin and the taxanes (paclitaxel or docetaxel). Docetaxel is particularly helpful in patients with liver metastases.

3. **Combinations of cytotoxic agents** (Table 10.4). The CMF regimen is a good choice for initial treatment, especially the "classic" version when combined with prednisone. Response rates of about 60% can be expected with a median duration of a year or more. The doxorubicin (Adriamycin) combinations of CA and FAC are also effective. The combination of doxorubicin with paclitaxel is reported to have much a higher response rate that requires confirmation.

Table 10.4 Chemotherapy regimens for breast cancer

4. **Failure of combination chemotherapy.** After failing CMF or CA, sequential single agents can be tried. Drugs for end-stage disease are paclitaxel (Taxol), docetaxel (Taxotere), fluorouracil, methotrexate, vinorelbine, mitomycin C, and prednisone.
5. **Herceptin** (anti–HER-2 monoclonal antibody), with or without concomitant cytotoxic agents, is useful in patients whose tumor overexpresses HER-2/ *neu* (*c-erbB-2*). Overexpression occurs in 25% to 30% of patients. The response rate to Herceptin when used alone is 15%, but the response is durable. Herceptin is synergistic with cytotoxic agents but significantly increases cardiotoxicity when used with doxorubicin.
6. **Bisphosphonates** are increasingly used to treat the hypercalcemia associated with malignant disease. Some trials suggest that bisphosphonates, particularly pamidronate, may also be useful in postponing "skeletal events," such as fractures or pain, in patients with breast cancer metastatic to bone.
7. **Bone marrow or stem cell transplantation** is of doubtful benefit for patients with advanced metastatic breast cancer.
D. **Local therapy for metastatic disease.** Metastatic disease is generally treated systemically, but some local problems benefit from local RT.
1. **Isolated painful bony metastases** usually respond well to local RT.
2. **Massive axillary metastases** usually require local RT, either with or without surgical resection.
3. **All cervical spine and femoral neck lesions** with or without symptoms should usually be treated with local RT. Femoral neck lesions may also require surgical fixation (see Chapter 33, section I).
4. **Brain and orbital metastases.** A few patients survive several years after RT.
5. **Chest wall recurrence.** These patients are generally treated first with systemic therapy. In some cases, RT may be used, especially when the patient is otherwise without evidence of disease.

VII. Management: locoregional treatment of breast cancer

A. **Carcinoma *in situ*** (CIS). Improvements in mammographic technique and the increased use of screening have resulted in a dramatically increased incidence of noninvasive breast tumors, particularly ductal CIS. About 30% of new breast cancer cases are CIS.
1. **Ductal CIS** (75% of cases) is clearly a malignant disease and recurs in about 35% of cases within 10 to 15 years if treated with excisional biopsy alone. The recurrence is invasive carcinoma in more than 25% of cases. When axillary node dissection has been performed, metastases have been found in less than 3% of cases. When mastectomy has been performed, the disease is multicentric (additional CIS lesions more than 2 cm away from the main lesion) in half of cases.
   a. The risk for recurrence is most increased by the presence and amount of comedo-type necrosis. Other factors that may increase the risk are high nuclear grade, tumor larger than 2 cm, and (perhaps) surgical margins that are involved with malignancy.
   b. Patients with small (less than 15 mm), well-differentiated (low-grade, noncomedo) lesions that are detected as microcalcifications on screening mammograms and that are removed with generous margins may require neither RT nor mastectomy.
   c. Mastectomy produces cure rates for intraductal CIS of greater than 90%. Mastectomy is usually necessary for patients with tumors that are larger or that have margins involved by tumor.
   d. Lumpectomy followed by RT appears to be as effective as mastectomy in treating patients who are motivated toward breast conservation and who have tumors that are small enough for total excision with clear margins and a residual breast that is cosmetically acceptable to the patient.
   e. Axillary node dissection does not appear to be necessary.
2. **Lobular CIS** (25% of cases; also called *lobular neoplasia*) is considered by many authorities to be a premalignant rather than a frankly malignant disease. This tumor tends to be multicentric and is commonly bilateral (about 30%). The risk for developing cancer is 20% to 30% in the affected breast and 15% to 20% in the contralateral breast. About 25% to 30% of patients with lobular CIS develop ductal CIS over 25 to 30 years. Treatment options include total mastectomy versus close follow-up with yearly mammograms and breast examinations by a physician every 4 months. High-risk patients may benefit from bilateral mastectomy.
B. **Limited local disease: stages I and II.** There is no clear-cut survival difference between total mastectomy with axillary node dissection ("modified radical mastectomy") and limited surgery ("lumpectomy," "tylectomy," "total gross removal" or "quadrantectomy") followed by definitive RT for the local treatment of breast cancer. In some cases, there are distinct medical reasons for choosing one form of local therapy over the other, and the patient should be so informed. However, the ultimate choice of therapy is strongly influenced by the personal values and fears of the individual patient, and the final choice is hers. The physician's primary responsibility is to help the patient decide by carefully describing the advantages and disadvantages of each treatment strategy. In either case, the Reach for Recovery Program of the ACS may facilitate the rehabilitation of the patient after the completion of primary therapy.
C. **Total mastectomy with axillary node dissection** (modified radical mastectomy) is the standard surgical procedure for patients who choose surgery as their only local treatment. Alternatively, some centers have replaced lymph node dissection with the "blue node" or "sentinel node" technique, which allows a more limited removal of lymph nodes for staging purposes and results in a lower rate of complications (particularly lymphedema). It is generally unnecessary to use adjunctive RT after this procedure unless there are large numbers of axillary lymph nodes involved by tumor or extensive lymphatic vascular invasion.
1. **Contraindications to surgery.** Patient cannot tolerate operation.
2. **Advantages of mastectomy**
   a. Mastectomy is the most efficient and reliable way to control local tumor.
   b. Mastectomy eliminates residual breast tissue that is at risk for a new primary neoplasm.
   c. If needed, adjuvant chemotherapy is much easier to administer after surgery than after RT.
3. **Disadvantages and complications of mastectomy**
   a. Lymphedema develops in about 5% of patients (see section VIII.A and section B); nerve damage may occur but is rarely significant.
   b. Cosmetic deformity, which can be largely corrected by reconstruction or managed by the use of a prosthesis
      1. **Indications for breast reconstruction** include the availability of adequate skin and soft tissue for a reasonable cosmetic result and realistic expectations on the part of the patient.
      2. **Contraindications to breast reconstruction** include inflammatory carcinoma, the presence of extensive radiation damage to the skin from prior treatment, unrealistic expectations on the part of the patient, and the presence of comorbid diseases that render surgery dangerous.
D. **Limited surgery followed by RT** involves the total gross removal of tumor by surgery (lumpectomy), an axillary node dissection or "sentinel node" for staging purposes, and then a protracted course of RT, which takes about 6 weeks. Most of the radiation is given as megavoltage gamma-irradiation to the entire breast (about 4500 to 5000 cGy), and the remainder is given as a boost to the area of the biopsy (1000 to 2000 cGy).
1. **Contraindications to limited surgery plus RT**
   a. Tumor more than 5 cm in diameter
   b. Multicentric carcinoma in the breast (a relative but not absolute contraindication)
   c. Paget's disease (relative contraindication)
   d. Very extensive intraductal CIS in the original biopsy or reexcision specimen with positive or uncertain margins. This predicts a high rate of local recurrence after RT (about 25%).
   e. Worrisome mammographic abnormalities:
      1. Diffuse indeterminate-type calcifications
      2. Residual disease on postoperative mammogram
      3. Original carcinoma not visualized by mammography (a relative contraindication that relates to the need to follow these patients for local recurrence after RT)
   f. Situations in which difficulties with RT are anticipated:
      1. Large, pendulous breasts
      2. Pregnancy (first or second trimester)
      3. Collagen vascular diseases, particularly scleroderma or systemic lupus
2. **Advantages of limited surgery plus RT**
   a. Cosmetic appearance
   b. Retention of breast
3. **Disadvantages and complications of limited surgery plus RT**
   a. The retained breast can be a site of recurrent breast cancer or a new primary neoplasm. Careful follow-up with physical examination and mammography

is, therefore, mandatory. Local recurrence mandates mastectomy.
   b. RT is protracted and may be complicated by skin erythema, ulceration, inflammatory fibrosis of the breast, radiation pneumonitis or pericarditis, rib fractures, chest wall ulcers (see section VIII.D), myocardial infarction (left-sided lesions), delayed carcinogenesis, or lung cancer (in smokers).
   4. **Preoperative chemotherapy** for early-stage breast cancer decreases the number of lymph nodes involved with metastases, increases the number of candidates for lumpectomy, but does not affect disease-free survival.

E. **Advanced regional disease: stage III**
   1. **Stage IIIA (operable).** Firm guidelines for the management of stage III breast cancer do not exist. Surgical therapy is clearly of value in controlling local disease and is generally indicated. RT may be useful, but the bulk of tumor in such patients precludes a high chance of local control with RT alone. The biggest problem with these patients is early relapse and death from metastatic disease. Because of these considerations, the first step in treatment for most patients is combination chemotherapy followed by total mastectomy with axillary lymph node dissection. Subsequent treatment is individualized.
   2. **Stage IIIB (inoperable) and inflammatory carcinoma.** The management of this group of patients is also controversial. Increasingly, however, these patients are treated initially with 3 or 4 months of chemotherapy (CMF, CA, or FAC; Table 10.4). RT is then given, followed in most cases by mastectomy. Systemic treatment is then resumed with combination chemotherapy, tamoxifen (for hormone-positive tumors) or both.

F. **Adjuvant therapy: rationale.** Most women with invasive carcinoma of the breast have a systemic disease in which micrometastases have already occurred by the time of initial treatment with surgery. Adjuvant therapy has been given immediately after local treatment with the intent of curing the patient of residual micrometastases and is now a standard part of medical practice.

Table 10.5 summarizes the results of a meta-analysis of 67,000 women treated with endocrine therapy, chemotherapy, or both. This population constituted 90% of patients ever entered into reported randomized trials before 1990 comparing various adjuvant treatment modalities for operable breast cancer. This analysis was a major effort to increase statistical power. Observed improvements were highly significant statistically (2 p usually < 0.00001). The overview of randomized studies demonstrated the following:

Table 10.5 Adjuvant therapy of early breast cancer: Meta-analysis of randomized trials

1. **Adjuvant tamoxifen therapy** given for 5 years for early breast cancer substantially reduced breast cancer recurrence (50% to 60% reduction) and improved 10-year overall survival, irrespective of age, menopausal status, or whether chemotherapy was given. Treatment with tamoxifen for 5 years resulted in the following:
   a. Significant improvement (about two-fold) when compared with treatment for 1 or 2 years. The improvement in recurrence rate is greatest during the first 5 years. The improvement in survival grew steadily throughout the 10 years.
   b. Nearly 50% reduction in the development of contralateral breast cancers
   c. A four-fold increase in endometrial carcinoma, but the number of cases was relatively small and amounted to about half of the reduced number of contralateral breast cancers.
   d. Benefits of therapy that were greatest in patients with node positive disease and in patients with greater relative positivity of the ER assay. Patients who had ER-negative disease achieved minimal benefit.
2. **Adjuvant combination chemotherapy** for 3 to 6 months reduced breast cancer recurrence (by 35% for women younger than 50 years of age and by 20% for those 50 to 69 years of age) and improved 10-year overall survival, irrespective of age, menopausal status, ER status, or whether tamoxifen was given. Combination chemotherapy also resulted in the following:
   a. Improvement in recurrence rate, which was greatest during the first 5 years. The improvement in survival grew steadily throughout the 10 years. The reductions in risk were similar for women with node-negative and node-positive disease.
   b. About a 20% reduction in the development of contralateral breast cancers
   c. No adverse effect on deaths from causes other than breast cancer
   d. Data were insufficient to analyze patients 70 years of age or older, specific combination chemotherapy regimens, or drug components.
3. **The combination of chemotherapy and endocrine therapy** yielded additional benefit compared with either modality alone. The therapies were complementary.

G. **Adjuvant therapy: recommendations.** Women at sufficiently high risk to warrant such treatment include nearly all women with positive axillary lymph nodes and many with high-risk, node-negative disease as well. The absolute benefit of chemotherapy for early breast cancer decreases with advancing age. Treatment recommendations must be made with a blend of the science and art of medicine.
   1. **Adjuvant systemic therapy is not indicated in the following circumstances:**
      a. In women with a good prognosis without such treatment, including those with the following conditions:
         1. Noninvasive CIS of any size in women of any age
         2. Very small primary tumors (smaller than 1 cm; T1a, T1b) and negative axillary lymph nodes, irrespective of the status of hormone receptors in the primary tumor
      b. In women with comorbid medical conditions that make survival beyond 5 years unlikely or that make the potential adverse effects of therapy unacceptable
   2. **Premenopausal women with positive axillary nodes** are offered either a 6-month course of chemotherapy with CMF or with a Adriamycin-containing regimen (FAC or CA), starting within 4 weeks of surgery. Dosages for CMF, CA, and FAC are shown in Table 10.5.
      a. **For patients with hormone-receptor–positive tumors,** tamoxifen or ovarian ablation may be added after chemotherapy. Ovarian ablation (see section VI.B.6) improved both recurrence-free and overall survival for younger women but had no effect in women older than 50 years of age.
      b. **Patients with four or more positive nodes** are offered a Adriamycin-based regimen for four cycles followed by four cycles of a taxane. The best taxane, dose, and schedule have not been determined.
   3. **Postmenopausal women with positive axillary lymph nodes and positive hormone receptors** are generally offered tamoxifen, 20 mg daily, for 5 or more years postoperatively. Because of the concern about the development of aggressive endometrial carcinomas in these patients, they should have an annual pelvic examination and proper evaluation of abnormal uterine bleeding.
      a. Many clinicians also treat these patients with chemotherapy if the adverse effects of treatment are justified. Chemotherapy is especially offered for younger postmenopausal women with several lymph nodes involved (and perhaps other adverse prognostic features). "Classic CMF" may be more effective than the every-3-week CMF regimen.
      b. RT to the axilla is recommended for axillary lymphadenopathy that is palpable or involved in large numbers.
   4. **Postmenopausal women with positive axillary lymph nodes and negative hormone receptors** are generally offered adjuvant chemotherapy, provided they have a life expectancy of at least 5 years.
   5. **Women with high-risk, node-negative disease** who are offered systemic therapy include those with the following conditions:
      a. **Hormone receptor–negative tumors that are larger than 1 cm,** especially with other adverse features, such as high tumor grade: offered chemotherapy alone, particularly in younger women
      b. **Hormone receptor–positive tumors that are larger than 1 cm but 2 cm or smaller (T1c):** offered tamoxifen alone
      c. **Hormone receptor–positive tumors that are larger than 2 cm (T2 or T3):** offered chemotherapy and tamoxifen, particularly in younger women
   6. **Dose intensification.** Women with 7 to 10 or more positive lymph nodes are offered dose-intensive therapy in many centers, usually with autologous stem cell transplantation (often as part of a clinical trial, but occasionally "off study"). Data on this therapy, however, are fraught with preselection bias, and results are not encouraging. Raising the dose of cyclophosphamide or doxorubicin is not beneficial, but the occurrence of myelodysplasia increases with higher doses of alkylating agents.
   7. **Anthracyclines** appear to achieve a real but small benefit when included in the adjuvant chemotherapy regimen. The overriding factor in deciding whether doxorubicin should be included is whether the potential toxicity from the drug is worth it in the individual patient.
   8. **Concurrent versus sequential chemohormonal therapy** appears to yield no difference in results. However, a higher rate of thromboembolic events has been reported when hormonal therapy and chemotherapy are given concurrently.
   9. **Concurrent versus sequential chemotherapy and RT.** For patients at substantial risk for systemic metastases, it is preferable to give chemotherapy before RT.

H. **Patient follow-up after primary therapy of locoregional breast cancer**
   1. Repeat mammography after RT (if it is used) and then once yearly thereafter. The goal of follow-up is to detect locoregional recurrent disease that is still amenable to curative therapy.
   2. Other laboratory studies should be chosen with the goal of cancer screening for unrelated, nonmammary malignant neoplasms (such as colon cancer and ovarian cancer, especially in patients with a strong family history of these disorders).

3. Liver scans, bone scans, and other radiographic studies should not be done in the absence of abnormalities in symptoms or signs elicited on history and physical examination because treatment of advanced disease that is detected early has not been shown to improve survival compared with treatment when metastases become clinically evident.

VIII. Special clinical problems

A. **Postsurgical edema of the arm without pain** was regularly associated with the traditional radical mastectomy but also occurs with less extensive surgery. The incidence is increased in patients who receive postoperative RT. The edema usually develops within a month after surgery. Therapy is not always helpful but includes elevation of the arm, arm stockings, the Jobst pump, and exercise. The best treatment is prevention by good surgical technique and avoidance of postoperative irradiation of the axilla.

B. **Lymphangiosarcoma of the arm** is rare but develops as a complication of the chronically edematous arm 5 or more years after radical mastectomy. Typically, an area of ecchymosis resembling a bruise appears first. The edema worsens, and the tumor ulcerates. Lymphangiosarcoma has a poor prognosis because of recurrence and metastatic spread after radical amputation. Although experience is limited, chemotherapy followed by RT may control this tumor.

C. **Edema of the arm with pain or paresthesias** occurring more than 1 month after surgery almost always reflects recurrent tumor. The cancer is often not clinically discernible because it resides high in the apex of the axilla or lung. Patients complain of tingling or pain in the hands and progressive weakness and atrophy of the hand and arm muscles (see Chapter 32, section IV.A). If sufficient time passes, a tumor mass becomes palpable in the axilla or supraclavicular fossa, but the patient is usually left with a paralyzed hand unresponsive to therapy. These patients should receive RT to the axilla and supraclavicular fossa even if there is no evidence of tumor on physical examination or radiograph. Such "blind" irradiation probably carries a more favorable risk-to-benefit ratio than exploration of the axilla and lung apex to confirm a tumor recurrence.

D. **Chest wall radiation-induced ulcers** may occur as late as 25 years after treatment in women who had radical mastectomies followed by extensive RT. The ulcers occur in radiation ports involving thin skin stretched over bony prominences, are often progressive, and can penetrate through the chest wall. Management requires skilled surgical curettage to exclude the possibility of recurrent cancer. Therapy with hyperbaric oxygen is costly and requires several months but heals benign radiation-induced ulcers of less than 1-cm diameter in about 30% of cases. Generally, plastic surgery repair is necessary.

E. **Silicone-injected breasts** are potential sites for undetectable malignancies. Mammography does little for early detection, and palpable lumps cannot be clinically evaluated. Patients with silicone-injected breasts should be fully informed about the risk for undetectable cancer and referred to a plastic surgeon for implant removal and breast reconstruction, if necessary.

F. **Breast cancer in men** is rare (less than 2% of cases) and is managed according to the principles observed in women with breast cancer.

G. **Pregnancy and fertility** considerations in patients with breast cancer are discussed in Chapter 26.

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Chapter 11 Gynecologic Cancers

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General Aspects

I. Epidemiology. Malignancies of the genital tract constitute about 20% of visceral cancers in women. The incidence and mortality rates according to primary site are shown in Table 11.1.

Table 11.1 Cancers of the female genital tract in the United States

II. Diagnostic studies

A. **Papanicolaou** (Pap) **smears**
 1. **Frequency.** Early detection has greatly reduced the morbidity and mortality of cervical and endometrial cancer. The traditional annual Pap smear has been questioned because it usually takes years for dysplasia to develop into invasive squamous cell carcinoma. Some invasive lesions may develop *de novo,* however, and bypass evolution through stages of dysplasia. In addition, the Pap smear may give a false-negative result, and the incidence of adenocarcinoma of the cervix is on the rise; the natural history of this malignancy and its precursors is less well understood than is that of squamous cell carcinomas. Thus, we recommend yearly Pap smears.
 2. **Technique.** The false-negative rate for Pap smears is 10% to 20% under optimal circumstances. The squamocolumnar junction, where cervical cancer arises, recedes upward and inward with advancing age. This process decreases the usefulness of cervical scraping alone to make the diagnosis. Sampling should be done by aspirating the cervical os with a glass pipette and scraping the exocervical circumference of the squamocolumnar junction with a divided wooden-blade spatula. The specimens are smeared on clean glass slides and fixed immediately. Vaginal pool cytologies probably contribute little.
 3. **Pap smears are graded using the Bethesda system,** as follows:

 Within normal limits

Infection or reactive and reparative changes

Atypical squamous cells or glandular cells of undetermined significance

Low-grade squamous intraepithelial lesion; corresponds to human papillomavirus (HPV) atypia, cervical intraepithelial neoplasia type 1 (CIN 1; old class III)

High-grade squamous intraepithelial lesion; corresponds to CIN 2 and 3 and carcinoma *in situ* (CIS; old class III to IV)

Squamous cell carcinoma (old class V)

B. **Staging evaluation** is necessary regardless of the site of the primary lesion after cancer of the female genital tract is proved histologically. Potentially valuable studies include the following:
   1. Pelvic and rectal examinations (to determine whether the adnexae, vagina, or pelvic wall is involved)
   2. Complete blood count, serum electrolytes, liver function tests (LFTs), and renal function tests
   3. Chest radiograph (for pulmonary metastases)
   4. Bone scan (if history, physical examination, or routine blood chemistries suggest an abnormality)
   5. Intravenous pyelogram (to look for ureteral obstruction or deviation)
   6. Abdominal ultrasonography and computed tomography (CT) scans (to delineate abnormal areas)
   7. Sigmoidoscopy with biopsy of abnormal areas and barium enema (for mucosal involvement or mass lesions)
   8. Cystoscopy with biopsy of abnormal areas (to look for bladder mucosal involvement) for cancers of the vulva, vagina, cervix, or endometrium
   9. Cytologic evaluation of effusions

III. Managing treatment-related sexual dysfunction
Patients treated for cancers of the female genital tract often have difficulty performing sexual intercourse.

A. **Broaching the subject**
   1. Address changes in sexual function directly, preferably before therapy is undertaken; the patient's sexual partner should also be included.
   2. Inquire about current sexual activities and about fears the patient or sexual partner might have about the cancer or therapy. Patients should be specifically reassured that the cancer is not contagious, that a small amount of bleeding after intercourse is not hazardous, and that a reasonably normal sex life is expected and desirable for most patients after therapy. See Chapter 26 for discussion of these issues.
B. **Specific sexual problems**
   1. **After radiation therapy** (RT)
      a. **External-beam RT.** Patients receiving external-beam RT should be advised to continue their normal sexual activity; continued intercourse may help prevent vaginal stenosis. Should vaginal dryness develop, the patient should be advised to use water-soluble lubricants. Estrogen is also useful for treating vaginal dryness in patients with cervical cancer.
      b. **Radiation implants.** Patients with radiation implants should be advised against intercourse until several weeks after treatment. Implants are usually removed before discharge from the hospital. Manual foreplay to the point of orgasm is advised as a temporary substitute for intercourse.
      c. **Vaginal stenosis secondary to RT** may make penile penetration difficult. This complication is often preventable by using dilation and lubrication during the course of irradiation. Manual foreplay, anogenital sex, and orogenital sex are alternatives. Surgical reconstruction by excision of scar tissue and placement of a split-thickness skin graft may yield good results.
   2. **After radical hysterectomy,** the vaginal cuff may be foreshortened, resulting in dyspareunia. Vaginal reconstruction usually has good results. Alternatively, the woman can place her hips on a pillow to provide a better angle for penetration. The man can approach from the rear, which may be more comfortable. If these measures are unsatisfactory, lubricated hands placed at the base of the penis may give the sensation of a longer vagina.
   3. **After vulvectomy,** a major sensory modality for foreplay may be removed. The patient should be apprised of this and the sexual partner instructed to stimulate other erogenous zones.
   4. **After pelvic exenteration,** the physician should emphasize the need to allow adequate time for healing of the wound and adjustment to the ostomies. Thereafter, sexual management is as recommended for the stenotic vagina (see section B.1.c). Patients can be advised that vaginal reconstruction can be accomplished during exenteration.
   5. **After vaginectomy.** Reconstruction is performed at the time of primary surgery. Both sexual and reproductive function can often be preserved after treatment of vaginal cancer. The gynecologist determines when intercourse can be resumed.

IV. Locally advanced cancer in the pelvis

A. **Pathogenesis.** Massive pelvic metastases commonly develop in the course of gynecologic and urologic cancers, rectal carcinomas, and some sarcomas. Locally advanced cancers in the pelvis produce progressive pelvic and perineal pain, ureteral obstruction with uremia, and lymphatic and venous obstruction with pedal and genital edema. Invasion of the rectum or bladder can lead to erosion with bleeding, sloughing of tumor into the urine or bowel, and bladder or bowel outlet obstruction.
B. **Management**
   1. **Drug therapy** is preferred initially in some tumors, depending on the primary site.
   2. **RT** frequently relieves symptoms and is useful when the tumor does not respond to chemotherapy.
   3. **Surgery.** A bowel resection, colostomy, or suprapubic cystostomy may relieve bowel or urethral obstruction. Ureteral bypass can be accomplished by placement of ureteral stent catheters or by nephrostomy.
   4. **No therapy.** Patients with progressive pelvic disease unresponsive to irradiation or chemotherapy usually die from uremia. Uremia is usually the least painful death possible. Urinary stream bypass techniques are not recommended for patients with progressive, unresponsive pelvic pain syndromes or relentlessly eroding tumors.

V. Adverse effects of radiation to the pelvis

A. **Radiation cystitis**
   1. **Acute transient cystitis** may occur during RT to the pelvis. The possibility of urinary tract infection should be investigated. Urinary tract analgesics and antispasmodics may be helpful for pain (see Chapter 5, section V).
   2. **Late radiation cystitis** occurs when high-dose, curative RT to the urinary bladder has been preceded by extensive fulgurations. The bladder becomes contracted, fibrotic, and subject to mucosal ulcerations and infections. Urinary frequency and episodes of pyelonephritis or cystitis (often hemorrhagic) are the clinical findings. If symptomatic management is not successful, cystectomy may be required.
B. **Radiation vulvitis** of a moist and desquamative type usually begins at about 2500 cGy and may require temporary discontinuation of treatment for 1 to 2 weeks in up to half of patients.
C. **Radiation proctitis.** See Chapter 30, section VI.D.
D. **Vaginal stenosis.** See General Aspects, section III.B.1.c.
E. **Effects on gonads.** See Chapter 26, section III.

Cancer of the Uterine Cervix

I. Epidemiology and etiology

A. **Incidence** (Table 11.1). The mortality of rate cervical cancer has declined by 50% since the 1950s, largely as a result of early detection and treatment.
B. **Relationship to sexual history.** The common denominator for increased risk for cervical cancer is early age at first sexual intercourse. The incidence is also higher in patients with an early first pregnancy, multiple sexual partners, and venereal disease, especially HPV infection.
C. **Relationship to HPV.** A large body of evidence supports the relationship among HPV, cervical intraepithelial neoplasia (dysplasia), and invasive carcinoma. DNA transcripts of HPV have been identified by Southern blot analysis in more than 60% of cervical carcinomas. The viral DNA is typically integrated into the human genome rather than remaining in an intact viral capsid. More than 60 HPV subtypes have been identified. Types 6 and 11 are usually associated with benign condyloma acuminata, whereas types 16, 18, 31, and 33 are more likely to be associated with malignant transformation. Type 18 has been associated with poorly differentiated histology and a higher incidence of lymph node metastases. (See Chapter 36, section IV.D.2.)

D. **Relationship to smoking.** There is evidence that a personal history of smoking significantly increases the risk for cervical cancer.

II. Pathology and natural history

A. **Histology.** About 80% of cervical carcinomas are squamous cancers, and 20% are adenocarcinomas. Sarcomas are rare. The disease is believed to start at the squamocolumnar junction. A continuum from CIN to invasive squamous cell carcinoma is apparent. The average age of women with CIN is 15 years younger than that of women with invasive carcinoma, suggesting a potentially slow progression. The natural history of HPV infection is in part influenced by the host immune system; that all stages of CIN may regress spontaneously, remain unchanged, or progress to invasive carcinoma reflects this fact. A small percentage of lesions appear to bypass this progression and may evolve over a substantially shorter period of time.

B. **Metastases.** After invasive cancer is established, the tumor spreads primarily by local extension into other pelvic structures and sequentially along lymph node chains. Uncommonly, patients with locally advanced tumors may have evidence of blood-borne metastases, most often to the lung, liver, or bone.

III. Diagnosis

A. **Symptoms and signs**
   1. **Symptoms** of early-stage invasive cervical cancer include vaginal discharge, bleeding, and particularly postcoital spotting. More advanced stages often present with a malodorous vaginal discharge, weight loss, or obstructive uropathy.
   2. **Signs.** Findings on pelvic examination include the appearance of obvious masses on the cervix; gray, discolored areas; and bleeding or evidence of cervicitis. If a tumor is present, the extent should be noted; involvement of the vagina or parametria is an important prognostic factor.
B. **Pap smears and biopsies.** Most patients with cervical cancer do not have symptoms, and cases are detected by routine Pap smear screening (see General Aspects, section II.A). Biopsy specimens should be taken of all visibly abnormal areas, regardless of the findings on the Pap smear. Diagnostic conization may be required if the biopsy shows microinvasive carcinoma, if endocervical curettage shows high-grade dysplasia, or if adenocarcinoma *in situ* is suspected from cytology.
C. **Patients with a positive Pap smear and no visible lesion** generally undergo colposcopy, which can detect 90% of dysplastic lesions. The colposcope is a magnifying instrument (10–20×) that usually detects class III to V lesions. Biopsy specimens are taken from areas that appear abnormal by colposcopy.
D. **Endocervical curettage** (ECC) is required when the Pap smear shows a high-grade lesion but colposcopy does not reveal a lesion; when the entire squamocolumnar junction cannot be visualized; when atypical endocervical cells are present on the Pap smear; or when women previously treated for CIN develop new high-grade findings on cytology. If the ECC reveals a high-grade squamous intraepithelial lesion, patients should undergo cervical conization with a knife or a loop electrosurgical excision procedure (LEEP).
E. **Further diagnostic studies** in patients whose biopsy report shows cancer depend on the depth of invasion.
   1. For early CIS, other studies are not necessary.
   2. If blood or lymphatic vessels are invaded, or if the tumor penetrates more than 3 mm below the basement membrane, pretherapy staging studies are required (see General Aspects, section II.B).

IV. Staging system and prognostic factors

A. **Staging system** (Table 11.2)

Table 11.2 Staging system for cervical cancer

B. **Prognostic factors** in each stage include size of the primary tumor (tumor bulk), presence of lymph node metastases, and tumor grade; patients with poorly differentiated tumors do not do well.

V. Prevention and early detection (see General Aspects, section II.A).

VI. Management*

A. **CIN 1 to 3 (including CIS).** The management of patients with positive cytologic findings or early carcinoma of the cervix is diagramed in Fig. 11.1. Treatment modalities include superficial ablative therapies, LEEP, cone biopsy, and hysterectomy. CIN 1 lesions may be observed if the patient has good follow-up or may be treated with ablative therapy. Patients with high-grade (CIN 2 and 3) squamous lesions are suitable for ablative therapies, provided the entire transformation zone is visible on colposcopy, the histology of the biopsies is consistent with the Pap smear, the ECC is negative, and there is no suspicion of occult invasion. Ablative techniques include cryosurgery, carbon dioxide laser therapy, and electrocoagulation diathermy. LEEP, which involves the use of wire loop electrodes with radiofrequency alternating current to excise the transformation zone under local anesthesia, has become the preferred treatment for CIN that can be adequately assessed by colposcopy. Cone biopsy is preferred for lesions that cannot be assessed colposcopically or when adenocarcinoma *in situ* is suspected. If the patient has other gynecologic indications for hysterectomy, a vaginal or an extrafascial (type I) abdominal hysterectomy may be performed.

Figure 11.1 Management of patients with positive Pap smear cytology and early carcinoma of the uterine cervix. CIN, cervical intraepithelial neoplasia; CIS, carcinoma *in situ*; ECC, endocervical curettage. (*) If invasion is not found on conization, patients are followed with Pap smears, biopsies, or repeat conization, depending on the patient and patient's age.

B. **Concurrent chemotherapy (CCT) with RT** reduces recurrence by 30% to 50% and improves 3-year survival rates by 10% to 15% over adjuvant treatment with RT alone.
   1. **CCT is indicated** in the following circumstances:
      a. High-risk stages I to IIa (e.g., with lymph node involvement or positive margins)
      b. Stages IIb, III, and IVa
   2. **Regimens.** Several combination chemotherapy regimens involving cisplatin and 5-fluorouracil (5-FU) have been effective. Representative regimens are as follows:
      a. Cisplatin, 40 mg/m^2 weekly for 6 weeks (with or without 5-FU infusions)
      b. Cisplatin, 50 mg/m^2 on days 1 and 29, and 5-FU, 1000 mg/m^2 per day by continuous IV infusion for 4 days beginning on days 1 and 29. Extension of treatment to four courses is being investigated.
C. **Stage I disease** (Table 11.3)

Table 11.3 Treatment of stage I cervical carcinoma

   1. **Stage Ia1 disease** with less than 3 mm invasion may be treated with excisional conization, provided the lesion has a diameter of less than 7 mm and no lymph or vascular space invasion. A vaginal or extrafascial hysterectomy is also appropriate if further childbearing is not desired.
   2. **Stage Ia2 disease.** For patients with stage Ia2 disease and 3 to 5 mm of stromal invasion, the risk for nodal metastases is 5% to 10%. Bilateral pelvic lymphadenectomy should be performed in conjunction with a modified (type II) radical hysterectomy.
   3. **Stage Ib disease** carries a 15% to 25% risk for positive pelvic lymph nodes and should be treated with a radical (type III) hysterectomy, bilateral pelvic lymphadenectomy, and paraaortic lymph node evaluation. In patients who are poor surgical candidates or in whom the tumor is large (generally larger than 5 cm), RT is preferred. In patients with high-risk features (e.g., lymph node metastasis), postoperative RT with CCT with cisplatin or 5-FU as a radiation

sensitizer should be given.

D. **Stage II disease.** Stage IIa disease is treated in the same manner as stage Ib disease. When the tumor extends to parametrium (IIb), patients should be treated with RT and CCT involving 5-FU, cisplatin, or both (see section B).

E. **Stage IIb and III disease.** When the parametrium (IIb), the distal vagina (IIIa), or the pelvic sidewall (IIIb), is involved, clear surgical margins are not possible to achieve, and patients should be treated with maximum-dose (8500 cGy) RT delivered both externally and by brachytherapy. CCT with 5-FU as radiation sensitizers improves survival rates when compared with RT alone (see section B).

F. **Recurrent and stage IV disease.** Advanced cancer in the pelvis is discussed in General Aspects, section IV, and obstructive uropathy is discussed in Chapter 31, section II.

1. **Lower vaginal recurrence** can occasionally be cured by RT or exenteration.
2. **Pelvic exenteration.** A pelvic exenteration may also be considered for central pelvic recurrent disease after primary RT when spread is confined to the bladder or rectum. Exenteration carries a higher morbidity rate. Metastatic cancer outside the pelvis and poor medical condition of the patient are contraindications to exenteration. Ureteral obstruction, leg edema, and sciatic pain usually suggest sidewall disease. Surgery should be abandoned if there is more extensive cancer than was clinically suspected.
3. **RT.** Radiation alone or with chemotherapeutic sensitizers can occasionally cure stage IVA disease. External-beam RT is combined with intracavitary or interstitial radiation to a total dose of about 8500 cGy. If disease persists after chemoradiation, pelvic exenteration can be performed.
4. **Chemotherapy** for metastatic disease is not curative. Distant metastases or incurable local disease should be treated as for any advanced malignancy. A number of chemotherapeutic drugs (e.g., cisplatin, carboplatin, paclitaxel, bleomycin, and mitomycin C) produce short-term responses in 40% to 50% of patients.

G. **Complications of surgery or RT**

1. **LEEP.** Bleeding occurs in 1% to 8% of cases, cervical stenosis occurs in 1%, and pelvic cellulitis or adnexal abscess occurs rarely.
2. **Conization.** Hemorrhage, sepsis, infertility, stenosis, and cervical incompetence occur rarely.
3. **Radical hysterectomy.** Acute complications include blood loss (average, 800 mL), urinary tract fistulas (1% to 3%), pulmonary embolus (1% to 2%), small bowel obstruction (1%), and febrile morbidity (25% to 50%). Subacute complications include transient bladder dysfunction (30%) and lymphocyst formation (less than 5%). Chronic complications include bladder hypotonia or atonia (3%) and, rarely, ureteral strictures.
4. **Pelvic exenteration.** The surgical mortality rate is less than 10%. The postoperative recuperative period may be as long as 3 months, and the massive fluid shifts and hemodynamic status that sometimes occur may require monitoring. Most postoperative morbidity and mortality result from sepsis, pulmonary embolism, wound dehiscence, and intestinal complications, including small bowel obstruction and fistula formation. A reduction in gastrointestinal complications can be achieved by using unirradiated segments of bowel and closing pelvic floor defects with omentum. The 5-year survival rate for patients undergoing total pelvic exenteration is 30% to 50%.
5. **Pelvic irradiation.** Radiation proctitis and enteritis with intractable diarrhea or obstruction, cystitis, sexual dysfunction because of vaginal stenosis and loss of secretions, loss of ovarian function, fistula formation, and 0.5% mortality either from intractable small bowel injury or pelvic sepsis (see General Aspects, section V)

VII. Special clinical problems

A. **Chance finding of cancer at hysterectomy.** Cancer found in hysterectomy specimens removed for other reasons carries a poor prognosis unless treated with additional surgery or postoperative RT soon after surgery.

B. **Uncertainty of recurrent cancer.** Recurrent cancer is usually manifested by pelvic pain, particularly in the sciatic nerve distribution; vaginal bleeding; malodorous discharge; or leg edema. Recurrence must be demonstrated by biopsy specimen because these symptoms and even physical findings are similar to radiation changes. If no tumor is found using noninvasive measures, a surgeon experienced in pelvic cancer should perform exploratory laparotomy.

C. **Postirradiation dysplasia.** Abnormal Pap smears on follow-up examinations may represent postirradiation dysplastic changes or a new primary cancer. Suspected areas should undergo biopsy. If the biopsy findings show cancer, surgical removal is usually recommended.

Cancer of the Uterine Body

I. Epidemiology and etiology

A. **Incidence** (Table 11.1). Endometrial cancer is the most common malignancy of the female genital tract in the United States. The peak incidence is in the sixth and seventh decades of life; 80% of patients are postmenopausal. Most premenopausal women with endometrial carcinoma have the Stein-Leventhal syndrome. Less than 5% of all cases are diagnosed before the age of 40 years.

B. **Risk factors**

1. Risk factors appear to be related to estrogen exposure that is unopposed by progesterone. The risk for endometrial carcinoma from exogenous estrogen administration is increased four- to eight-fold. Tamoxifen acts as a weak estrogen. Data suggest that the use of tamoxifen is associated with a two-fold increased risk for endometrial cancer.
2. **Medical conditions producing increased exposure to unopposed estrogens** and associated with increased risk of endometrial carcinoma
   a. Polycystic ovarian disease (anovulatory menstrual cycles with or without hirsutism and other endocrine abnormalities)
   b. Anovulatory menstrual cycles
   c. Obesity
   d. Granulosa cell tumor of the ovary, or any other estrogen-secreting tumor
   e. Advanced liver disease
3. **Other medical conditions** associated with increased risk for endometrial carcinoma
   a. Infertility, nulliparity, irregular menses
   b. Diabetes mellitus
   c. Hypertension
   d. History of multiple cancers in the family
   e. Patient history of breast or rectal cancer

II. Pathology and natural history

A. **Histology.** About 90% of uterine cancers are endometrial adenocarcinomas, and 10% are adenosquamous carcinomas. A small percentage are clear cell, small cell, or squamous carcinomas and sarcomas.

B. **Role of estrogens.** Classically, unopposed estrogens cause a continuum of endometrial changes from mild hyperplasia to invasive carcinoma. More recent investigations, however, suggest that endometrial hyperplasia and endometrial neoplasia are two biologically different diseases. About 75% of women with endometrial hyperplasia that lacks cytologic atypia respond to progestin therapy and are *not* at increased risk for cancer. Endometrial hyperplasia with cytologic atypia should be considered endometrial intraepithelial neoplasia; 80% to 90% of these patients respond to progestins, and the remainder of cases persist.

C. **Mode of spread.** Tumors are confined to the body of the uterus (stage I) in 75% of cases. Endometrial cancer most commonly spreads by direct extension. Deep myometrial invasion and involvement of the uterine cervix are associated with a high risk for pelvic lymph node metastases. It is rare to find positive paraaortic nodes in the absence of positive pelvic nodes. The presence of cells in peritoneal washes suggests retrograde flow of exfoliated cells along the fallopian tubes. Hematogenous spread is an uncommon late finding in adenocarcinoma but occurs early in sarcoma. The lungs are the most frequent site of distant metastatic involvement.

III. Diagnosis

A. **Symptoms and signs**

1. **Abnormal vaginal bleeding** is the most common complaint (97%).
   a. **Premenopausal women** with prolonged menses, excessive menstrual bleeding, or intermenstrual bleeding must be evaluated for endometrial cancer, particularly if they have a history of irregular menses, diabetes mellitus, hypertension, obesity, or infertility.
   b. **All postmenopausal women** with vaginal bleeding more than 1 year after the last menstrual period are considered to have endometrial cancer unless proved otherwise. Even women who have been on estrogens to control postmenopausal symptoms must have histologic proof that withdrawal bleeding is not the result of an unrelated endometrial cancer.
2. **Patients without symptoms** and with abnormal Pap smears require evaluation for endometrial cancer if cervical cancer is not found; 3% of cases are

detected in this manner. The findings of atypical histiocytes or normal endometrial cells in postmenopausal patients or in the second half of the menstrual cycle in premenopausal patients require histologic evaluation.

3. **Locally extensive tumors** may be palpable on pelvic examination.
4. **Advanced disease** is the original manifestation of cancer in 5% of cases. Presenting problems include ascites, jaundice, bowel obstruction, or respiratory distress from lung metastases.

B. **Endocervical curettage and office endometrial biopsy** should be performed in all patients suspected of having endometrial carcinoma. The preferred technique is to use a small flexible plastic catheter (e.g., pipelle). An endometrial biopsy should be made for optimal interpretation. The accuracy of endometrial sampling is 95% to 98%. All patients with symptoms and a negative biopsy must undergo dilation and curettage.

C. **Fractional curettage** is the diagnostic method of choice for endometrial cancer. The technique involves scraping the endocervical canal and then, in a set sequence, the walls of the uterus. If cancer is found by histologic evaluation, the fractional scrapings help to locate the tumor site. The gross appearance of the scrapings often suggests cancerous tissue, which is gray, necrotic, and friable.

D. **Pap smears.** Conventional Pap smears from endocervical aspiration or brushing have a much lower yield than fractional curettage or jet-washout. Pap smears alone should not be used to exclude suspected endometrial cancer. Only half of patients with endometrial cancer have abnormal cells on Pap smear.

E. **Transvaginal ultrasound** with and without color-flow imaging is under investigation. Early data suggest a strong association between thickness of the endometrial strip and endometrial disease. Normal endometrium is usually less than 5 mm thick, and false-positive results based on this criterion alone may be excessively high.

F. **Staging evaluation.** See General Aspects, section II.B.

IV. Staging system and prognostic factors

A. **Staging system** is shown in Table 11.4. In the rare patient who is not a candidate for surgery, the 1971 International Federation of Gynecology and Oncology (FIGO) clinical staging system is used. This system is based on endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, and radiographs of the chest and bones.

Table 11.4 Surgical staging system for cancer of the uterine body

B. **Prognostic factors**
1. **Histologic grade and myometrial invasion.** Increasing tumor grade and myometrial penetration are associated with increasing risk for pelvic and paraaortic lymph node metastases, positive peritoneal cytology, adnexal metastases, local vault recurrence, and hematogenous spread and thus have great prognostic value.
2. **Tumor histology.** Histologic types ranked from best to worst prognosis are adenocanthoma, adenocarcinomas, adenosquamous carcinomas, clear cell carcinomas, and small cell carcinomas.
3. **Vascular space invasion.** Vascular space invasion is an independent prognostic factor for recurrence and death from endometrial carcinoma of all histologic types.
4. **Hormone receptor status.** The average estrogen receptor (ER) and progesterone receptor (PgR) levels are, in general, inversely proportional to the histologic grade. However, ER and PgR levels have also been shown to be independent prognostic indicators, with higher levels corresponding to longer survival.
5. **Nuclear grade.** Criteria for nuclear atypia vary, and intraobserver and interobserver reproducibility is poor. Despite these difficulties, a number of researchers have shown that nuclear grade is a more accurate prognosticator than histologic grade.
6. **Tumor size.** The larger the tumor, the larger the risk for lymph node metastases and, therefore, the worse the prognosis.
7. **DNA ploidy.** Aneuploid tumors constitute a fairly small percentage (25%) of endometrial carcinomas as compared with ovarian and cervical cancers. Aneuploidy is, however, associated with increased risk for early recurrence and death.

V. Prevention and early detection

A. **Prevention.** Unopposed exogenous estrogen administration should be avoided in postmenopausal women, and women who are anovulatory or who have endometrial hyperplasia should be treated with cyclic progestins.

B. **Early detection.** Patients in whom evaluation for endometrial carcinoma is necessary include postmenopausal women who have abnormal bleeding on exogenous estrogens; obese postmenopausal women, particularly with a strong family history of endometrial, breast, bowel, or ovarian cancer; and premenopausal women with chronic anovulatory cycles (i.e., polycystic ovarian disease). Women in whom endometrial carcinoma must be excluded include all postmenopausal women with significant bleeding or with pyometra; perimenopausal women with severe intermenstrual or increasingly heavy periods; and premenopausal women with unexplained abnormal uterine bleeding, especially if chronically anovulatory.

VI. Management

A. **Early disease**
1. **Surgery**
   a. **Total abdominal hysterectomy with bilateral salpingo-oophorectomy** (TAH/BSO) is the treatment of choice for patients with persistent hyperplasia after adequate progestin treatment and for all medically fit patients with stage I and stage II endometrial carcinoma with microscopic endocervical involvement and no expansion of the cervix. Removal of the vaginal cuff is not necessary. Any peritoneal fluid should be sent for cytology; if no fluid is found, a peritoneal wash with 50 mL normal saline should be performed. Any enlarged pelvic or paraaortic lymph nodes are resected.
      1. If the lymph nodes are not enlarged or are negative and the patient has stage Ia or Ib disease with grade 1 or 2 histology and the tumor measures less than 2 cm, no further treatment is necessary. All other patients should have complete surgical staging, including pelvic and paraaortic lymphadenectomy.
      2. In young women who have well-differentiated lesions, the use of high-dose progestin hormones can be curative. We recommend medroxyprogesterone (Megace), 80 to 320 mg/day for 3 months, followed by a dilation and curettage to confirm the response. After the disease is gone, the patient must undergo cyclic hormonal therapy to avoid anovulatory hyperplasia.
   b. **Stage II disease** is treated with combined RT and surgery or only hysterectomy, BSO, and bilateral pelvic lymphadenectomy. Patients with an expanded cervix may be treated with a type II (modified radical) hysterectomy; those with microscopic involvement of the cervix may be treated with an extrafascial hysterectomy.
2. **RT**
   a. **RT alone** is used only for patients at high risk for surgical mortality because of concomitant medical conditions. The survival rate of patients with stage I or II disease treated with RT alone is significantly inferior to the rates associated with surgery alone or surgery combined with RT.
   b. **Postoperative RT.** To facilitate accurate surgical staging, many investigators have moved in favor of postoperative rather than preoperative RT.
      1. Stage I patients with moderate-grade malignancies who have undergone full surgical staging with negative lymph nodes can be treated with intracavitary vaginal vault radiation.
      2. External pelvic irradiation (about 5000 cGy) is indicated in all patients with grade 3 lesions, or stage Ic or II occult disease.
      3. Extended-field RT to the paraaortic nodes (4500 cGy) should be given to patients with biopsy-proven paraaortic nodal metastases, grossly positive or multiple positive pelvic nodes, grossly positive adnexal metastases, and stage Ic disease if grade 2 or 3.
   c. **Preoperative RT**
      1. The use of preoperative brachytherapy is still sometimes advocated for patients with grade 3, stage I lesions.
      2. Clinical stage II disease (cervical enlargement) is often treated with preoperative external pelvic irradiation and intracavitary radiation followed in 6 weeks by TAH/BSO.
3. **Chemotherapy** has a role in the management of early endometrial cancers when they are papillary serous or clear cell carcinomas. Treatment with paclitaxel and carboplatin is recommended (see Ovarian Cancer, section VI.E.4 for regimen dosages).

B. **Advanced disease**
1. **Stage III disease** treatment should be individualized. It should aim to include TAH/BSO initially, except in the presence of parametrial extension, when initial external and intracavitary radiation are more appropriate. Surgical removal of all macroscopic disease is of prime prognostic importance; all enlarged pelvic and paraaortic lymph nodes should be removed. Whole-abdominal irradiation should be considered for patients with positive peritoneal washings or

micrometastases to the upper abdomen.

2. **Stage IV disease** is rare and should also entail individualized treatment. Treatment usually consists of a combination of surgery, RT, and progestins. If the tumor is removed, it should be sent for ER and PgR levels. Pelvic exenteration may be considered for the occasional patients with disease extension limited to the bladder or rectum.

3. **Drug therapy.** Patients with widespread metastases or with previously irradiated, recurrent local disease are treated with hormones and cytotoxic agents.

   a. **Hormones.** Response to progestins occurs in 20% to 40% of patients. The average duration of response is 1 year, and expected survival in responding patients is twice that of nonresponders. A few patients survive in excess of 10 years. Hormone receptor studies are of predictive value. The following drugs are most frequently used:

      1. Repository form of medroxyprogesterone acetate (Depo-Provera), 1.0 g IM weekly for 6 weeks and monthly thereafter
      2. Megestrol acetate (Megace), 40 mg PO four times daily
      3. Tamoxifen, 10 mg PO twice daily

   b. **Chemotherapy.** Patients not responding to hormonal therapy can be treated with chemotherapy. Drug regimens containing platinum and doxorubicin can be effective; response may be produced in up to 40% of patients, which improves their expected survival by several months. For papillary serous or other histologies, carboplatin and paclitaxel should be used, and the patients should be treated as if they have advanced ovarian carcinoma (see Ovarian Cancer, section VI.E.4 for regimen dosages).

VII. Special clinical problems. Daily estrogen replacement therapy for younger patients with stage I disease is important to protect against osteoporosis and cardiovascular disease. This treatment has not been associated with deleterious effects, as previously feared. Other complications are discussed in General Aspects.

Vaginal Cancer

I. Epidemiology and etiology

A. **Incidence.** Primary carcinoma of the vagina constitutes 1% to 2% of cancers of the female genital tract. Dysplastic changes of the vaginal mucosa appear to be precursors of CIS. The likelihood of vaginal carcinoma is increased in women with a history of cervical carcinoma. About 80% to 90% of cases of vaginal cancer are metastatic in origin and are treated according to the primary lesion.

B. **HPV.** HPV is associated with dysplastic changes of the vaginal mucosa referred to as *vaginal intraepithelial neoplasia* (VIN). The exact potential of VIN to progress to frankly invasive carcinoma is unknown but appears to be in the range of 3% to 5% when the dysplasia is treated with various methods.

C. **Estrogens**

1. The 2,000,000 daughters of women treated with diethylstilbestrol (DES) during the first 18 weeks of gestation are at risk for developing vaginal clear cell adenocarcinomas. As of February 1992, 580 cases of clear cell vaginal and cervical carcinomas had been reported by the Registry for Research on Hormonal Transplacental Carcinogenesis. DES exposure accounted for two thirds of the reported cases. The actual risk for clear cell adenocarcinoma in DES-exposed women is estimated to be 1 in 1000, with the highest risk in women exposed before 12 weeks' gestation.

2. Vaginal adenosis is present in nearly 45% of women exposed to DES, and 25% have structural abnormalities of the uterus, cervix, or vagina. Almost all women with vaginal clear cell carcinoma also have vaginal adenosis.

3. This tumor is decreasing in incidence owing to the discontinuation of DES circa 1970.

II. Pathology and natural history

A. **Histology.** About 85% of vaginal carcinomas are squamous carcinomas, and the remainder are adenocarcinomas, melanomas, and sarcomas.

B. **Location.** Primary vaginal cancers most commonly arise on the posterior wall of the upper one third of the vagina. If the cervix is involved, the disease is defined as cervical rather than vaginal cancer. If the vulva is involved, the disease is defined as vulvar cancer.

C. **Mode of spread**

1. **Direct extension** to adjacent soft tissues and bony structures, including paracolpos and parametria, bladder, urethra, rectum, and bony pelvis, usually occurs when the tumor is large.

2. **Lymphatic dissemination** occurs to pelvic and then paraaortic nodes from the upper vagina, whereas the posterior wall is drained by inferior gluteal, sacral, and deep pelvic nodes. The anterior wall drains into lymphatics of the lateral pelvic walls, and the distal one third of the vagina drains into the inguinal and femoral nodes.

3. **Hematogenous spread** occurs late and is most often to lung, liver, bone, and supraclavicular lymph nodes.

III. Diagnosis

A. **Symptoms and signs.** The most frequent presenting complaints are vaginal discharge and bleeding. Vaginal adenosis is usually asymptomatic but may produce a chronic watery discharge. Bladder pain and urinary frequency may occur early on. Advanced posterior tumors may cause tenesmus or constipation.

B. **Diagnostic studies**

1. Diagnosis of vaginal carcinomas is often missed on initial examination, especially when the tumor is located in the distal two thirds of the vagina, where the blades of the speculum may obscure the lesion. The speculum should always be rotated as it is withdrawn and the vaginal mucosa inspected carefully.

2. Vaginal Pap smears and biopsy of abnormal areas on pelvic examination are the mainstays of diagnosis. If no lesion is detected with an abnormal Pap smear, application of Lugol's iodine and inspection with a colposcope may be helpful in identifying lesions.

3. Staging procedures are discussed in General Aspects, section II.B.

IV. Staging system and prognostic factors

A. **Staging system.** Several staging systems are used. Despite their clear influence on prognosis, however, tumor bulk and location of the primary lesion in the vagina are not included. Because expected survival depends on clinical stage, variable survival rates have been reported. A representative staging system and approximate survival rates are as follows:

Stage	Extent	Five-year survival (%)
0	Carcinoma *in situ*	100
I	Limited to vagina	70
II	Invasion of subvaginal tissues but not extending to pelvic wall	50
III	Extension to pelvic wall	20
IV	Extension beyond true pelvis or biopsy proof of bladder or rectal involvement	<10

B. **Prognostic factors.** Generally, the greater the tumor size, the worse the prognosis. Cancers located in the upper vagina, however, have a better prognosis than those located in the lower vagina (upper posterior tumors can become large before invading the muscularis and changing the stage of disease).

V. Prevention and early detection

A. **Pap smears** are the basis of screening the general population. Up to 30% of patients with vaginal cancer have a history of *in situ* or invasive cervical cancer; these patients should be screened with annual Pap smears.

B. **Females with a history of *in utero* exposure to DES** should have a pelvic examination and Pap smear yearly from the time of menarche. Younger girls who have been exposed to DES should be examined at the first sign of bleeding or discharge because clear cell carcinomas can occur in childhood. All suspected areas should undergo biopsy, and careful palpation of all mucosal surfaces is extremely important.

VI. Management

A. **Early disease**

1. **Surgery.** The close proximity of bladder, urethra, and rectum restricts the surgical margins that can be obtained without an exenterative procedure. In

addition, attempts to maintain a functional vagina and the associated psychosocial issues play an important role in treatment planning.
  a. Vaginal mucosa stripping has been used for CIS.
  b. Stage I disease involving the upper posterior vagina may be managed with radical hysterectomy, partial vaginectomy, and bilateral pelvic lymphadenectomy. In a patient with prior hysterectomy, radical upper vaginectomy with bilateral pelvic lymphadenectomies can be used.
  c. Pretreatment exploratory laparotomy in patients requiring radiation allows for the following:
    1. More precise determination of disease involvement
    2. Resection of bulky involved lymph nodes
    3. Ovariopexy (ovarian transposition) to minimize the chance of radiation-induced infertility
  d. Vaginal reconstruction may be performed using split-thickness skin grafts from the thighs or with myocutaneous flaps, usually with gracilis muscle.
  2. **RT** is an alternative treatment for patients with stage I disease; there are no controlled studies to prove that RT is as effective as surgery. Radiation is the treatment of choice for all higher stages, usually using combined external-beam and intravaginal RT.
  3. **Chemotherapy.** Topical fluorouracil, applied twice daily, has been used for CIS. Intense vaginal burning results. The long-range benefits of topical fluorouracil are not yet proved; this modality cannot be recommended as standard practice.
  4. **Laser therapy** is useful for stage 0.
  B. **Advanced disease** is managed as for cancer of the cervix (see Cancer of the Uterine Cervix, section VI.B). In otherwise healthy patients with stage IV disease or central recurrence after previous RT, an exenterative procedure may be performed.

VII. Special clinical problems. Loss of genitalia and vaginal stenosis are discussed in General Aspects, section III.

Vulvar Cancer

I. Epidemiology and etiology

  A. **Incidence.** Carcinomas of the vulva constitute 3% to 4% of malignant lesions of the female genital tract. The disease is most common in women older than 50 years of age, with a mean age at diagnosis of 65 years.
  B. **Etiology**
    1. **Viruses** are suspected to play a role in the development of vulvar cancer. HPV has been isolated from vulvar condylomas, and about 5% of patients with vulvar cancer have genital condylomas. Herpes simplex virus type II nonstructural proteins have been demonstrated in invasive vulvar lesions, but no structural antigens have been demonstrated.
    2. **Intraepithelial neoplasia** of the vulva, VIN, and CIN increase a woman's risk for carcinoma of the vulva.
    3. **Medical history** associated with increased risk of vulvar cancer includes obesity, hypertension, diabetes mellitus, arteriosclerosis, menopause at an early age, and nulliparity.

II. Pathology and natural history

  A. **Histology.** Malignant tumors of the vulva are squamous cell carcinoma in more than 90% of cases and melanoma in 5% to 10%. Adenocarcinoma, sarcoma, basal cell carcinoma, and other tumors constitute the remainder.
  B. **Location.** The sites of tumor in order of decreasing frequency are labia majora, labia minora, clitoris, and perineum.
  C. **Natural history**
    1. **Squamous cell carcinomas** in the vulva have not been shown to develop as a continuum from vulvar intraepithelial neoplasia to CIS to invasive carcinoma. Most studies report that only about 2% to 4% of vulvar intraepithelial neoplasia lesions become invasive cancer. These cancers tend to grow locally, spread to superficial and deep groin lymph nodes, and then spread to pelvic and distant nodes. Hematogenous spread usually occurs after lymph node involvement, and death usually results from cachexia or respiratory failure secondary to pulmonary metastases.
    2. **Malignant melanoma** of the vulva accounts for 5% of all melanoma cases, despite the comparatively small surface area involved and the paucity of nevi at this site (see Chapter 16, Malignant Melanoma). Therefore, all pigmented vulvar lesions should be removed.
    3. **Paget's disease of the vulva** is a preinvasive lesion with thickened epithelium infiltrated with mucin-rich Paget's cells, which are derived from the stratum germinativum of the epidermis. Research shows that only 1% to 2% of patients with Paget's disease have an associated underlying adenocarcinoma of the vulva. Many older publications have reported a higher incidence of adenocarcinoma with Paget's disease, but this is probably a reflection of the underdiagnosis of the disorder. Paget's disease is associated with a synchronous primary cancer in another genital tract site in 25% of patients.
    4. **Bartholin gland adenocarcinoma** is extremely rare and is usually seen in older women. Inflammation of this gland is uncommon in women older than 50 years of age and is virtually nonexistent in postmenopausal women; gland swelling in women in these age groups should arouse suspicion for the presence of cancer.
    5. **Basal cell carcinomas and sarcomas** of the vulva have natural histories similar to that of primary tumors located elsewhere.

III. Diagnosis

  A. **Signs and symptoms**
    1. Squamous cell carcinomas most often present with a vulvar lump or mass, often with a history of chronic vulvar pruritus. The tumors often ulcerate or become fungating. Bleeding, superinfection, and pain can develop with continued growth.
    2. Paget's disease has a characteristic lesion that is velvety red, with raised, irregular margins. Lesions are pruritic, with secondary excoriation and bleeding.
    3. Basal cell carcinomas and melanomas are discussed in Chapter 16.
    4. Lymph node enlargement may be palpable in the inguinal or femoral regions or in the pelvis.
  B. **Indications for wedge biopsy**
    1. Patches of skin that appear red, dark brown, or white
    2. Areas that are firm to palpation
    3. Pruritic or bleeding lesions
    4. Any nevus in the genital region
    5. Enlargement or thickening in the region of Bartholin's glands, particularly in patients 50 years of age or older
  C. **Staging evaluation** (see General Aspects, section II.B).

IV. Staging system and prognostic factors for squamous cell carcinoma

  A. **Staging system.** FIGO has adopted a surgically based TMN staging system to avoid the problems associated with clinical assessment of lymph nodes.

FIGO stage	TNM stage	Clinical/pathologic findings
I	T1 N0 M0	Tumor confined to the vulva or perineum, <2 cm in greatest dimension, lymph nodes negative
II	T2 N0 M0	Tumor confined to the vulva and/or perineum, <2 cm in greatest dimension, lymph nodes negative
III	T3 N0 M0	Tumor of any size with: adjacent spread to lower urethra or anus (T3) or unilateral regional lymph node
	T1,2,3 N1 M0	spread (N1)
IVA	T1,2,3 N2 M0	Tumor invades upper urethra, bladder mucosa, rectal mucosa, or pelvic bone (T4) or bilateral regional
	T4, Any N, M0	lymph node spread (N2)
IVB	Any T, Any N, M1	Any distant metastasis, including pelvic lymph nodes

  B. **Prognostic factors and survival.** Survival is determined by stage, structures invaded, and tumor location.
    1. **Lymph node involvement** is exceedingly important. Metastases to pelvic or periaortic nodes are rare in the absence of inguinal or femoral lymph node metastases.
    2. **The 5-year survival rate** in patients with negative or one microscopically positive lymph node is 95%. In contrast, the 5-year survival rate for patients with two positive nodes is 80%, and that for patients with three or more positive nodes is 15%. Note that the risk for hematogenous spread with three or more positive nodes is 66%, in contrast to the risk with two or fewer nodes, which is only 4%.

V. Prevention and early detection The routine history and physical examination of all postmenopausal women should include specific questioning regarding vulvar soreness and pruritus followed by careful inspection and palpation of the vulva and palpation for firm or fixed groin nodes. All suspicious lesions should undergo biopsy.

VI. Management

A. **Surgery is the treatment of choice for early-stage lesions.**
   1. **Vulvar intraepithelial neoplasia.** Wide local excision for small lesions. Carbon dioxide laser of the warty variety is acceptable.
   2. **Paget's disease.** This lesion usually extends well beyond the macroscopic lesion and requires a wide local excision. Underlying adenocarcinoma is usually apparent, but to avoid missing such a lesion, the underlying dermis should be removed for histologic evaluation.
   3. **Invasive carcinoma with less than 1 mm invasion.** Radical local excision
   4. **Stage I disease with greater than 1 mm but less than 5 mm invasion.** Radical local excision (modified radical vulvectomy) with ipsilateral groin lymph node dissection for lateralized lesions and bilateral node dissection for centralized lesions
   5. **Stage II lesions** may be treated with bilateral groin lymph node dissection and radical local excision (modified radical vulvectomy) provided that at least 1 cm of clear margins in all directions can be achieved while preserving critical midline structures.
      a. **Complications** include wound breakdown, local infection, sepsis, thromboembolism, and chronic edema of the lower extremities. Using separate incisions for the groin node dissections reduces the incidence of wound breakdown and leg edema.
      b. **Pelvic lymphadenectomy** is reserved for patients with clinically suspicious groin nodes or three or more proven unilateral groin nodes.
B. **RT**
   1. RT may be used to shrink stage III and IV tumors that involve the anus, rectum, rectovaginal septum, or proximal urethra preoperatively to improve resectability.
   2. RT has been shown to improve survival and decrease groin recurrence when two or more groin nodes are positive.
   3. Postoperative RT to the vulva may be used to reduce local recurrence when tumors exceed 4 cm or there are positive surgical margins.
   4. External-beam RT to 5000 cGy with follow-up biopsy should be considered for small anterior tumors involving the clitoris, especially in young women to prevent the psychosocial issues involved with surgery.
   5. Patients who have medical conditions precluding surgery may be treated with RT alone.
C. **Chemotherapy**
   1. 5-FU or cisplatin chemotherapy can be used as a radiation sensitizer.
   2. Systemic treatment with agents active against squamous cell carcinomas, such as cisplatin, methotrexate, cyclophosphamide, bleomycin, and mitomycin C, may be used for metastatic disease, but partial response rates are low (10% to 15%) and usually last only a few months.

Ovarian Cancer

I. Epidemiology and etiology

A. **Incidence** (Table 11.1). Ovarian cancer is the fourth most frequent visceral malignancy in the United States and is the most lethal of all the gynecologic cancers. No major improvement of overall survival has been made during the last 30 years. The average age at diagnosis is 55 years.
B. **Risk factors**
   1. The highest rates of ovarian cancer are recorded in industrialized countries. Physical, chemical, or dietary products may be etiologic. For example, Japanese women emigrating to the United States incur a higher risk than those who remain in Japan. No specific carcinogens have been determined.
   2. Fewer than 5% of epithelial ovarian cancers have a familial or hereditary pattern. Patients at highest risk are those with two or more first-degree relatives with documented epithelial ovarian cancer. Women with a personal history of breast or endometrial cancer also have an increased risk for ovarian cancer.
   3. Nulliparity with "incessant ovulation" is a risk factor.

II. Pathology and natural history

A. **Histology.** The World Health Organization's classification of neoplasms of the ovary is shown in Table 11.5.

Table 11.5 Histology of ovarian neoplasms

B. **Histologic grade.** The percentage of undifferentiated cells present in tissue determines the grade of the tumors (as defined by Broder).
   Grade Percentage of undifferentiated cells
   G1   0–25
   G2   25–50
   G3   <50
C. **Biologic behavior**
   1. **Borderline tumors,** also called "tumors of low malignant potential," tend to occur in premenopausal women and remain confined to the ovary for long periods of time. Metastatic implants may occur, and some may be progressive, leading to bowel obstruction and death.
   2. **Other histologic subtypes** behave similarly when grade and stage are considered. Even in early stages, careful exploration frequently reveals subdiaphragmatic and omental implants. Organ invasion and distant metastases are less likely than is spread over serosal surfaces. The lethal potential of ovarian cancer is most frequently related to encasement of intraabdominal organs. Death usually results from intestinal obstruction and inanition.
D. **Associated paraneoplastic syndromes**
   1. Neurologic syndromes are common. Peripheral neuropathies, organic dementia, amyotrophic lateral sclerosis–like syndrome, and cerebellar ataxia are the most frequent occurrences.
   2. Peculiar antibodies that cause difficulties in cross-matching blood can be corrected with prednisone.
   3. Cushing's syndrome
   4. Hypercalcemia
   5. Thrombophlebitis

III. Diagnosis

A. **Symptoms and signs.** Early ovarian carcinoma is typically asymptomatic. Symptoms, when they do occur, are often nonspecific and include irregular menses if premenopausal, urinary frequency, constipation, abnormal vaginal bleeding, abdominal discomfort, and distention. Physical findings include ascites and abdominal masses. Any pelvic mass in a woman who is more than 1 year postmenopausal is suspicious for ovarian cancer.
B. **Tissue diagnosis.** Diagnosis requires biopsy of ovarian or other suspected abdominal masses.
   1. **Adnexal masses**
      a. **Masses that are smaller than 8 cm** in premenopausal women are most commonly benign cysts. Patients should undergo ultrasound to confirm the cystic nature of the mass and receive suppression with oral contraceptives for 2 months. Benign lesions should regress.
      b. **Surgical evaluation** is necessary for masses with the following characteristics:
         1. Less than 8 cm in diameter and cystic but still present after 2 months of observation in premenopausal women
         2. Smaller than 8 cm in premenopausal women and solid on ultrasound
         3. Larger than 8 cm in premenopausal women
         4. Present in any postmenopausal patient
   2. **Pap smears** are not sensitive enough to detect ovarian cancer (25% yield).
C. **Serum tumor markers** (see Chapter 1, section III.D that are useful to monitor the response to therapy are CA 125 and CEA. b-human chorionic gonadotropin (b-HCG) and a-fetoprotein (a-FP) are useful in germ cell malignancies. None is useful for screening.

D. **Staging evaluation** (see General Aspects, section II.B).

IV. Staging system and prognostic factors

A. **Staging system and 5-year survival rate for epithelial tumors** (Table 11.6)

Table 11.6 Staging system and 5-yr survival rates for epithelial tumors

B. **Prognostic factors.** Extent, stage, and grade of disease are more important than specific histologic types. The extent to which the disease can be surgically debulked also affects prognosis.

V. Prevention and early detection
Women with strong family histories of epithelial ovarian cancer are at a two-fold increased risk for epithelial ovarian cancer compared with other women, and women with family histories of breast or ovarian cancer or a personal history of breast cancer also are at a two-fold increased risk. Women with a mutation in *BRCA-1* or *BRCA-2* account for 5% to 10% of all patients with ovarian cancer. The risk for ovarian cancer is 10% to 27% in these women. The risk for ovarian cancer in women with Lynch II syndrome (see Chapter 9, Table 9.2) is two to four times the general risk.

All of these groups should undergo proper genetic counseling and consider prophylactic oophorectomy when childbearing has been completed. Women should be advised that prophylactic oophorectomy does not offer absolute protection because peritoneal carcinomas occasionally occur after bilateral oophorectomy. The value of CA 125 for screening and transvaginal ultrasound in these women has not been clearly established.

VI. Management of epithelial ovarian cancers (see A in Table 11.5)

A. **Surgical staging evaluation**
   1. The ovarian tumor should be removed intact, if possible, and sent for frozen section. If the tumor is confined to the pelvis, a thorough surgical evaluation should be carried out.
   2. Any free fluid, especially in the pelvic cul-de-sac, should be sent for cytologic evaluation. If no free fluid is found, peritoneal washings should be obtained with 50 to 100 mL normal saline from the cul-de-sac, from each paracolic gutter, and from beneath each hemidiaphragm.
   3. Systematic exploration of all peritoneal surfaces and viscera is performed. Any suspicious areas or adhesions of peritoneal surfaces should undergo biopsy.
   4. The diaphragm should be sampled by biopsy or by scraping and preparation of a cytologic smear.
   5. The omentum should be resected from the transverse colon (an infracolic omentectomy).
   6. The retroperitoneal surfaces are then explored to evaluate the pelvic and paraaortic lymph nodes. Any enlarged lymph nodes are submitted for frozen section. If frozen section is negative, a formal pelvic lymphadenectomy is performed.
B. **Borderline tumors.** Treatment is surgical resection of the primary tumor. There is no evidence that subsequent chemotherapy or radiation improves survival. Even in most patients who have multifocal disease, adjuvant therapy probably has no role. Chemotherapy can be used for patients with invasive implants.
C. **Stage Ia and Ib, grade 1**
   1. **Premenopausal patients** in this category may, after staging laparotomy is completed, undergo unilateral oophorectomy to preserve fertility. Follow-up should include regular pelvic examinations and determinations of CA 125 levels. Generally, the other ovary and uterus are removed when childbearing is completed.
   2. **Postmenopausal patients** and women in whom childbearing is not an issue should undergo TAH/BSO.
D. **Stage Ia and Ib, grades 2 and 3, and stage Ic** are treated with TAH/BSO followed by either chemotherapy or radiation.
   1. **Chemotherapy** with cisplatin or carboplatin plus paclitaxel for three to six cycles is recommended for most patients (see section E.4 for regimen dosages). It may be preferable to give older patients a course of single-agent chemotherapy with paclitaxel, carboplatin, or melphalan for four to six cycles.
   2. **RT** with intraperitoneal radioactive phosphorus (^{32}P) is an acceptable alternative for patients without significant adhesions.
E. **Stages II, III, and IV**
   1. **Surgery** with exploration and removal of as much disease as possible should be carried out. Removal of the primary tumor and as much metastatic disease as possible is referred to as *cytoreductive surgery* or *debulking*. Performance of a retroperitoneal lymph node dissection appears to improve survival.
   2. **Adjuvant therapy and results of debulking**
      a. **Optimal debulking with no macroscopic residual disease** warrants treatment with six cycles of chemotherapy or whole-abdominal irradiation.
      b. **Optimal debulking with macroscopic disease less than 2 cm** warrants treatment with six cycles of chemotherapy.
      c. **Nonoptimal debulking** should be followed by three cycles of chemotherapy and interval cytoreduction if there is a partial response to chemotherapy.
   3. **Second-look laparotomy,** which may follow adjuvant therapy if there is no clinical evidence of disease, provides excellent prognostic information. The decision about whether to perform a second-look laparotomy must be individualized, particularly older women not on a research protocol. Laparoscopy is a less invasive alternative, although visibility may be more limited.

      Serial CA 125 determinations should be followed. CA 125 levels greater than 35 U/mL are nearly always associated with finding disease at second-look operations. Normal CA 125 levels, however, are not predictive of a negative second look.

      a. If there is no pathologic evidence of disease at the second-look procedure, the patient may be observed or may be given consolidation chemotherapy.
      b. Microscopic or macroscopic lesions smaller than 5 mm after second cytoreduction should be followed by intraperitoneal chemotherapy, and possibly RT and further chemotherapy using new agents.
      c. Residual lesions larger than 5 mm after second cytoreduction should be treated with experimental protocols or palliative care.
   4. **Chemotherapy**
      a. Cisplatin-based combination regimens have been the mainstay of treatment for advanced ovarian cancer. Carboplatin and paclitaxel (CP regimen) is now the preferred therapy; cisplatin can be substituted for carboplatin. CP is given every 3 weeks for six cycles as follows:

      Paclitaxel, 135 to 175 mg/m^2 (given before carboplatin or cisplatin)
      Carboplatin, AUC 5 to 6 (or, cisplatin, 75 mg/m^2)

      b. Carboplatin has fewer gastrointestinal, neurologic, and renal side effects than cisplatin but more hematotoxicity. When paclitaxel is infused over 3 hours, it is associated with more neurologic toxicity and less hematologic toxicity than when it is infused over 24 hours.
      c. Single-agent oral therapy with melphalan is reserved for patients who cannot tolerate more toxic regimens or as a second-line therapy.
   5. **RT** (whole-abdominal irradiation) appears to be useful, as an alternative to chemotherapy, in patients who have optimal or microscopic disease.
F. **Salvage therapy**
   1. **Cytotoxic drugs.** If disease relapses later than 12 months or more after completion of primary therapy, the original drugs (presumably CP) may be retried. If disease progresses on first-line therapy or relapses a short time after completion of primary therapy, other drugs should be used. Chemotherapeutic agents that may be helpful after failure of first-line therapy include oral etoposide (100 mg/day for 14 days of each 21 day cycle), topotecan, gemcitabine, vinorelbine (Navelbine), ifosfamide, hexamethylmelamine, and liposomal doxorubicin. Combinations of drugs have not been shown to be more effective than single agents. Response rates are about 15% to 30%.
   2. **High-dose chemotherapy** with autologous stem cell support has been disappointing for the treatment of ovarian cancer. More dose-intense approaches have not yielded better results than standard intravenous schedules.
   3. **Secondary cytoreductive surgery**
      a. May be beneficial for patients who responded to chemotherapy and who have gross residual disease found at second-look laparotomy. Similarly, such surgery may be beneficial for patients who develop recurrent cancer after a disease-free interval following complete clinical or pathologic response. This benefit depends on the ability to cytoreduce tumors to microscopic disease; these patients also appear to achieve improved survival. Laparoscopy may assist in selecting patients for additional surgery.
      b. Is not beneficial for patients with disease that is not responsive to chemotherapy
   4. **Palliative surgery** may be considered in patients who develop bowel obstruction and resistance to chemotherapy but have a reasonably good performance status; this is usually a difficult recommendation to make for all concerned. The goal is to allow the patient sufficient oral intake to maintain hydration or some

nutrition at home. If successful, the procedure may allow 3 to 6 months of relief. Unfortunately, the complication and mortality rates from surgery are high, and the success rate is low. The patient and her family must clearly understand these limitations when decisions are made.

G. **Patient follow-up** after disease-free second-look operations is clinical because there are no reliable means of surveillance. CA 125 levels should be followed, but CT and ultrasound have proved too insensitive to detect early recurrent disease. CT may be used to follow known masses.

VII. Müllerian peritoneal tumors. The histology of peritoneal mesothelium is identical to that of germinal epithelium. The peritoneum may transform into different forms of benign and malignant müllerian epithelia that may mimic metastatic papillary adenocarcinoma. A synonym is *papillary peritoneal neoplasia.*

A. **Benign cystic mesothelioma** is a benign cystic proliferation of peritoneal epithelia throughout the peritoneal cavity. Local recurrence after surgery is common but not fatal.

B. **Malignant müllerian peritoneal tumors** resemble advanced epithelial ovarian carcinoma and present as implants throughout the peritoneal cavity (including ovarian surfaces). Management is the same as for stage III epithelial ovarian carcinoma.

VIII. Germ cell tumors (see B in Table 11.5)

A. **Epidemiology.** Germ cell tumors make up 20% to 25% of all ovarian neoplasms, but only 3% of these tumors are malignant. These malignancies constitute fewer than 5% of all ovarian cancers in Western countries and up to 15% in Asian and African populations. Germ cell tumors constitute more than 70% of ovarian neoplasms in the first two decades of life, and in this age range, one third are malignant.

B. **Signs and symptoms.** These tumors grow rapidly and often present with subacute pelvic pain and pressure and menstrual irregularity. Acute symptoms related to torsion or adnexal rupture are often confused with acute appendicitis. Adnexal masses greater than 2 cm in premenarchal girls and in premenopausal women are suspicious; they usually require surgical investigation.

C. **Diagnosis.** Young patients should be tested for serum b-HCG and a-FP titers along with other routine blood work. A karyotype should be obtained because of the propensity of these tumors to arise from dysgenetic gonads. A chest radiograph is essential because germ cell tumors may metastasize to lungs or mediastinum.

D. **Tumor types**
  1. **Dysgerminoma**
     a. **Natural history.** Dysgerminomas are the most common germ cell malignancy and represent up to 10% of ovarian cancers in patients younger than 20 years of age. Three fourths of dysgerminomas occur between the ages of 10 and 30 years. About 5% are found in dysgenic gonads. Three fourths of cases are stage I, and 10% to 15% are bilateral. Unlike other ovarian malignancies, dysgerminomas often spread earlier through the lymphatics than to peritoneal surfaces.
     b. **Treatment** is primarily surgical; the minimal operation is unilateral oophorectomy with complete surgical staging. The chance of recurrence in the other ovary during the next 2 years is 5% to 10%, but these lesions are sensitive to chemotherapy. When fertility is an issue, the uterus and contralateral ovary should be preserved even in the presence of metastatic disease. If fertility is not an issue, TAH/BSO should be performed. If a Y chromosome is found by karyotyping, both ovaries should be removed, but the uterus may be left in place.
        1. **Chemotherapy** is the adjuvant treatment of choice for metastatic disease. A combination of bleomycin, etoposide, and cisplatin (BEP regimen) is most often used. **BEP** dosages are as follows:

           Bleomycin, 15 U/m^2 per week for 5 weeks; then on day 1 of the fourth course

           Etoposide, 100 mg/m^2 per day for 5 days every 3 weeks

           Cisplatin, 20 mg/m^2 per day for 5 days, or 100 mg/m^2 on 1 day, every 3 weeks
        2. **RT.** If fertility is not an issue, metastatic disease may be treated with radiation because these tumors are very sensitive to it.
     c. **Prognosis.** The 5-year survival rate for patients with stage Ia disease is more than 95% when the disease is treated with unilateral oophorectomy alone. Recurrence is most likely in patients with lesions larger than 10 to 15 cm in diameter, who are younger than 20 years of age, and who have an anaplastic histology. Patients with advanced disease that is treated with surgery followed by BEP chemotherapy have a 5-year survival rate of 85% to 90%.
  2. **Immature teratoma**
     a. **Natural history.** Pure immature teratomas account for less than 1% of all ovarian cancers but are the second most common germ cell malignancy. They constitute 10% to 20% of ovarian malignancies in patients younger than 20 years of age and account for 30% of ovarian cancer deaths in this group. Serum tumor markers (b-HCG, a-FP) are not found unless the tumor is of mixed type. The most common site of spread is the peritoneum; hematogenous spread is uncommon and occurs late.
     b. **Treatment.** In premenopausal women in whom the lesion is confined to one ovary, a unilateral oophorectomy with surgical staging is warranted. In postmenopausal women, TAH/BSO is performed. For patients with stage Ia, grade 1 tumors, no adjuvant therapy is required. For stage Ia, grade 2 or 3, or for higher stages with gross residual disease, adjuvant chemotherapy with BEP should be used. Chemotherapy is also indicated for patients with ascites, regardless of grade. RT is reserved for patients with localized disease after chemotherapy. Second-look laparotomy is best reserved for patients at high risk for treatment failure (i.e., patients with macroscopic disease at the start of chemotherapy) because there are no reliable tumor markers for this disease.
     c. **Prognosis.** The most important prognostic feature of immature teratomas is their histologic grade. The 5-year survival rate is 80% to 100%. Patients whose lesions cannot be completely resected before chemotherapy have a 5-year survival rate of only 50%, as compared with 94% for completely resected disease.
  3. **Endodermal sinus tumors** or yolk sac carcinomas are rare. The median age at diagnosis is 18 years. Pelvic or abdominal pain is the most common presenting symptom. Most of these lesions secrete a-FP, and serum levels are useful in monitoring response to treatment. Treatment consists of surgical staging, unilateral oophorectomy, and frozen section for diagnosis. All patients are given adjuvant or therapeutic chemotherapy. BEP appears to be most effective. A seven-drug regimen has been developed for high-risk germ cell tumors of any histologic type and may be used in patients with massive metastatic disease or with liver or brain metastases.
  4. **Embryonal carcinoma** is an extremely rare tumor that occurs in young women and girls, with a median age of 14 years. These tumors may secrete estrogens, producing symptoms of precocious pseudopuberty or irregular bleeding. Two thirds are confined to one ovary at presentation, and they frequently secrete a-FP and b-HCG, which are useful to follow response to therapy. Treatment is unilateral or bilateral oophorectomy followed by chemotherapy with BEP.
  5. **Choriocarcinoma of the ovary** is extremely rare; most patients are younger than 20 years of age. b-HCG is often a useful tumor marker. Half of premenarchal patients present with isosexual precocity. The prognosis is usually poor, but complete responses have been reported with combination methotrexate, actinomycin D, and cyclophosphamide (Cytoxan; MAC III regimen; see Gestational Trophoblastic Neoplasia, section VI.B.3.b).
  6. **Mixed germ cell tumors** most commonly have a dysgerminoma or endodermal sinus component. Secretion of a-FP or b-HCG depends on component parts. Lesions should be managed with unilateral oophorectomy and chemotherapy with BEP. A second-look laparotomy may be indicated when macroscopic disease is present at the start of chemotherapy to determine response to therapy in components that do not produce tumor markers.

IX. Sex cord stromal tumors (see C in Table 11.5) account for 5% to 8% of all ovarian cancers. Most tumors are a combination of cell types derived from the sex cords and ovarian stroma or mesenchyme.

A. **Granulosa–stromal cell tumors** include granulosa cell tumors, thecomas, and fibromas. Thecomas and fibromas are rarely malignant and are then called *fibrosarcomas.* Granulosa cell tumors are low-grade, estrogen-secreting malignancies that are seen in women of all ages. Endometrial cancer occurs with granulosa cell tumors in 5% of cases, and 25% to 50% are associated with endometrial hyperplasia. Inhibin, which may be secreted by some granulosa cell tumors, may be a useful tumor marker. Surgery alone is usually sufficient therapy; RT and chemotherapy are reserved for women with recurrent or metastatic disease. Granulosa cell tumors have a 10-year survival rate of about 90%. DNA ploidy correlates with survival.

B. **Sertoli-Leydig tumors** have a peak incidence between the third and fourth decades. These rare lesions are usually low-grade malignancies. Most produce androgens, and virilization is seen in 70% to 85% of patients. Usual treatment is unilateral salpingo-oophorectomy with evaluation of the contralateral ovary. TAH/BSO is appropriate for older patients. The utility of radiation or chemotherapy is yet to be proved.

X. Other tumors (see D Table 11.5)

A. **Lipoid cell tumors** are extremely rare, with only slightly more than 100 cases reported. They are thought to arise from adrenal cortical rests near the ovary. Most are virilizing and are benign or low-grade malignancies. Treatment is surgical extirpation.

B. **Ovarian sarcomas** are also extremely rare, and most occur in postmenopausal women. They are aggressive lesions with no effective treatment. Most patients

die within 2 years.
  C. **Lymphoma** can involve the ovaries, usually bilaterally, especially with Burkitt lymphoma. A hematologist-oncologist should be consulted intraoperatively when lymphoma is found to determine the need for surgical staging. Treatment is as for lymphomas elsewhere in the body.

XI. Special clinical problems

  A. **Pseudomyxoma peritonei** occurs in the setting of mucinous cystadenocarcinoma or "benign" mucinous adenomas. The peritoneum becomes filled with jelly-like material that compresses bowel and produces painful abdominal distention. Chemotherapy may impede cellular production of the mucoid material but usually has little direct effect on the tumor. Periodic surgical debulking may be the only way to provide relief of abdominal symptoms. It is now believed that these lesions are typically associated with mucinous adenocarcinomas of the appendix.
  B. **Obstructive complications.** Intestinal obstruction is discussed in Chapter 30, section II. Rectal or urinary tract obstruction or dyspareunia in patients with advanced pelvic cancers may respond to either systemic chemotherapy or local irradiation (see General Aspects, section IV). We prefer to use chemotherapy first and retain the flexibility to use further cytotoxic agent treatment later in the course.
  C. **Pregnancy with ovarian cancer** (see Chapter 26). Pregnancy is rarely complicated by the development of ovarian cancer. All pregnant patients have luteal cysts, which should be less than 5 to 6 cm in diameter. Masses that are larger or continue to enlarge over several weeks should be examined by laparoscopy at 16 weeks of gestation. Management of pregnant patients with ovarian cancer is the same as for nonpregnant patients who desire childbearing.
  D. **Fallopian tube cancers** account for 0.3% of all cancers of the female genital tract. They are seen most frequently in the fifth and sixth decades of life. The classic triad of symptoms is a prominent watery vaginal discharge, pelvic pain, and pelvic mass; however, this triad is seen in fewer than 15% of patients. The histologic features, evaluation, and treatment are similar to those of ovarian cancer.

Gestational Trophoblastic Neoplasia

I. Epidemiology and etiology Gestational choriocarcinoma accounts for less than 1% of malignancies in women. The etiology is unknown, but certain risk factors and the relationship with hydatidiform mole are well recognized.

  A. **Hydatidiform mole**
    1. Hydatidiform mole develops in about 1 in 2000 pregnancies in North America and Europe. The incidence is 5 to 10 times greater in Asia, Latin America, and other countries.
    2. Other factors that are associated with the occurrence of hydatidiform mole include the following:
        a. Patients who have had a prior molar pregnancy
        b. Extremes of reproductive age
        c. Presence of twin pregnancy
  B. **Malignant transformation.** About 10% to 20% of molar pregnancies develop malignant trophoblastic neoplasia; two thirds of the cases are locally invasive moles (chorioadenoma destruens), and one third are choriocarcinoma. Thus, choriocarcinoma develops in 3% to 5% of moles. However, only 50% of choriocarcinoma cases have an antecedent hydatidiform mole; 25% follow pregnancies terminated by abortion, 20% follow delivery of a viable fetus, and 5% follow an ectopic pregnancy. The risk for choriocarcinoma is five times greater for an ectopic gestation than for an intrauterine gestation.

II. Pathology and natural history

  A. **Pathology.** The fetal placenta is composed of mesenchymal tissue with blood vessels (the villus) and a covering epithelium (trophoblast). Hydatidiform mole results from an easily recognized, grapelike hydropic degeneration of the villus (which may or may not be associated with changes in the trophoblast). Choriocarcinoma results from the malignant transformation of the trophoblast and is characterized by the absence of villi. A fine line separates benign from malignant disease. However, histology is not the crucial feature of these disorders; the clinical course determines whether the growth is benign or malignant. Occasionally, malignant growth may not become clinically evident until years after the last gestation.
  B. **Dissemination.** These tumors disseminate locally to the vagina and pelvic organs. Choriocarcinoma disseminates rapidly and widely through the bloodstream. The liver and lungs are the most common and important sites of distant metastases.

III. Diagnosis

  A. **Symptoms** of molar pregnancy or malignant trophoblastic disease include the following:
    1. Vaginal bleeding during pregnancy (nearly all cases of molar pregnancy or malignant trophoblastic disease cause bleeding)
    2. Hyperemesis gravidarum
    3. Passage of grapelike villi from the uterus
    4. Sweating, tachycardia, weight loss, and nervousness resulting from paraneoplastic hyperthyroidism (see section VII.A)
    5. Pulmonary symptoms as a consequence of lung metastases
    6. Right upper quadrant pain or jaundice as a consequence of liver metastases
    7. Any neurologic abnormality resulting from brain metastases
    8. Abdominal (uterine) pain early in pregnancy
  B. **Physical findings**
    1. The uterus is usually, but not always, larger than expected for the duration of pregnancy.
    2. Fetal heart tones are absent (the coexistence of a viable fetus and a partial hydatidiform mole is uncommon).
    3. The patient develops signs of toxemia of pregnancy (hypertension, retinal sheen, sudden weight gain, proteinuria, or peripheral edema). If signs occur in the first or second trimester, a molar pregnancy is strongly suspected.
  C. **Preliminary laboratory studies**
    1. Complete blood count, platelet count, alkaline phosphatase level, LFTs
    2. b-HCG production is maximal in early pregnancy and decreases thereafter. Normal HCG values for pregnancy depend on the assay method used by the laboratory. HCG is elevated in all patients with choriocarcinoma; the serum concentration directly reflects the tumor volume. The serum half-life of HCG is 18 to 24 hours.
  D. **Special diagnostic studies**
    1. Ultrasonography of the uterus and Doppler examination reveal no evidence of fetal parts or heart beat in trophoblastic disease. If these examinations show no fetus, plain radiographs of the pelvic organs are obtained for confirmation.
    2. A chest radiograph should be obtained in patients with molar pregnancy.
    3. Radionuclide and CT scans are used to detect brain, liver, or other abdominal metastases. Scans and films of the abdomen and pelvis must be avoided until the absence of a fetus is proved.
    4. Thyroid studies (serum thyroxine concentration and triiodothyronine-resin uptake) are obtained in patients with clinical evidence of hyperthyroidism.

IV. Staging systems and prognostic factors
A staging system for choriocarcinoma is not yet established. A system in use at some centers divides patients into low- and high-risk groups.

  A. **Low-risk patients** have a 5-year survival expectancy of almost 100%. These patients have the following characteristics:
    1. Less than a 4-month history suggestive of metastatic disease
    2. A serum HCG titer of less than 50 mIU/mL
    3. No evidence of liver or central nervous system metastases
  B. **High-risk patients** have a 5-year survival expectancy of 50%. These patients have at least one of the following characteristics:
    1. More than a 4-month history of metastatic disease
    2. A serum HCG titer of more than 50 mIU/mL
    3. Liver or brain metastases
    4. Disease after term pregnancy
    5. Failure of chemotherapy

V. Prevention and early detection Early detection depends on careful attention to the signs and symptoms of trophoblastic disease in pregnant and postpartum patients.

VI. Management. All forms of gestational trophoblastic neoplasia, from hydatidiform mole to choriocarcinoma, are almost invariably lethal if not treated.

    A. **Early disease** signifies a molar pregnancy without evidence of distant metastases by history, physical examination, LFTs, chest radiograph, or scans.

        1. **Surgery.** Molar tissue is removed by suction curettage while oxytocin is being administered, and then by sharp curettement. Hysterectomy is recommended for women older than 40 years of age. Disappearance of HCG is achieved within 8 weeks in 80% of patients treated by surgery; virtually all of these patients are cured. The patient is followed with weekly blood assays for HCG.

        2. **RT** has no role in early disease.

        3. **Chemotherapy.** After surgical treatment of a molar pregnancy with no suggestion of metastatic disease, weekly serum HCG titers are obtained. Chemotherapy is started for histologic diagnosis of choriocarcinoma, rising HCG titer (for 2 weeks), plateau of HCG titer (for 3 weeks), documentation of metastatic disease, or return of titers with no other explanation after achieving a zero titer. So long as titers continue to decrease, treatment is usually not started; in the past, treatment was started after a predetermined number of weeks.

           a. **Methotrexate** is the drug of choice in early gestational trophoblastic neoplasia. Methotrexate, 15 to 30 mg, is given IV daily for 5 days every 2 weeks. If there is significant toxicity, the drug is stopped. When the blood counts have become normal and other signs of toxicity have resolved, the drug is reinstituted at a dose reduced by 25%.

           b. **Actinomycin D** is used instead of methotrexate in patients with renal function impairment (creatinine clearance less than 60 mL/ min). The dose is 8 to 13 μg/kg (usually 10 μg/kg) given in the same schedule as methotrexate.

    B. **Advanced disease**

        1. **Surgery** is used to evacuate or excise the uterus for the same indications outlined in early disease (see <u>section A.1</u>).

        2. **RT,** in combination with chemotherapy, is clearly indicated for the primary management of patients with liver or brain metastases.

        3. **Chemotherapy** is the mainstay of management for metastatic trophoblastic disease. All patients undergo the restaging evaluation described in <u>section III.C</u>, <u>section III.D</u>, and <u>section IV</u>.

           a. **Low-risk patients** are treated with methotrexate or actinomycin D, as for early-disease patients. Patients not responding to one of these agents are switched to the alternative drug.

           b. **High-risk patients** are treated with combination chemotherapy regimens, such as EMA-CO or EMA-CE (described subsequently). RT is given if the liver or brain is involved by metastases. Chemotherapy dosage schedules are as follows (cycle intervals should not be extended without good cause):

               1. **EMA-CO** is given in 14-day cycles.

                  Etoposide, 100 mg/m^2 IV on days 1 and 2

                  Methotrexate, 100 mg/m^2 IV push, followed by 200 mg/m^2 by continuous IV infusion over 12 hours on day 1; leucovorin, 15 mg PO or IM, every 12 hours for four doses beginning 24 hours after the start of methotrexate

                  Actinomycin D, 0.5 mg (*not* per m^2) IV push on days 1 and 2

                  Cyclophosphamide, 600 mg/m^2 IV on day 8

                  Vincristine (Oncovin), 1.0 mg/m^2 IV push on day 8 (maximum 2 mg)

               2. **EMA-CE** is given in 14-day cycles.

                  Etoposide, 100 mg/m^2 IV on days 1 and 2

                  Methotrexate, 100 mg/m^2 IV push, followed by 1000 mg/m^2 by continuous IV infusion over 12 hours on day 1; leucovorin, 30 mg PO or IM, every 12 hours for six doses beginning 32 hours after starting methotrexate

                  Actinomycin D, 0.5 mg (*not* per m^2) IV push on days 1 and 2

                  Cisplatin, 60 mg/m^2 IV on day 8 with prehydration

                  Etoposide, 100 mg/m^2 IV on day 8

            c. **Duration of treatment.** Chemotherapy should be continued until no HCG is demonstrable in the serum for three consecutive weekly assays. If the HCG titer rises or plateaus between any two measurements, the chemotherapy regimen must be changed.

    C. **Patient follow-up**

        1. The HCG level is the single most important tumor marker in trophoblastic neoplasia. The assay should be repeated weekly during therapy. After therapy is completed, HCG titers are obtained according to the following schedule: every 2 weeks for 2 months; every month for the next 3 months; every 2 months for the next 6 months; and every 6 months thereafter.

        2. Other studies that demonstrated disease at the start of therapy should be repeated monthly until complete remission is documented.

VII. Special clinical problems

    A. **Thyrotoxicosis** and even "thyroid storm" may result from the thyroid-stimulating hormone–like effect of high concentrations of HCG. Clinical evidence of hyperthyroidism in choriocarcinoma occurs in the presence of widespread metastases and is associated with a poor prognosis. Laboratory confirmation requires a serum thyroxine concentration and triiodothyronine-resin uptake levels compatible with hyperthyroidism. If the symptoms are mild, propylthiouracil or methimazole can be used. In severe cases, patients must be given propranolol and Lugol's solution.

    B. **Development of choriocarcinoma** long after the last pregnancy or even hysterectomy can occur. This development serves to emphasize that histologic diagnosis is necessary in metastatic cancer when the primary tumor is not evident. The diagnosis of choriocarcinoma can lead to life-saving therapy.

    C. **Subsequent pregnancies.** Women with a history of trophoblastic disease can have normal pregnancies after successful treatment of the cancer.

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* *Point A* and *point B* are common terms used in the management of cervical cancer. Point A is 2 cm proximal and 2 cm lateral to the cervical os. Point B is 3 cm lateral to point A.

Chapter 12 Testicular Cancer

Lawrence H. Einhorn

I. Epidemiology and etiology

A. **Epidemiology**
1. **Incidence.** Testicular cancer constitutes only 1% of all cancers in men but is the most common malignancy that develops in men between the ages of 20 and 40 years. About 6000 new cases are diagnosed annually in the United States.
2. **Racial predilection.** The incidence of testicular cancer in blacks is one sixth that in whites. Asians also have a lower incidence than whites.
3. **Bilateral cancer of the testis** occurs in about 2% of cases.
B. **Etiology**
1. **Cryptorchidism.** Male patients with cryptorchidism are 10 to 40 times more likely to develop testicular carcinoma than are those with normally descended testes. The risk for developing cancer in a testis is 1 in 80 if retained in the inguinal canal and 1 in 20 if retained in the abdomen. Surgical placement of an undescended testis into the scrotum before 6 years of age reduces the risk for cancer. However, 25% of cancers in patients with cryptorchidism occur in the normal, descended testis.
2. **Testicular feminization syndromes** increase the risk for cancer in the retained gonad by 40-fold. Tumors in these patients are often bilateral.
3. **Other risk factors.** The magnitude of other suggested risk factors, such as a history of orchitis, testicular trauma, or irradiation, is not known.

II. Pathology and natural history

A. **Histology.** Immunophenotypes of germ cell tumors are shown in Appendix C3.III.
1. Nearly all cancers of the testis in members of the younger age groups originate from germ cells (seminoma, embryonal cell, teratoma, and others). Other types, which account for less than 5% of cases, include rhabdomyosarcoma, lymphoma, and melanoma. Rarely, Sertoli's cell tumor, interstitial cell tumor, or other mesodermal tumors develop.
2. In men older than 60 years of age, 75% of neoplasms are not germinal cancers. Lymphomas are the most common testicular tumors in this age group.
3. Metastatic cancer to the testis is most often associated with prostatic carcinoma, lung cancer, melanoma, or leukemia.
B. **Histogenesis.** Each type of germinal cancer is thought to be a counterpart of normal embryonic development (Fig. 12.1). Seminoma is the neoplastic counterpart of the spermatocyte. The tissues of the early cleavage stage are the most undifferentiated and pluripotential and give rise to both the embryo and the placenta; the malignant counterpart is embryonal cell carcinoma. Teratomas are the neoplastic counterparts of the developing embryo. Choriocarcinoma is actually a more highly undifferentiated cancer; its aggressive biologic behavior reflects the capacity of its normal counterpart (the placenta) to invade blood vessels. The histologic similarity between germ cell cancer and normal embryology is illustrated by the following observations:

Figure 12.1 Histogenesis of testicular neoplasms. Embryonic *counterparts* and tumor marker production are shown. b-HCG, b-subunit of human chorionic gonadotropin; a-FP, a-fetoprotein.

1. Pure choriocarcinomas metastasize only as choriocarcinomas.
2. Seminomas usually metastasize as seminomas; those that do not are believed to represent mixed tumors undetected on the original histologic examination.
3. Metastases from embryonal carcinomas may be found to consist of teratoma or choriocarcinoma elements.
4. In metastases from mixed tumors, chemotherapy destroys the rapidly growing, drug-sensitive embryonal cell elements. The more drug-resistant teratomatous elements may remain clinically evident but may become mature on histologic examination.
C. **Natural history.** The natural history of testis cancer varies with the histologic subtype. Both blood-borne and lymphatic metastases occur. Lymphatic drainage usually occurs in an orderly progression involving ileal and paraaortic lymphatic chains as well as more lateral nodes near the kidneys; inguinal and femoral nodes are normally not affected. Previous surgery, such as scrotal contamination with scrotal orchiectomy, disrupts normal lymphatic drainage patterns.
1. **Seminoma** (40% to 50% of testicular cancers) occurs in an older age group than other germ cell neoplasms, most commonly after the age of 30 years. Sixty percent of patients with cryptorchidism who develop testicular cancer have seminoma. Seminomas tend to be large, show little hemorrhage or necrosis on gross inspection, and metastasize in an orderly, sequential manner along draining lymph node chains. About 25% of patients have lymphatic metastases, and 1% to 5% have visceral metastases at the time of diagnosis. Metastases to parenchymal organs (usually lung or bone) can occur late. Seminoma is the type of testicular cancer most likely to produce osseous metastases. Three atypical forms of seminoma are the spermatocytic, poorly differentiated, and mixed subtypes.
   a. **Spermatocytic seminoma** (4% of seminomas) occurs mostly after the age of 50 years and is the most common germ cell tumor after 70 years of age. It is more often bilateral (6% compared with 2%) and appears to have a much lower incidence of both lymphatic and parenchymal metastases (even to draining lymph nodes) when compared with typical seminoma.
   b. **Anaplastic seminoma** (10% of seminomas) is defined as a seminoma with three or more mitoses per high-power field. These tumors are clinically aggressive; however, stage for stage, their management and prognosis is identical to that of typical seminoma.
   c. **Mixed tumors** consist of seminoma together with embryonal or choriocarcinoma elements. Their natural history reflects the most aggressive histologic subtype of all cancers of the testis. The presence of visceral metastases in a patient whose primary tumor was apparently pure seminoma suggests the presence of another germ cell type.
2. **Embryonal carcinoma and teratoma** (half of testicular cancers) occur predominantly in 20- to 30-year-old patients. About two thirds of these tumors are pure embryonal cell carcinomas, and one third have a preponderance of teratomatous features. The term *teratocarcinoma* refers to teratomas in combination with other elements. These subtypes are grouped together because teratomas appear to be dependent on the pluripotential embryonal cell line for their malignant potential. Any of the tissues in teratomas may become malignant (e.g., glandular structures may develop into adenocarcinoma).

These tumors grow extremely rapidly, tend to be bulky and to have areas of hemorrhage and necrosis, and spread by draining lymphatics and blood-borne metastases (particularly to the lung and liver). More than 65% of patients have evidence of metastatic disease at the time of presentation.

3. **Pure choriocarcinoma** (less than 0.5% of testicular cancers) metastasizes rapidly through the bloodstream to lungs, liver, brain, and other visceral sites.
4. **Yolk sac tumors** are common cancers in children and have a relatively unaggressive clinical course. Yolk sac elements in testicular cancer found in adult patients, on the other hand, portend a poor prognosis.
5. **Rare testicular tumors**
   a. **Gonadoblastomas** are found in patients with dysgenic gonads and chromosomal mosaicism. These tumors are mixtures of germ cell and stromal elements, such as Sertoli's cells. They vary in malignant potential, but all can metastasize.
   b. **Polyembryomas** have a natural history similar to that of embryonal carcinoma.
   c. **Dermoid cysts** are fully mature teratomas and are exceptionally rare in the testis.
   d. **Rhabdomyosarcoma** of the testis occurs most often before 20 years of age. Its clinical behavior is similar to that of embryonal carcinoma; metastases to draining lymph nodes and lung are common at the time it first appears.

III. Diagnosis

A. **Symptoms and signs**
  1. **Symptoms**
      a. **Mass and pain.** The most common symptom of testicular cancer is a painless enlargement, usually noticed during bathing or after a minor trauma. Painful enlargement of the testis occurs in 30% to 50% of patients and may be the result of bleeding or infarction in the tumor. Acute pain in a patient with a cryptorchid testis suggests the possibility of torsion of a testicular cancer; rupture into the abdomen results in manifestations that may be indistinguishable from acute appendicitis and other causes of an acute abdomen.
      b. **Acute epididymitis.** Nearly 25% of patients with mixed teratoma and embryonal cell tumor present with findings indistinguishable from acute epididymitis. The testicular swelling from tumor may even decrease somewhat after antimicrobial therapy.
      c. **Gynecomastia** is the first sign of testicular cancer in about 10% of cases.
      d. **Infertility** is the primary symptom in about 3% of patients.
      e. **Back pain** from retroperitoneal node metastases is a presenting feature in 10% of patients.
      f. **Other presenting symptoms.** Skin and retroorbital metastases are unusual but occur most frequently with choriocarcinoma. Pyloric obstruction from epigastric lymph node metastases and bone pain from skeletal metastases are rare.
  2. **Physical findings**
      a. **Scrotum.** A testicular mass is nearly always present. The testis should be palpated using bimanual technique; the finding of irregularity, induration, or nodularity is indication for further evaluation.
      b. **Lymph nodes.** Patients must be carefully examined for lymph-adenopathy, particularly in the supraclavicular region. Iliac nodes are especially liable to be affected in patients with spermatic cord or epididymal involvement. Herniorrhaphy alters the normal lymphatic drainage; as a result, the contralateral iliac and homolateral inguinal nodes become those likely to be involved.
      c. **Breasts.** Gynecomastia is associated with tumors that secrete high levels of HCG.
B. **Differential diagnosis**
  1. **Hydroceles** are usually benign, but about 10% of testicular cancers are associated with coexisting hydroceles. The finding of a hydrocele in a young man should increase suspicion for an associated neoplasm.
      a. Benign hydroceles extend along the spermatic cord, often cause groin swelling, and can give the penis a foreshortened appearance. Hydroceles can be transilluminated.
      b. If the fluid prevents adequate palpation of the testis, a urologist should aspirate the fluid and reexamine the testis. Aspiration must avoid piercing a cancer (dissemination of tumor cells can result). Hydrocele fluid is clear and straw colored; the presence of blood in the fluid mandates exploratory surgery.
  2. **Epididymitis** produces acute enlargement of the testis with severe pain, fever, dysuria, and pyuria. The same symptoms may be caused by an underlying testicular cancer.
      a. **Persistent pain or swelling** after treatment may result from a supervening testicular abscess or a coexisting tumor; surgical exploration is indicated.
      b. **Recurrent epididymitis** with a completely normal testis occasionally occurs. Surgical exploration should not be considered if physical examination between episodes is completely normal. Recurrent epididymitis *per se* does not necessarily indicate cancer.
  3. **Varicoceles** are swollen veins in the pampiniform plexus of the spermatic cord. The scrotum feels like it contains a "bag of worms." The veins collapse when the patient is in Trendelenburg's position.
  4. **Spermatoceles** are translucent masses that are located posterior and superior to the testis and feel cystic.
  5. **Inguinal hernias** generally are not a diagnostic problem.
  6. **Other masses** include gummatous and tuberculous orchitis, hematoma, and acute swelling from testicular torsion. None of these can be distinguished clinically from cancer, and all require exploratory surgery.
C. **Tumor markers** are the most crucial and sensitive indicators of testicular cancer (Fig. 12.1). HCG, particularly the b-subunit (b-HCG), and a-fetoprotein (a-FP) are the only markers of proven value. One or both of these serum markers are present in more than 90% of patients with nonseminomatous germ cell cancer of the testis. The incidence rates of these markers according to tumor histology are shown in Table 12.1.

Table 12.1 Incidence of tumor markers in testicular cancers

  1. **HCG** is made by chorionic elements of the tumor. It is composed of two chains, a and b.
      a. **Whole two-component HCG** is a nonspecific tumor marker and may be found in patients with a variety of other tumors, including melanoma, lymphoma and sarcoma, or carcinoma of the lung, breast, ovary, or gastrointestinal tract. Nonmalignant conditions associated with elevated HCG levels include cirrhosis, peptic ulcer disease, and inflammatory bowel disease. The whole HCG molecule has a half-life in the blood of 24 hours.
      b. **a-HCG** is a component of several normal pituitary hormones and has been helpful in detecting certain occult neoplasms. a-HCG has a blood half-life of only 20 minutes.
      c. **b-HCG is never found in normal men.** Its presence always indicates a malignancy, and it has proved to be the most useful tumor marker to monitor response to therapy. In testicular cancer, the presence of b-HCG after orchiectomy constitutes proof that the patient has residual cancer and requires further treatment. The absence of b-HCG, however, does not exclude the presence of active cancer, particularly in previously treated patients. The blood half-life of b-HCG is 18 to 24 hours.
  2. **a-FP** is produced by yolk sac elements and is most commonly associated with embryonal carcinomas and yolk sac tumors. Elevated levels of a-FP are never found in patients with pure seminoma or pure choriocarcinoma. Elevated levels may also be explained by hepatocellular carcinoma, other cancers (occasionally), fetal hepatic production in pregnant women, infancy, and nonmalignant liver diseases (e.g., hepatitis, cirrhosis, necrosis). Elevated levels of a-FP after surgery or cytotoxic agent therapy for testicular cancer indicate the presence of residual disease and the need for further therapy. The blood half-life of a-FP is 5 days.
D. **Laboratory evaluation**
  1. **Routine preoperative studies**
      a. Complete blood count, liver function tests (especially lactate dehydrogenase [LDH] and alkaline phosphatase levels), and renal function tests
      b. Chest radiograph, including posteroanterior and lateral projections
      c. Blood levels of b-HCG and a-FP
  2. **Routine postoperative studies** are undertaken after the diagnosis of testicular cancer is proved. Studies performed in patients with all cell types include the following:
      a. **Chest computed tomography** (CT) **scan** detects about 10% more metastatic lesions than do plain chest radiographs.
      b. **Abdominal CT scans** assist assessment of retroperitoneal disease.
  3. **Supraclavicular lymph nodes.** Palpable lymph nodes should undergo biopsy for staging, if clinically appropriate.

IV. Staging system and prognostic factors

A. **Staging system and survival.** The system presented is a pathologic staging system for nonseminomatous tumors for which lymphadenectomy is a standard practice. The system is also used for clinical staging of seminomas, for which lymph node sampling is not part of management.

The survival statistics for testicular tumors have been drastically altered by modern therapy. The 5-year survival rate in patients with seminoma treated with radiation therapy (RT) alone is 95% to 99% for stage A disease and 80% to 90% for stage B; most patients with stage C disease are cured with chemotherapy. The 5-year survival rate in patients with stage C nonseminomatous tumors is 70% to 80%.

Stage Extent of disease
A   Disease confined to the testis
B   Metastases to the retroperitoneal lymph nodes
  B1 Five or fewer encapsulated lymph nodes positive for tumor
  B2 More than five lymph nodes positive for tumor
  B3 Massive retroperitoneal lymph node disease

C   Tumor involving supradiaphragmatic nodes, lungs, liver, bone, or brain

B. **Prognostic factors**
1. Elevated serum levels of a-FP or b-HCG after orchiectomy is prima facie evidence that the patient has residual cancer.
2. Serum LDH levels correlate fairly well with tumor burden.
3. The prognosis is worsened in the following cases:
   a. Bulky abdominal disease that cannot be removed by surgery even after treatment with chemotherapy
   b. Liver or brain metastases
   c. Pure choriocarcinoma, which has a particularly poor prognosis in men because of the advanced disease present at the time of diagnosis
4. For patients receiving chemotherapy for disseminated nonseminomatous disease, the **International Staging System** is used to define prognostic groups. Poor-risk (advanced disease) includes one or more of the following clinical features:
   a. Primary mediastinal nonseminomatous germ cell tumor
   b. Nonpulmonary visceral metastases
   c. Serum HCG level higher than 50,000 mIU/mL
   d. a-FP level higher than 10,000 ng/mL
   e. Serum LDH level more than 10 times the upper limit of normal

V. Prevention and early detection
Cryptorchidism should be surgically corrected before puberty because the risk for malignancy is substantial. Prophylactic removal of undescended testes should be performed in postpubertal patients; the complication rate is minuscule, the testes are functionless, and prostheses are available to fill the empty scrotum.

The effectiveness of early detection by screening programs has not been tested. Most patients have symptoms or signs of a scrotal mass; few cases are detected by routine history and physical examination.

VI. Management

A. **Transinguinal orchiectomy** is performed to make the diagnosis for all testicular cancers in all stages and is the treatment for stage A disease. A transinguinal approach is essential; the blood supply of the spermatic cord is immediately controlled. Transscrotal orchiectomy has been proved to result in tumor seeding to the skin and inguinal nodes. Likewise, transscrotal needle biopsy of a suspected testicular mass is *absolutely contraindicated*.

The subsequent management of early-stage testicular tumors depends on whether the histopathology shows pure seminoma or nonseminomatous elements.

B. **Management of seminomas: stages A and B**
1. **Surgery.** No further surgery is necessary after orchiectomy.
2. **RT.** Abdominal and chest CT is performed postoperatively in patients with seminoma. The retroperitoneal lymph nodes are irradiated. Seminomas are exquisitely sensitive to RT. Prophylactic mediastinal irradiation should not be used.
3. **Chemotherapy** is not necessary in most patients with stage A or B seminoma. Patients with bulky stage B (more than 5 cm disease) or stage C disease are treated the same as those with nonseminomatous germ cell cancer, and the results are similar (see section D). Seminoma confers a favorable prognosis because none of these cases, even those with nonpulmonary visceral disease, is classified in the international staging system as poor-risk (advanced) disease.

C. **Management of nonseminomatous germ cell cancer: stages A and B**
1. **Surgery.** Retroperitoneal lymphadenectomy is the standard of practice at most centers in the United States when staging evaluation does not reveal distant metastases, and when there is no lymph node with a maximal transverse diameter of 3 cm on abdominal CT. If lymph node metastases are demonstrated at surgery, patients may be either treated with two courses of adjuvant chemotherapy or observed without treatment and achieve the same nearly 100% cure rate. Lymphadenectomy previously interrupted the sympathetic pathways and invariably resulted in sterility from failure of ejaculation, but not impotence (see Chapter 26, section I.C.2). Modern nerve-sparing retroperitoneal lymph node dissections, however, now routinely preserve fertility and allow antegrade ejaculation.
2. **Chemotherapy.** The agents used are discussed in section D. Indications for chemotherapy include the following:
   a. Rising serum levels of b-HCG or a-FP after primary treatment, or elevated levels of b-HCG or a-FP with normal abdominal CT scan.
   b. The presence of bulky retroperitoneal disease (more than 3 cm in maximal transverse diameter of a node on abdominal CT) requires chemotherapy. If the abdominal CT scan becomes normal, retroperitoneal lymphadenectomy is not necessary. Otherwise, postchemotherapy retroperitoneal lymph node dissection is usually performed.
3. **Surveillance** is an appropriate strategy for compliant patients with clinical stage A disease (normal markers, physical examination, and radiographic studies after orchiectomy). It is crucial that both the physician and the patient understand the necessity for close observation. Relapses are usually treated with chemotherapy.

If surveillance is chosen, history and physical examinations, serum markers, and chest radiographs (posteroanterior and lateral views) are obtained monthly during the first year. The same studies are obtained every 2 months during the second year, every 6 months during the third, fourth, and fifth years after orchiectomy, and then annually. Abdominal CT is performed every 2 months during the first year, every 4 months during the second year, and then every 6 months during the third, fourth and fifth years.

D. **Management of disseminated disease: stage C**
1. **Combination chemotherapy** with etoposide and cisplatin (EP regimen) or with EP plus bleomycin (BEP regimen) produces complete remission in 70% to 80% of patients. Complete remissions are obtained with all cell types and are long-lasting. Relapses may occur within 1 year of initiating therapy. Maintenance chemotherapy after achieving a complete remission is not necessary.
   a. Standard chemotherapy for good-risk patients is either BEP for three courses or EP for four courses. Patients with poor-risk (advanced) disease are treated with four courses of BEP.
   b. BEP is administered every 3 weeks for three or four cycles. Dosages are as follows:

   Bleomycin, 30 U IV weekly
   Etoposide, 100 mg/m^2 IV daily for 5 days
   Cisplatin, 20 mg/m^2 IV daily for 5 days

2. **Resection of residual disease.** After cytoreduction with chemotherapy, about half of patients who do not achieve a complete remission (an additional 10% to 15% of all patients) can become candidates for surgical resection of the residual localized disease in the chest or retroperitoneum. Radiologic findings cannot distinguish benign from malignant processes in these patients.
   a. The presence of elevated levels of tumor markers always signifies the continued presence of carcinoma and the need for further chemotherapy. The absence of tumor markers signifies that the residual disease in the thorax or retroperitoneum is either a benign process (fibrosis, inflammation), teratoma, or carcinoma.
   b. Surgical resection of residual disease defines the subsequent treatment strategy in all of these patients and is therapeutic in some.
      1. If surgical resection of residual disease reveals fibrosis or teratoma, no further treatment is required.
      2. If surgical resection reveals carcinoma, two more cycles of cisplatin and etoposide therapy are given.
3. **Salvage chemotherapy.** Patients who do not achieve a complete remission with BEP are treated with cisplatin, vinblastine (0.11 mg/kg IV on days 1 and 2 of each cycle), and ifosfamide. In addition, high-dose chemotherapy with autologous bone marrow transplantation or peripheral stem cells is used.

VII. Special clinical problems

A. **Gynecomastia and elevated blood** b-**HCG levels** are occasionally found in patients with clinically normal testes and no other evidence of cancer. A number of other cancers can also produce b-HCG. Patients should be evaluated with ultrasonography of the testes and CT of the abdomen and chest. Thereafter, it is best to follow such patients clinically until there is demonstrable cancer or rising HCG levels. Blind or random biopsies in this setting are not likely to reveal a diagnosis, can expose patients to unnecessary morbidity, and are contraindicated.
B. **Extragonadal germ cell neoplasms,** particularly seminomas, can occur in any anatomic site through which the normal germ cells migrate in the embryo. Such

sites include the pineal gland, mediastinum, and midretroperitoneal areas. Tumor markers (b-HCG and a-FP) should be measured. Chemotherapy with BEP should be used for nonseminomatous germ cell cancers. Results of treatment are less successful than for primary testicular cancer, especially for primary mediastinal nonseminomatous germ cell tumors.

C. **Solitary mediastinal masses with undifferentiated small cell histology** may represent lymphoma, small cell carcinoma, melanoma, neuroblastoma, Ewing's sarcoma, or testicular cancer. Differentiation by histo- pathology may be impossible. If differentiation is impossible and the patient is in the correct age group (20 to 30 years of age), a reasonable approach would be to treat the patient for disseminated nonseminomatous germ cell cancer. Mediastinal germ cell tumors are discussed in Chapter 19, section I.B.4.

Suggested Reading

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Chapter 13 Urinary Tract Cancers

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Renal Cancer

I. Epidemiology and etiology

A. **Incidence** (Table 13.1). Renal cell carcinoma (RCC) constitutes 3% of adult malignancies. The worldwide incidence is increasing at an annual rate of about 2%, with 28,000 new cases per year in the United States and 11,000 associated deaths. Men are affected twice as often as women. RCC is a tumor of adults, occurring primarily in those in their fourth and sixth decades. The incidence and mortality rates for blacks appear to be increasing in excess to those for whites in the United States.

Table 13.1 Cancer of the urinary tract in the United States

B. **Etiology.** The cause of RCC is unknown.
  1. **Factors that increase the risk for RCC** include the following:
      a. Smoking (relative risk is 2.3 for heavy smokers)
      b. Urban living
      c. Family history of renal cancer
      d. Thorotrast exposure
      e. Von Hippel-Lindau disease (*VHL* gene; 35% to 45% of these patients have RCC, mostly multiple and bilateral)
  2. **Unproven factors** that may increase the risk for RCC include polycystic kidney disease, diabetes mellitus, and chronic dialysis.

II. Pathology and natural history

A. **Adenocarcinomas** (historically named *hypernephromas* or *Grawitz's tumors*) make up nearly all renal cancers in adults. They are typically round and have a pseudocapsule that consists of condensed parenchyma and connective tissue. Bilateral tumors occur in 2% of sporadic cases, either synchronous or asynchronous.
  1. The histologic variants include papillary, clear cell, granular cell, and spindle cell subtypes.
  2. These tumors originate from proximal tubular cells, invade local structures, and frequently extend into the renal vein. Metastasis occurs through the lymphatics and bloodstream. The most common sites of distant metastases are the lungs, liver, bones, and brain. Adenocarcinomas may present with metastases to unusual sites, such as the fingertips, eyelids, and nose. A primary renal cancer may be diagnosed based on the characteristic histology of a metastatic deposit.
  3. The natural history of RCC is more unpredictable than that of most solid tumors. The primary tumor has variable growth patterns and may remain localized for many years. Metastatic foci may have long periods of indolent or apparently arrested growth and may be detected many years after removal of the primary tumor.
B. **Transitional cell carcinomas** are uncommon tumors that arise in the renal pelvis and often affect multiple sites of urothelial mucosa, including the renal pelvis, ureters, and urinary bladder (see Urinary Bladder Cancer, section II). These tumors usually are low grade but are being discovered late in the course of the disease. Transitional cell carcinomas occasionally have a peculiar disposition to spread over the posterior retroperitoneum in a sheetlike fashion, encasing vessels and producing urinary tract obstruction. Hematogenous dissemination occurs, particularly to lung and bone.
C. **Rare renal tumors**
  1. **Nephroblastomas** (Wilms' tumors) appear as large, bulky masses in children, but rarely occur in adults (see Chapter 18, Wilms' Tumor).
  2. **Lymphomas and sarcomas** arising in the kidney have clinical courses similar to their counterparts elsewhere in the abdomen.
  3. **Juxtaglomerular tumors** (reninomas) are rare causes of hypertension and are usually benign.
  4. **Hemangiopericytomas** are renin-secreting tumors associated with severe hypertension and are occasionally malignant (15% of cases).
  5. **Benign renal adenomas.** The existence of benign renal adenoma is controversial because it is not possible to determine malignant or benign biologic behavior only by histology on any lesion less than 3 cm in diameter.
D. **Metastatic tumors.** The kidney is a frequent metastatic landing site for many malignancies, mainly cancers of the lung, ovary, colon, and breast.

E. **Paraneoplastic syndromes** commonly occur with renal adenocarcinomas.
   1. **Erythrocytosis.** Renal adenocarcinomas are associated with erythrocytosis in 3% of patients and account for 15% to 20% of cases of inappropriate secretion of erythropoietin. A left flank mass of RCC may be mistaken for an enlarged spleen resulting from polycythemia vera. The differential diagnosis of erythrocytosis is discussed in Chapter 34, Increased Blood Cell Counts, section I. Tumor production of erythropoietin may identify a subset of patients responsive to immunotherapy with interleukin-2 (IL-2) and interferon- a (IFN-g).
   2. **Hypercalcemia** occurs in about 5% of patients and is associated with parathyroid hormone–like proteins. Hypercalcemia may be associated with widespread bony metastases.
   3. **Fever** caused by tumor occurs in 10% to 20% of patients.
   4. **Abnormal liver function (Staufer's syndrome)** occurs in 15% of patients. Leukopenia, fever, and areas of hepatic necrosis without liver metastases are noted. The resulting elevated serum levels of alkaline phosphatase and transaminase are reversed after nephrectomy.
   5. **Hypertension** associated with renin production by the tumor occurs in up to 40% of patients and is alleviated by removal of the tumor.
   6. **Hyperglobulinemia** can result in elevated erythrocyte sedimentation rate.
   7. **Amyloidosis** occasionally occurs.

III. Diagnosis

A. **Symptoms and signs.** Symptoms other than hematuria usually indicate large, advanced tumors. The classic triad of flank pain, a flank mass, and hematuria occurs in less than 10% of patients with RCC. The combined picture of anemia, hematuria, and fever is rare but suggestive of renal cancer. The widespread use of ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) changed significantly the typical presentation of RCC. Two thirds of all locally confined tumors are found serendipitously (as an incidental finding), and thus a substantial proportion of patients are symptom free at the time of diagnosis.
   1. **Symptoms**
      a. Gross hematuria occurs in 38% of patients.
      b. A steady, dull flank pain occurs in 41% of patients. Colicky pain may develop if blood clots are passed into the ureter.
      c. Weight loss is a presenting feature in 36% of patients.
      d. Sudden onset of a left-sided or a right-sided varicocele is rare and usually suggests invasion into the renal vein or inferior vena cava, respectively.
      e. Leg edema is the result of locally advanced disease, which causes venous or lymphatic obstruction.
      f. Fever, plethora, or symptoms of hypercalcemia or anemia may be presenting features.
   2. **Physical findings**
      a. A flank mass is palpable in 24% of patients.
      b. Fever occurs in up to 18% of patients.
      c. Pallor from anemia occurs in about 36% of patients.
B. **Diagnostic studies**
   1. **Urinalysis** may reveal proteinuria and hematuria. One third of patients have neither gross nor microscopic hematuria. *All patients with macroscopic or microscopic hematuria of any degree must have a thorough urologic evaluation.*
   2. **Routine studies**
      a. Complete blood count (CBC), liver function tests (LFTs), and renal function studies
      b. Hyperglobulinemia is frequently present in patients with RCC because acute-phase reactant proteins are elevated.
      c. Chest radiographs may reveal multiple, large, round (cannonball-like) metastatic deposits that are characteristic of metastatic genitourinary neoplasms.
   3. **CT scanning of the kidneys** is the most minimally invasive and most cost-effective method for evaluating a suspected renal mass and should be the first study for that purpose. Extension through the capsule is usually diagnosed correctly. CT does not detect minimal lymph node involvement.
   4. **MRI** may be as accurate as CT. MRI images extension of tumor into the renal vein and vena cava more reliably in preparation for surgery.
   5. **Ultrasonography** with duplex Doppler may assist in imaging tumor thrombus in the inferior vena cava and in defining its extension. It cannot be used for local staging because regional lymph node involvement cannot be imaged.
   6. **Older studies**
      a. **Intravenous pyelography** (IVP) with infusion nephrotomography was previously the primary diagnostic step at many institutions. Cross-sectional imaging (CT and ultrasound), however, has become the cornerstone for the diagnosis of a renal lesion because it can detect small, low-stage tumors with better prognosis.
      b. **Inferior vena cavography** was performed to locate tumor thrombi in all patients with large tumor masses but has been replaced by MRI and duplex Doppler ultrasound.
      c. **Renal angiography** precisely distinguishes malignant from benign lesions but is invasive and is associated with complications. The prevalent use of speed helical CT and ultrasound has resulted in a striking reduction in the indications for renal angiography.
   7. **Scans for staging** should be performed in the following situations:
      a. Bone scan, if there is bone pain or elevated serum alkaline phosphatase levels
      b. CT scan of the brain, if there are signs of central nervous system abnormalities
      c. Abdominal CT scan, if there is hepatomegaly or abnormal LFTs
   8. **Percutaneous thin-needle aspiration biopsy of a renal mass** may result in tumor seeding in the needle track. This procedure should be restricted to patients with medical conditions that make angiography or surgery unduly hazardous, patients with metastatic disease for which a tissue diagnosis is necessary, and patients who have findings strongly suggestive of a benign cyst.
   9. **Exploratory surgery or nephrectomy** may be necessary to define renal masses that cannot be accurately assessed by noninvasive methods.
C. **Renal cysts** are usually classified using CT according to the chance of harboring malignancy (Bosniak's classification). The following approach is recommended to evaluate potential renal cysts:
   1. If a renal cyst is suspected or demonstrated and the findings are not strongly suggestive of cancer, ultrasound is performed to determine whether the mass is cystic. If a simple cyst or a fatty tumor is demonstrated, no further follow-up is usually indicated. If a hyperdense cyst is imaged, the patient should have follow-up studies.
   2. If a complex cyst is diagnosed, a fluoroscopically directed, thin-needle aspiration is performed in some institutions. If fluid is obtained, radiocontrast agent is injected to delineate the cyst walls. The cyst fluid is evaluated for cytology, glucose, lactate dehydrogenase level, and protein content. The findings from the cyst fluid analysis usually predict the outcome.
   3. Sometimes, all imaging modalities, including cyst puncture, are not diagnostic, and surgical exploration is indicated.

IV. Staging system and prognostic factors

A. **Staging system.** Although Robson's staging system is still employed, the TNM staging system is universally used to stage renal cancer.
   1. **TNM classification** (adapted from the 1997 American Joint Commission on Cancer [AJCC] Cancer Staging Manual). A different TNM classification system, which is more similar to that of the urinary bladder, applies to cancers of the renal pelvis and ureter; the reader is referred to a current AJCC manual for these differences.

Stage Extent of tumor

Stage	Extent of tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor £7.0 cm and confined to the kidney
T2	Tumor >7.0 cm and confined to the kidney
T3a	Tumor invades adrenal gland or perinephric tissue but not beyond the Gerota's fascia
T3b	Tumor extends into the renal vein or inferior vena cava below the diaphragm
T3c	Tumor extends into the inferior vena cava above the diaphragm
T4	Tumor invades beyond Gerota's fascia
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than one regional lymph node
M0	No distant metastasis

M1   Distant metastasis is present

2. **Stage groupings**

Stage	Description	5-year survival rate (%)
I	T1 N0 M0	100
II	T2 N0 M0	96
III	T1-2 N1 M0; T3a, b, c N0-1 M0	59
IV	T4 N0-1 M0; any T N2 M0; any T any N M1	16

B. **Prognostic factors.** The survival rate for untreated patients is less than 5% at 3 years and less than 2% at 5 years.
   1. **Pathologic stage** is the most important prognostic indicator.
      a. **Tumor size** larger than 10 cm is associated with poor prognosis in comparison to smaller lesions.
      b. **Venous extension.** Renal vein or vena caval involvement is not associated with a hopeless prognosis if managed properly; 25% to 50% of patients survive for 5 years.
   2. **Histology.** Sarcomatous patterns of RCC have a poor prognosis.
      a. **Nuclear grade** correlates with survival across all tumor stages. Fuhrman's four-tiered system is most commonly used; it takes into consideration nuclear size, nuclear shape, and nucleolar appearance.
      b. **Nuclear ploidy** was proposed as a potential prognostic marker for survival. Nondiploid tumors are thought to harbor a less favorable prognosis.
   3. **Disease-free interval.** The length of time between nephrectomy and the development of metastases affects the survival of patients with metastatic disease.
      a. Nearly all patients who have metastases at the time of surgery or who develop metastases or local recurrence within 1 year of surgery die within 2 years if untreated.
      b. Patients who develop metastases more than 2 years after nephrectomy have a 20% 5-year survival rate from the time metastases are recognized.

V. Prevention and early detection
The incidence of renal cancer might be reduced if tobacco smoking habits could be controlled. Early detection depends on prompt attention to hematuria and other symptoms suggestive of these cancers.

VI. Management

A. **Early disease**
   1. **Surgery**
      a. **Nephrectomy** with removal of Gerota's fascia, the adrenal gland, and tumor in the renal vein or vena cava is the treatment of choice.
      b. **Partial nephrectomy** (or, nephron-sparing surgery [NSS]) is indicated for patients with localized RCC and a concomitant urologic or medical condition that jeopardizes overall renal function. NSS for patients with a normal contralateral kidney probably gives equivalent results to radical nephrectomy for small peripheral or polar lesions (less than 4 cm). Patients with bilateral cancer and only one functional kidney may undergo NSS. It is rarely necessary to remove the kidney entirely, excise the tumor ("bench nephrectomy"), and then perform autotransplantation. Bilateral nephrectomy or single-kidney nephrectomy and delayed transplantation are also options in selected cases.
      c. **Preoperative occlusion of the renal artery** using angiographic techniques has been advocated by some urologists but is seldom indicated. The hypervascular nature of renal cancer does often result in hemorrhage during surgery, particularly with large, bulky tumors. Occlusion procedures make the operation technically easier, but the patient may suffer considerable discomfort from pain, fever, and nausea.
      d. **Contraindications to surgery** include high surgical risk because of unrelated medical diseases. The presence of distant metastases is no longer considered an absolute contraindication to surgery because of the possible use of immune therapy ("adjunctive nephrectomy").
   2. **RT** has no established role in the management of early renal cancers.
   3. **Chemotherapy** has no established role in the management of early renal cancers.
B. **Advanced disease**
   1. **Surgery**
      a. **Nephrectomy.** The chance of a spontaneous regression of metastases after nephrectomy is well known but rare (less than 1%) and is far exceeded by the associated surgical morbidity and mortality. The hope for spontaneous regression is never an indication for surgery. Palliative nephrectomy is indicated in patients with metastases to alleviate severe symptoms such as pain, paraneoplastic syndrome, or severe hemorrhage, if all of the following criteria are met:
         1. The performance status of the patient is at least 30% on Karnofsky's scale (see inside back cover) or is expected to improve substantially if hemorrhage was controlled.
         2. The only symptoms are in the area of the primary tumor. Sites of metastatic disease must be asymptomatic.
         3. The tumor should have a reasonable chance of being resectable.
      b. **Resection of metastases.** Metastases of RCC can be considered for resection only if the following criteria are met:
         1. The interval from nephrectomy to the detection of metastases is at least 2 years.
         2. The metastasis is proved to be solitary by all of the following studies: physical examination, normal LFTs (normal CT scan if LFTs are abnormal), bone scan, chest CT scan, and CT scan of the brain if the patient has neurologic symptoms.
   2. **RT** is used to control bleeding and pain from the primary tumor and to palliate symptoms from metastases to the central nervous system and bone. Generally, renal tumors are relatively radioresistant.
   3. **Drug therapy**
      a. **IL-2** administered alone in high-dose regimens produces a response rate of 15% to 20% in good-risk patients and durable remissions lasting for more then a decade. Significant morbidity and mortality have been associated with high-dose IL-2 therapy. IL-2 administered in lower dosages or in combination with IFN produces comparable response rates with less morbidity and mortality, but the durability of response has not yet been confirmed in phase III trails. IL-2 was approved by the U.S. Food and Drug Administration in 1992 for the treatment of metastatic RCC. The future treatment of RCC incorporates new immunologic technology, including gene therapy, dendritic cell tumor vaccine, and antibody therapy.
      b. **IFN-a** has been reported to have a response rate of 15% to 20% (particularly for intrathoracic metastases) but no effect on survival.
      c. **Progestins** used for the treatment of patients with metastatic RCC are associated with response rates of less than 15% and no improvement in survival.
      d. **Cytotoxic agents** have produced negligible effects on metastatic RCC and no improvement in survival. Agents reported to produce occasional responses (15% to 20% of patients) include the fluoropyrimidines and vinblastine. Transitional cell cancers of the renal pelvis and ureters may respond to the M-VAC regimen (see Bladder Cancer) or paclitaxel plus cisplatin (or carboplatin).

Urinary Bladder Cancer

I. Epidemiology and etiology

A. **Incidence** (Table 13.1). Bladder cancers constitute 5.5% of all cancers in the United States. The disease is 2.5 times more frequent in men than women and is most frequent in industrial northeastern cities. The average age of onset is the sixth to seventh decade.
B. **Risk factors and carcinogens**
   1. **Occupational exposure** is associated with 20% of cases. Historically, aniline dye workers were afflicted 30 times more than the general population. Aromatic amines and related compounds are the most abundant bladder carcinogens today. These are chemical intermediates of anilines, rather than the aniline dyes themselves. Leather, paint, and rubber industry workers also appear to have an increased risk for bladder cancer. Proven chemical carcinogens in these industries are 2-naphthylamine, benzidine, 4-aminobiphenyl, and 4-nitrobiphenyl.
   2. *Schistosomum haematobium* infection of the bladder is associated with bladder cancer, particularly with squamous cell histology, in endemic regions of Africa and the Middle East.
   3. **Smoking** increases the risk for bladder cancer four-fold in a dose-dependent fashion. Eighty-five percent of men who die of bladder cancer have a history of smoking.
   4. **Pelvic irradiation** increases the risk for bladder cancer four-fold.
   5. **Drugs.** Cyclophosphamide unequivocally increases the risk for bladder cancer. Other drugs that have been implicated in animal studies but not proved in humans are phenacetin, sodium saccharin, and sodium cyclamate.

II. Pathology and natural history

A. **Pathology**
1. **Histology.** Ninety percent of bladder cancers are transitional cell (urothelial), and 8% are squamous cell types. Adenocarcinomas, sarcomas, lymphomas, and carcinoid tumors are rare.
2. **Sites of involvement.** Bladder tumors involve the posterior and lateral walls often and involve the superior wall least often. Patients with bladder carcinoma also frequently have carcinomas in other urinary tract sites.
3. **Types of bladder cancer**
   a. Single papillary cancers are the most common type (70%) and the least likely to show infiltration.
   b. Diffuse papillary growths with minimal invasion
   c. Sessile cancers are often high grade and invasive.
   d. Carcinoma *in situ* (CIS; flat intraepithelial growth) appears either the same as normal mucosa or a as velvety red patch.
4. **The "field defect."** Bladder cancer appears to be associated with premalignant changes throughout the urothelial mucosa. This so-called "field defect" is suggested by the following observations:
   a. Up to 80% of patients treated for superficial tumors develop recurrences at different sites in the bladder.
   b. Multiple primary sites are present in 25% of all patients with bladder cancer.
   c. Random biopsies of apparently normal areas of mucosa in bladder cancer patients frequently show CIS.
   d. Depending on the reported series, patients with bladder CIS also have ureteral CIS (10% to 60%) and urethral CIS (30%).
   e. About 40% of patients presenting with carcinoma of the renal pelvis or ureter develop tumors elsewhere in the urinary tract, usually in the bladder.
B. **Natural history**
1. **CIS of the bladder** is multifocal and can affect the entire urothelium. Up to 80% of patients with untreated CIS develop invasive bladder cancer within 10 years after diagnosis; the disease is lethal for most of these patients.
2. **Low-grade superficial carcinomas** have a better prognosis than CIS. Even though the recurrence rate is 80%, 80% of patients with these tumors survive 5 years. Invasive cancer develops in only 10% of patients with superficial tumors, often in association with CIS. More than 80% of patients with both superficial cancers and CIS develop invasive malignancies.
3. **High-grade or invasive tumors** are associated with adjacent areas of CIS in 85% of cases. Squamous cell cancers are usually high grade and are the most aggressive carcinomas of the bladder.
4. **Mode of spread.** Bladder cancers spread both by lymphatic channels and the bloodstream. High-grade lesions are more likely to metastasize. Thirty percent of patients with distant metastases do not have involvement of the draining lymph nodes. Distant sites of metastases include bone, liver, lung, and, less commonly, skin and other organs. Uremia from local extension into pelvic organs, inanition from advancing cancer, and liver failure are the usual causes of death.
5. **Iatrogenic tumor implantation.** High-grade bladder cancer cells exfoliated by cystoscopy, brushing, transurethral biopsy, or resection were reported to seed other areas of the bladder. Mucosal sites damaged by inflammation or instrumentation appear to be most receptive to such implants.
6. **Associated paraneoplastic syndromes**
   a. Systemic fibrinolysis
   b. Hypercalcemia
   c. Neuromuscular syndromes

III. Diagnosis

A. **Symptoms and signs**
1. **Symptoms**
   a. Hematuria occurs as a presenting feature in 90% of patients.
   b. Bladder irritability occurs in 25% of patients. Hesitancy, urgency, frequency, dysuria, and post-voiding pelvic discomfort may mimic prostatitis or cystitis. These symptoms occur in patients with CIS as well as those with tumors that are large, extensive, or near the bladder neck.
   c. Pain in the pelvis or flank is associated with locally advanced disease.
   d. Edema of the lower extremities and genitalia develops from venous or lymphatic obstruction.
2. **Physical findings.** The patient is carefully examined for metastatic sites. It is mandatory that a bimanual examination is performed by the urologist through the rectum each time the patient is put under general anesthesia or having a cystoscopy done. The importance of the bimanual examination cannot be overemphasized. It supplies pertinent information concerning local extension of the disease not obtainable by current imaging modalities.
B. **Diagnostic studies**
1. **Routine studies**
   a. CBC, LFTs, and renal function tests
   b. Urinalysis
   c. Chest radiograph
2. **Cystoscopy** is the cornerstone for diagnosing bladder cancer. Biopsy is performed on abnormal areas. Biopsies of normal areas at random are performed to search for CIS. Cystoscopy is followed by bimanual pelvic examination under anesthesia in both men and women. Cystoscopy is indicated for patients with the following clinical features:
   a. Any type of hematuria (gross or microscopic) and a normal IVP (except female patients with a single episode of acute bacterial cystitis who are younger than 40 years of age)
   b. Unexplained or chronic lower urinary tract symptoms
   c. Urine cytology that is positive for cancer
   d. A history of bladder cancer
3. **Urography.** An IVP is performed in all patients with unexplained hematuria or cystoscopic or cytologic evidence of tumor in an attempt to search for primary sites in the ureters or renal pelvis. It is advisable to perform an IVP before cystoscopy because if a poorly visualized upper system or nonconclusive filling defect are imaged, retrograde pyelography may be performed using a ureteral catheter inserted during the same cystoscopy session.
4. **Urine cytology,** often accompanied by flow cytometry, detects about 70% of bladder cancers that are subsequently diagnosed by cystoscopy. Cytologic evaluation should not be the primary diagnostic method for patients suspected of having bladder cancer. Urine cytology is useful for the following purposes:
   a. Following patients with a history of bladder cancer
   b. Screening symptom-free patients who are exposed to environmental carcinogens
   c. Evaluating patients with chronic irritative bladder symptoms before cystoscopy is done
5. **Bladder tumor markers.** Bladder tumor antigen (BTA), nuclear matrix protein 22 (NMP-22), telomerase activity, fibrin degradation products assay, and others are being tested to replace or decrease the frequency of cystoscopy, serve in follow-up of transitional cell carcinoma (TCC) patients, and assist in screening and evaluation of hematuria. Some of these tests are promising, but the standard care for a patient with hematuria or history of TCC remains cystoscopy.
6. **Scans.** Abdominal CT and bone scans should be performed in patients with bone pain or elevated serum alkaline phosphatase or transaminase levels.

IV. Staging system and prognostic factors

A. **Staging system.** The AJCC staging system for bladder cancer is:

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Ta Noninvasive papillary carcinoma (confined to the urothelial layer)

Tis Transitional cell carcinoma *in situ* ("flat tumor")

T1 Lamina propria invasion

T2a Superficial muscle invasion (inner half)

T2b Deep muscle invasion (outer half)

T3a Perivesical fat invasion - microscopic

T3b Perivesical fat invasion - macroscopic (mass)

T4a Invasion of adjacent pelvic organs (prostate, uterus, vagina)

T4b Invasion of abdominal or pelvic walls

NX Regional nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis to a single node £2 cm in dimension

N2 Metastasis to multiple nodes or to a single node >2 cm and <5 cm

N3 Metastasis in a node >5 cm

M0 No distant metastasis

M1 Distant metastasis is present

B. **Stage groupings**

Stage 0a   Ta N0 M0

Stage 0is   Tis N0 M0

Stage I   T1 N0 M0

Stage II   T2a,2b N0 M0

Stage III   T3a,3b,4a N0 M0

Stage IV   T4b N0 M0; any T N1,2 M0; any T any N M1

C. **Prognostic factors.** The most important clinical prognostic factors are tumor stage, tumor grade, and the presence of CIS. Untreated patients have a 2-year survival rate of less than 15% and a median survival of 16 months.

1. **Histology.** Squamous cancers and adenocarcinomas have poorer prognoses than transitional cell carcinomas.

2. **Invasion** of muscle, lymphatics, or perivesical fat is associated with a poor prognosis. Invasive cancer is associated with a 50% mortality rate in the first 18 months after diagnosis.

3. **CIS** progresses to invasive carcinoma in 80% of patients within 10 years of diagnosis.

4. **Tumor grade**
   a. There is a close relationship between tumor grade and stage. Tumor grade alone affects survival in patients with superficial tumors. The 5-year survival rate is 85% with low-grade lesions and 30% with high-grade lesions. Virtually all high-grade superficial tumors become invasive if left untreated.
   b. Chromosome number correlates with tumor grade. Tetraploid and aneuploid cells, as opposed to diploid cells, are associated with invasive tumors.
   c. Several phenotypic properties that have been offered as markers for biologically more aggressive disease include enhanced expression of the Lewis x antigen; expression of defective p53, together with overexpression of the *Rb* gene and abnormal epidermal growth factor receptor; reduced expression of transforming growth factor b1, p27, and p15.

5. **Size of the primary tumor** does not correlate with the risk for dissemination. Large superficial lesions, however, are more likely to recur after therapy than are small lesions.

V. Prevention and early detection

A. **Prevention.** Protecting factory workers in certain industries from continuous exposure to bladder carcinogens (e.g., with protective clothing) may be beneficial. The benefit gained by reducing the intake of coffee or artificial sweetener has not been determined. All people should be discouraged from smoking. The place and technique for bladder cancer screening are not yet defined.

B. **Early detection** depends on prompt evaluation of all patients with hematuria or chronic irritative bladder symptoms.

VI. Management

A. **Early disease: Overview**

1. **Superficial low-grade tumors** not associated with CIS are managed by transurethral resection and intravesical chemotherapy (see section VI.D.1). Although the recurrence rate is 80% with this management, the prognosis is good. Fulguration is added if there are excessive numbers of small lesions.

2. **CIS** is usually multifocal, persistent, and recurrent; it is highly likely to evolve into invasive cancer, which often involves the urethra and ureters. Choice of therapy may be based on the degree of urothelial atypia; however, the pathologic distinction between severe dysplasia and CIS is often difficult to make.
   a. **Borderline cases.** Patients should have repeated urine cytology; cystoscopy and biopsy are repeated every 3 to 6 months. Some cases have an indolent course, with years passing before frank CIS is found.
   b. **True CIS.** Opinion is divided on the optimal therapeutic approach for apparently localized CIS. Localized, unifocal areas of CIS may be fulgurated. CIS localized to the bladder, without ureteral or urethral involvement, may be initially treated by intravesical therapy (see section VI.D.1), provided there is no history of invasive tumor. Multifocal CIS (particularly if high grade, diffuse, or symptomatic) is treated with radical cystectomy; urethrectomy, ureterectomy, or both may also be necessary.

3. **Invasive tumors or superficial tumors with CIS** are best treated by pelvic lymph node dissection and radical cystectomy in women and radical cystoprostatectomy in men. Segmental resections of the bladder may be used in highly selected cases (see section VI.B.2). Radiotherapy and chemotherapy may be appropriate in some cases (see section VI.C and section VI.D).

B. **Early disease: surgery**

1. **Transurethral resection of bladder tumor** (TURBT) is the corner stone for treating and T staging newly diagnosed bladder neoplasia. One or more TURBT procedures and follow-up cystoscopy constitute sufficient treatment for most superficial tumors.

2. **Segmental resection** (partial cystectomy) is associated with a high risk for recurrence. Less then 5% of patients are candidates for this procedure. Segmental resection can be considered for tumors with the following characteristics:
   a. Solitary
   b. Localized to the bladder dome
   c. Not associated with areas of CIS sought by multiple biopsies of urothelial mucosa
   d. Able to be removed with a 3-cm margin of healthy tissue

3. **Radical cystectomy** includes excision of the bladder, perivesical fat, and attached peritoneum. Men undergo removal of the entire prostate and seminal vesicles; women undergo *en bloc* removal of the uterus, adnexa, and cuff of the vagina. Lymphadenectomy is controversial; it does not improve survival but adds little morbidity and provides information for staging.
   a. **Urinary diversion procedures.** The ureters are diverted into either a loop of ileum that functions as a conduit to an abdominal stoma (Bricker's procedure) or into a reservoir in carefully selected cases. Generally speaking, reservoirs are created by detubularizing and oversewing a bowel segment.

   The reservoir may be implanted orthotopically as a neobladder draining through the urethra using the native sphincter mechanism or attached to a continent conduit drained periodically by using self-intermitted catheterizations of the conduit stoma (*continent diversion*). Alternative urinary drainage procedures, such as cutaneous implantation of the ureters and ureterosigmoidostomy, were largely abandoned because of severe complications.

   b. **Indications for radical cystectomy**
      1. Muscle invasive tumors
      2. True, severe CIS not responsive to intravesical therapy
      3. Superficial low-grade tumors that are diffuse, multiple, and frequently recurring and becoming difficult to control with recurrent TURBT and intravesical therapy
      4. High-grade tumors refractory to conservative measures
   c. **Complications of cystectomy**
      1. Mortality rate of 1% to 3%
      2. Blood loss
      3. Rectal injury, ureterocutaneous fistulas, wound dehiscence or infection, or small bowel obstructions or fistulas may occur. Small bowel fistulas are associated with a substantial mortality rate.

      4. Thrombophlebitis, pulmonary embolism, and other cardiocirculatory complications
      5. Impotence in men; potency can be preserved in some men by sparing the corporal nerves.
   d. **Complications of urinary diversion**
      1. Urinary tract infection
      2. Obstruction due to stenosis (fibrosis or tumor growth)
      3. Urinary calculi occasionally occur after Bricker's procedure; calcium stones are most common.
      4. Metabolic acidosis: the type of diversion (reservoir versus conduit) and the specific type of bowel segment used determine the extent of acid–base imbalance and the type and gravity of the accompanied electrolyte impairment. The prototype is hyperchloremic metabolic acidosis resulting from the rapid reabsorption of ammonium followed by chloride from the urine-containing lumen through the intestinal epithelium to the plasma. The most severe metabolic derangements were reported for diversions using sigmoid colon or jejunum. Diversions using stomach are used rarely in bladder cancer patients and compose a different set of metabolic impairments.

C. **Early disease: radiotherapy** (RT) does not appear to alter the course of CIS favorably.
   1. **Indications for RT**
      a. RT alone is an alternative to surgery in patients who desire to retain their bladder and potency and are willing to accept a 20% lower cure rate.
      b. RT combined with cisplatin alone or M-VAC (see section VI.E.3) may spare the bladder in patients who are not candidates for cystectomy.
      c. Preoperative radiation is seldom employed. RT does not appear to improve expected survival beyond that achieved by radical surgery alone, although local recurrence is reduced.
      d. Postoperative radiation has no proven role in bladder cancer.
   2. **Complications of RT** are discussed in Chapter 11, General Aspects, section V.A (Radiation cystitis) and Chapter 30, section VI.D (Radiation proctitis).

D. **Early disease: chemotherapy**
   1. **Topical therapy.** Superficial low-grade bladder cancers may be treated with intravesical chemotherapy or immunotherapy after sites of gross disease are resected transurethrally. The incidence of tumor recurrence is reduced with topical therapy, but how much topical therapy improves survival is not known. Thiotepa, mitomycin C, doxorubicin, and Bacillus Calmette-Guérin (BCG) are effective agents for intravesical therapy. Patients with CIS may benefit from BCG or mitomycin C.

     BCG (40 to 150 mg according to the manufacturer's recommendation) is the most commonly used topical agent. The active suspension is diluted to 50 to 100 mL in normal saline and instilled through a catheter into the previously emptied bladder and retained for 2 hours. Instillation is performed once a week for 6 weeks. Clotting impairments may reduce the effectiveness of BCG. The side effects of BCG instillation include bladder irritation, prostatitis, flu-like disease, and rarely, severe systemic infection mandating prompt treatment with antituberculosis medications.

   2. **Adjuvant therapy with systemic cytotoxic agents** for patients undergoing cystectomy has been associated with a delay in time to progression (8 to 12 months). Benefits have been shown with the M-VAC, CISCA, and similar regimens (see section E.3).
   3. **Neoadjuvant therapy** is an attempt to provide the earliest possible treatment of micrometastatic disease and to facilitate definitive local therapy. Multiple single-institution trials of M-VAC (see section E.3) indicate high response rates (60%) and complete responses (20% to 25%) on surgical resection. This approach remains experimental pending ongoing randomized trials.

E. **Advanced disease**
   1. **Surgery.** An attempt to fulgurate large tumors that are bleeding uncontrollably or causing severe irritative symptoms is worthwhile. Occasionally, these symptoms force the caregiver to perform palliative cystectomy and urinary diversion.
   2. **RT** ameliorates hemorrhage in about half of patients and provides substantial local pain relief in areas of bone involvement. Tumor masses that threaten extension through the skin, particularly in the perineum, should be irradiated early. Bacterial cystitis should be treated effectively before the institution of RT if possible.
   3. **Chemotherapy.** Cisplatin-based combination chemotherapy regimens have produced sustained complete responses in up to 40% of patients and represent the best current therapy for advanced bladder cancer, although toxicity can be substantial. Arterial infusion of these agents is experimental.
      a. **M-VAC** is administered in 28-day cycles in the following dosages:

     Methotrexate, 30 mg/m^2 IV on days 1, 15, and 22
     Vinblastine, 3 mg/m^2 IV on days 2, 15, and 22
     Doxorubicin (Adriamycin), 30 mg/m^2 IV on day 2
     Cisplatin, 70 mg/m^2 IV on day 2

      b. **CISCA** is administered in 21- to 28-day cycles in the following dosages:

     Cisplatin, 100 mg/m^2 IV on day 2
     Cyclophosphamide, 650 mg/m^2 IV on day 1
     Doxorubicin (Adriamycin), 50 mg/m^2 IV on day 1

F. **Patient follow-up**
   1. Patients with severe urothelial dysplasia should have urine cytology repeated every 2 to 3 months and cystoscopy with random biopsies every 3 to 6 months.
   2. Patients with superficial low-grade cancer treated with intravesical chemotherapy should have cystoscopy performed at 3-month intervals.
   3. Patients who have undergone cystectomy should be evaluated every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter. Urinalysis and urine cytology should be performed at 6-month intervals to search for the development of new primary cancers in the upper urinary tract. Hematuria or a positive cytology should be evaluated with intravenous urography.
   4. For patients after cystectomy having an ileal conduit or continent diversion, urethral washing for cytology is advisable periodically to diagnose local recurrence in the urethra. For the same purpose, patients having orthotopic diversions should have follow-up cystoscopy.

VII. Special clinical problems

A. **Gross hematuria** may complicate the course of locally advanced bladder cancer. Transurethral fulguration may help. The bladder may be catheterized and filled with sterile water under pressure to attempt tamponade. Some physicians advocate instillation of 4% formaldehyde and 1% silver nitrate into the bladder under general anesthesia; the agent is retained for 15 minutes, then thoroughly rinsed out with 10% alcohol followed by normal saline. Irrigation of the bladder with dilute alum is effective in controlling hemorrhage. RT is effective for controlling bleeding from tumor in half of cases; side effects of bladder irritation or proctitis are treated symptomatically.

B. **Obstructive uropathy.** Uremia may develop in patients with any type of urinary diversion. Obstruction due to benign conditions, such as stones or stenosis, must be excluded. The urine should be examined for malignant cells, crystals, and blood. If the ureteral orifice can be located, a retrograde pyelogram is performed. Otherwise, IVP or renal radionuclide scan may show obstruction.

   Endoscopy may be used to dilate stenotic lesions with some success. Exploratory surgery should be considered to solve the problem in patients who otherwise are clinically free of cancer. Patients with advanced disease commonly benefit from external diversion with percutaneous nephrostomies or internally using ureteral stents.

C. **Impotence.** Despite nerve-sparing technique, impotence complicates radical cystectomy in men. Oral agents, intraurethral preparations, intracavernosal injection, and penile prostheses are the available solutions that usually permit restoration of potency and, often, orgasm in these patients.

D. **Management of urinary symptoms** is discussed in Chapter 5, section V.

Prostate Cancer

I. Epidemiology and etiology

A. **Incidence** (Table 13.1) of prostate cancer (CaP) rose continuously for more than 20 years. In 1987, it crossed the line of 100 cases per 100,000 (age adjusted, all male population). The peak incidence was seen in 1992 (191 per 100,000). The rise in incidence is basically explained by improved detection capability,

mainly using prostate-specific antigen (PSA) and transrectal ultrasound (TRUS). In 1993 and 1994, prostate cancer incidence was first reported to decline in white and black men.

The risk for prostate cancer increases steeply with age. One percent incidence is reached at 67 and 72 years of age for black and white men, respectively. A rise in death rate accompanies the rise in the incidence. An age-adjusted death rate peak of 27 per 100,000 was reported in 1991 in the United States. Thereafter, death rates declined slowly.

B. **Etiology.** The cause of prostate cancer is unknown. Several factors are associated with an increased risk.
1. **Demography.** The risk for developing prostate cancer is highest in Sweden, intermediate in the United States and Europe (and Japanese men who migrated to the United States), and lowest in Taiwan and Japan. Blacks are afflicted 30% more often than are whites. Corrected for stage, blacks also have lower survival rates.
2. **Positive familial history of prostate cancer** in the father or brother of a subject increases his risk seven-fold over the general population if the affected relative was diagnosed by 50 years of age. The relative risk declines to four-fold if the diagnosis of the first-degree relative was made after 70 years of age.
3. **Hormones.** Altered estrogen and androgen metabolite levels have been suggested as a causative mechanism leading to prostate cancer occurrence.
4. **Other suggested risk factors,** which are not fully established, are increased intake of vitamin A, decreased intake of vitamin D, and occupational exposure to cadmium.

II. Pathology and natural history

A. **Histology.** Almost all prostate cancers are adenocarcinomas. Transitional, small, and squamous cell carcinomas and sarcomas are rare. The prostate may be the site of metastases from bladder, colon, or lung cancer or from melanomas, lymphomas, or other malignancies.
B. **Location.** Prostate cancer tends to be multifocal and frequently (70%) arises from the peripheral zone of the prostate (the surgical capsule). Both of these characteristics make removal by transurethral resection of the prostate (TURP) unfeasible for curative intent.
C. **Mode of spread.** The biology of adenocarcinomas of the prostate is strongly influenced by tumor grade. Low-grade tumors may remain localized for long periods of time. The disease locally invades along nerve sheaths and metastasizes through lymphatic chains. Distant metastases may occur without evidence of nodal involvement. Distant metastases are nearly always present when lymph nodes are involved.
D. **Metastatic sites.** Bone is the most common site of prostate cancer metastases, almost always producing dense osteoblastic metastatic lesions. Occasionally, patients demonstrate uncharacteristic osteolytic lesions. Liver involvement also occurs, but metastases to the brain, lung, and other soft tissues are rare.
E. **Associated paraneoplastic syndromes**
1. Systemic fibrinolysis
2. Neuromuscular abnormalities

III. Diagnosis

A. **Symptoms and signs**
1. **Symptoms**
a. Early prostatic cancer is usually asymptomatic and can be detected as a result of routine digital rectal examination (DRE) and serum PSA measurement or during TURP for glandular hyperplasia. The presence of symptoms usually indicates advanced disease. Symptoms include hesitancy, urgency, nocturia, poor urine stream, dribbling, and terminal hematuria.
b. The sudden onset and rapid progression of symptoms of urinary tract obstruction in men of the appropriate age is most likely to be caused by prostate cancer.
c. Pain in the back, pelvis, shoulders, or over multiple bony sites is the most common presenting complaint in patients with distant metastases.
d. The sudden onset of neurologic deficiencies, such as paraplegia and incontinence resulting from extradural spinal metastases, may be a presenting feature or may develop during the course of the disease.
2. **Physical examination**
a. Check for induration or nodularity of the prostate, which often represents prostatic cancer. Nodules of prostatic cancer are typically stony hard and not tender.
b. Examine for normal lateral sulci and palpable (i.e., abnormal) seminal vesicles.
c. Evaluate inguinal nodes for metastatic disease.
d. Evaluate for distant metastases by palpating the skeleton for tender foci and by performing an oriented neurologic examination.
B. **Differential diagnosis of the enlarged prostate**
1. **Acute prostatitis.** Bacterial infection causes dysuria, pain, and often fever. The prostate is tender and enlarged but not hard. Examination and culture of prostatic fluid obtained by prostate massage usually reveals the infectious agent.
2. **Chronic and granulomatous prostatitis** caused by bacterial, tuberculous, fungal, or protozoan infection may produce a mass that cannot be clinically distinguished from cancer. Biopsy may be necessary to make the diagnosis.
3. **Nodular hyperplasia** (benign prostatic hypertrophy) is found in men older than 30 years of age and in 80% of men by 80 years of age. Urinary obstructive symptoms are common. Palpable nodules that are indistinguishable from cancer necessitate biopsy.
4. **Other possibilities.** Rarely, calculi, amyloidosis, benign adenomas, or infarction of a hyperplastic nodule may cause obstruction or a mass suggestive of cancer.
C. **Diagnostic studies**
1. **Routine studies.** Urinalysis, CBC, renal function tests, LFTs, alkaline phosphatase, calcium, and chest radiographs
2. **PSA** is a protease that serves as a marker unique to the prostate. Using PSA increases the number of biopsies performed and thus augments the number of patients diagnosed. It significantly augments the yield of DRE in diagnosing prostate cancer in general and organ-confined disease in particular.
a. **False-positive results.** About 15% of patients with nodular hyperplasia have elevated PSA levels. PSA values can also be increased with prostatic inflammation, surgery, or endoscopy, but not with rectal examination. After a prostate biopsy, PSA is reported to be elevated for at least 6 to 8 weeks. Increased serum PSA concentration has been reported rarely in patients with malignancies other then prostate cancer.
b. **Free PSA** is the fraction of PSA that is not bound to the plasma antiproteases a_1-antichymotrypsin and a_2-macroglobulin. An increased ratio of free to total PSA is associated with increased probability of prostate cancer. For patients with elevated PSA and no suspect findings on palpation of the prostate, it is recommended to proceed with watchful waiting after one negative biopsy if the free-to-total PSA ratio exceeds 25%.
c. **Age-specific PSA.** The normal range of PSA in patients without prostate cancer rises with age, mainly as a result of gland enlargement.

Age (years)	Age-specific serum PSA reference range (ng/mL)
40–50	0–2.5
50–60	0–3.5
60–70	0–4.5
70–80	0–6.5

d. **PSA density** indices are mathematic modifications of PSA. The indices adjust serum PSA levels for the prostate gland volume (*PSA density* = PSA ÷ gland volume) or for the transition zone (TZ) volume (PSA TZ = PSA ÷ TZ volume). The TZ is located centrally, is one of the PSA-producing parts of the prostate, and is usually increased in size when benign prostate hyperplasia occurs. These indices were found to improve positive-predictive and negative-predictive values in patients with total PSA levels of 4 to 10 ng/mL. PSA TZ is also reported to assist in staging, screening, and sparing prostate biopsies in some patients.
e. **Clinical utility of PSA.** PSA can detect primary or recurrent tumors of very low volume and is useful for both diagnosis and follow-up. Although PSA is not sensitive enough to be the sole screening method for prostate cancer, it is useful when combined with DRE and TRUS. About 25% of patients with biopsy-proven prostate cancer have serum PSA levels of less than 4 ng/mL. When PSA is combined with TRUS and prostatic biopsies, cancer is detected in 20% of patients with PSA values between 4 and 10 ng/mL and in 60% of patients with values exceeding 10 ng/mL.

PSA values may show a progressive increase several years before metastatic disease becomes evident. Such a rise is an indication to look for local recurrence in previously treated patients using physical examination or TRUS but not an indication to conduct a detailed, unbeneficial search for metastatic disease.

3. **Acid phosphatase,** previously the only marker for prostate cancer, is seldom used today. Although serum levels are increased in 70% to 80% of the patients with disseminated disease, this test is not sensitive and specific enough for use in patients with localized disease. About 10% of patients with metastatic prostate cancer have elevated acid phosphatase levels with normal PSA levels.
4. **Biopsy techniques**
   a. **TRUS-guided true-cut biopsy** is the standard method to diagnose prostate cancer. Classically, a six-core set is taken by sampling the base, apex, and midgland on each side of the gland. More cores may be sampled to increase the yield, especially in larger glands. Most cancers have a hypoechoic appearance in TRUS, although up to 30% of cancers may be isoechoic. When the indication for TRUS-guided biopsy is a PSA of more than 4 ng/mL, the expected yield for diagnosing prostate cancer reaches 24%. When PSA is more than 4 ng/mL, the DRE is suspicious, and a hypoechoic lesion is imaged by TRUS, the yield rises to 45%.
   b. **TURP.** Prostate cancer may be found in 5% to 10% of TURPs performed for benign hyperplasia (see staging in section IV.A).
5. **Bone scans.** Although bone scans are performed in all patients with a histologic diagnosis of prostate cancer at some centers, their routine use for staging prostate cancer is questionable. Evidence suggests that the probability of a positive scan is extremely low when the PSA is less than 10 ng/mL or symptoms are absent.
6. **CT scans and MRI** are insensitive methods to assess tumor spread into lymph nodes or the pelvis. These studies are warranted only in high-risk patients who have a tumor that is confluent with the pelvic side wall on DRE, a high Gleason's score (see grading in section IV.B.1), or PSA greater than 20 ng/mL.

IV. Staging and prognostic factors

A. **Staging system.** The 1992 TNM classification is as follows:

Grouping	Stage	Extent of disease
	TX	Primary tumor cannot be assessed
	T0	No evidence for primary tumor
T1: Subclinical tumor not evident by palpation or imaging	T1a	£5% cancerous tissue found incidentally on TURP
	T1b	>5% cancerous tissue found incidentally on TURP
	T1c	Diagnosed by needle biopsy performed only for elevated PSA
T2: Palpable tumor confined to the prostate	T2a	Tumor involves one lobe
	T2b	Tumor involves both lobes
T3: Palpable tumor extends beyond capsule	T3a	Extracapsular penetration (unilateral or bilateral)
	T3b	Seminal vesicle(s) involvement
T4: Local extension beyond seminal vesicles	T4	Invades bladder neck, rectum, external sphincter, levator muscles, and/or pelvic wall
N: Regional lymph-nodes involvement	NX	Regional nodes cannot be assessed
	N0	No regional node involvement
	N1	Metastasis in regional node(s)
M: Distant spread	MX	Cannot be assessed
	M0	No distant metastasis
	M1a	Nonregional lymph node involvement (e.g., supraclavicular)
	M1b	Bony metastasis
	M1c	Metastasis to sites other than lymph nodes or bone (e.g., liver)

B. **Prognostic factors**
1. **Tumor grade** strongly affects prognosis. Higher tumor grades are more frequently associated with lymph node and distant metastases. The **Gleason's scoring system** is most commonly used. This system is founded on the glandular appearance and architecture at relatively low-power magnification. Two scores of 1 to 5 points are given for a primary (predominant) site and a secondary (second most prevalent) site. Therefore, Gleason's score can sum from 2 to 10 points. Patients having Gleason's score of 7 and above have a worse prognosis than patients with lower scores.
2. **Involvement of seminal vesicles** is associated with a poor prognosis, even in apparently early disease.
3. **The Alan Partin tables** are clinically useful and integrate the serum PSA concentration, Gleason's score, and clinical stage to predict pathologic stage as reflected in organ confines and lymph nodes involvement.

V. Prevention and early detection
Screening for prostate cancer remains controversial, but it is becoming more evident that early detection as a result of elevated PSA only (T1c disease) results in the identification of more patients with organ-confined disease. A more aggressive diagnostic approach should be considered in men with positive familial or racial (blacks) risk factors.

VI. Management

A. **Overview and philosophy.** The management of all stages of prostate cancer is highly controversial. This disease often has a long natural history; therefore, substantial numbers of patients survive 15 years or longer after the diagnosis (even without treatment). Furthermore, because the disease occurs in older men (who often have significant comorbid illnesses), a large number of patients die from these conditions before they suffer symptoms or die from prostate cancer.
1. Investigators and clinicians vary widely in their use of surgery, RT, hormonal manipulation, and other measures for treating each stage of disease. Most clinicians agree, however, that treatment of early-stage disease with either surgery or RT results in comparable survival. It is unclear at this time whether similar survival rates could be achieved with systemic therapies.
2. We recommend that all options be explored when it comes to treatment selection for a specific patient. No data show an overall clear-cut advantage for radical retropubic prostatectomy over RT, or vice versa. The long-term results of modern cryotherapy and modern brachytherapy are not yet known. Watchful waiting is another option that should be considered. These options should be carefully explained to the patient, exploring the advantages and disadvantages of each modality of treatment. The treatment strategy should be tailored not only according to the patient's clinical data but also according to his expectations and lifestyle.
B. **Surgery for early disease (stages T1 and T2)**
1. **Stage T1a.** Prostate cancer is often discovered by histologic evaluation of specimens taken by TURP for hyperplasia. Management is controversial. The clinical course of stage T1a is variable. If left untreated, a small but significant proportion of patients are at risk for disease progression and death. Thus, it is acceptable to offer treatment for cure in selected cases of T1a disease (such as patients 60 years of age or younger and those with a high Gleason's score, TURP weight less than 30 g, or more than three chips containing adenocarcinoma). Otherwise, patients with stage T1a prostate cancer can usually be managed with "watchful waiting."
2. **Stages T1b to T2b.** These patients may be offered a treatment intended for cure (provided they do not have significant comorbidity), including radical prostatectomy, cryosurgery, RT, or brachytherapy. Most patients undergo pelvic lymphadenectomy during radical retropubic prostatectomy. Patients with significantly elevated PSA (e.g., more than 10 ng/mL) or Gleason's score (e.g., more than 7) may undergo lymphadenectomy before definitive therapy.
3. **Complications of prostatectomy and lymphadenectomy**
   a. **Radical prostatectomy** causes minor incontinence in 10% to 20% of patients. Severe incontinence is reported to occur in no more then 1% to 3%. Most patients suffer from mild to moderate stress incontinence. Potency can be preserved by a skilled surgeon in 60% to 80% of younger patients who undergo nerve-sparing radical prostatectomy.
   b. **Complications of staging lymphadenectomy** occur in about 20% of patients and include lymphocele, pulmonary embolus, wound infection, and lymphedema.
   c. **Persistent or recurrent disease** may occur in 10% to 40% of patients after radical prostatectomy, depending on tumor stage, Gleason's score, and pretreatment PSA.
4. **Contraindications to radical prostatectomy and lymphadenectomy.** Generally speaking, radical prostatectomy is reserved for men who are likely to be cured and who have a life expectancy of at least 15 years. Thus, the following constitute contraindications for radical prostatectomy:
   a. Physiologic age older than 70 to 75 years
   b. High-grade cancers, high serum PSA concentration (relative contraindications)

      c. Invasion of the seminal vesicles (stage T3b)
      d. Metastases to pelvic nodes
      e. Disseminated cancer

C. **RT for early disease (stages T1 to T3)**
  1. **Indications.** RT is widely employed in the treatment of patients with stages T1 and T2 disease. Neoadjuvant hormonal cytoreduction is used in most cases, with improved success and reduced complications. The use of three-dimensional conformal technique allows improved results and fewer side effects than standard RT.

    RT for patients with stage T3 disease is also controversial, but most authorities would support the use of RT integrated with hormonal cytoreduction and radiobiologic optimization. Increasing the relative integral dose is advisable in this selected group. This may be achieved by using conformal external-beam irradiation, proton therapy, or brachytherapy. Other indications for RT include the following:

      a. The patient's medical condition precludes surgery.
      b. Node involvement is found at staging lymphadenectomy (radical prostatectomy is not performed).
      c. Residual malignant pelvic disease is found after prostate surgery.
  2. **Complications** after about 7000 cGy given in 7 to 8 weeks and their approximate incidence rates in treated patients are as follows:
      a. Impotence: 50% (may be less with conformal RT or brachytherapy)
      b. Radiation proctitis with diarrhea, blood-streaked stools, and rectal urgency: less than 5% (see Chapter 30, section VI.D)
      c. Dysuria, urinary urgency, and frequency: less than 5% (see Chapter 11, General Aspects, section V.A)
      d. Perineal fistulas: less than 1%
      e. Fecal and urinary incontinence: 1% to 2%
      f. Urethral stricture: 1% to 5%
      g. Persistent tumor or recurrent disease: 10% to 40%, depending on tumor stage, Gleason's score, and pretreatment PSA
  3. **Other therapies intended for cure** are brachytherapy, cryotherapy, and high-intensity focused ultrasound. These modalities will be judged in the future when enough patients have been treated and long enough follow-up data are available.
  4. **Systemic therapy.** Neither hormonal manipulation nor chemotherapy clearly improves the survival of patients with early prostate cancer.

D. **Advanced disease**
  1. **Surgery.** TURP may be used to relieve bladder outlet obstruction even in the presence of advanced disease; however, orchiectomy alone is usually effective.
  2. **RT** is useful in treating the following problems commonly encountered in prostate cancer patients:
      a. Isolated, painful bony metastatic sites despite endocrine therapy
      b. Pelvic pain syndromes, urinary tract obstruction, and gross hematuria
      c. Metastases to retroperitoneal lymph nodes that produce back pain or scrotal and lower extremity edema
      d. Spinal cord compression from vertebral and extradural metastases is a common and rapidly progressive complication of prostate cancer. Cord compression is an emergency; MRI and definitive therapy must be undertaken within a few hours after onset of symptoms (see Chapter 32, section III).
  3. **Endocrine therapy** is the mainstay of treatment for symptomatic advanced prostate cancer. Patients with asymptomatic but advanced disease do not appear to have improved survival with treatment when compared with untreated patients. Thus, treatment of patients with asymptomatic, advanced disease is not essential. Orchiectomy, luteinizing hormone–releasing hormone (LHRH) agonists, and antiandrogens are the treatments available. Each produces symptomatic relief in 80% of patients. Improvement is often dramatic; many bedridden patients crippled with bone pain return to a more functional status.
      a. **Orchiectomy** produces rapid decline in testosterone level. It is an effective but irreversible procedure. It is advisable as primary treatment for advanced disease and also for patients who are noncompliant with androgen blockade.
      b. **LHRH agonists,** such as leuprolide (Lupron) and goserelin (Zoladex), appear to be as effective as orchiectomy. These depot drugs are given every 3 months (22.5 mg for leuprolide and 10.8 mg for goserelin). The cost of treatment with LHRH agonists is substantially greater than with orchiectomy.
      c. **Antiandrogens combined with LHRH agonists** are believed by some investigators to be superior to LHRH agonists alone and to result in a small but significant survival benefit by "total androgen blockade." Flutamide (Eulexin), 250 mg PO given three times daily; bicalutamide (Casodex), 50 mg PO daily; or other antiandrogens are given along with the LHRH agonist. Leuprolide is given at a dose of 7.5 mg IM monthly. Other studies failed to prove this benefit. The value of total androgen blockade is being evaluated in large-scale prospective studies.
      d. **Other agents** that may be helpful include the following:
        1. **Progestins,** such as megestrol acetate, 40 mg PO four times daily
        2. **Other drugs that inhibit androgen synthesis,** such as aminoglutethimide or ketoconazole (400 mg three times daily) have also been shown to be effective. These agents, however, are expensive and are often difficult to tolerate. The benefits of treatment with them are often difficult to separate from the benefits of corticosteroids, which are often given simultaneously.
        3. **Corticosteroids,** such as prednisone and dexamethasone, often provide symptomatic improvement and may be associated with reductions in PSA levels.
        4. **a_5-Reductase inhibitors** (e.g., finasteride), in combination with other anti-androgens, are being evaluated for efficacy in treating patients with advanced prostate cancer.
        5. **The beta emission of ^{89}Sr** is used in hormone refractory patients to relieve skeletal pain. Responses last about 6 months. Hematologic toxicity is anticipated in the first 2 weeks after administration.
  4. **Chemotherapy** provides relief in 20% to 30% of symptomatic patients with prostate cancer. Various regimens are being used. Estramustine, cisplatin, 5-fluorouracil, vinorelbine, and mitoxantrone are the most popular agents. Multiagent chemotherapy has not been shown to be superior to single agents.

VII. Special clinical problems

A. **Cytopenias in prostate cancer** are usually part of the end-stage process caused by extensive tumor involvement of the bone marrow or by RT to major marrow-bearing sites. The anemia is typically normochromic and normocytic and sometimes a part of a leukoerythroblastic peripheral blood smear. Other causes must be considered.
B. **Obstructive uropathy and uremia** may be the fatal complication of prostate cancer. Orchiectomy or RT (followed by endocrine therapy or chemotherapy) may relieve the obstruction. Unlike uremic patients with other pelvic tumors, some patients with prostate cancer and ureteral obstruction may benefit from surgical intervention. Patients without pelvic pain syndromes and low-grade cancers should be considered for ureteral bypass by stent catheters or percutaneous nephrostomy.
C. **Dense-bone sclerosis on radiograph** in an adult man of the appropriate age who has bone pain usually is diagnostic of prostate cancer. Bone containing prostate cancer is so densely sclerotic that attempts at marrow biopsy often result in "dry taps" and damaged biopsy needles. The radiologic appearance of Paget's disease is distinguished by the fluffy, cotton-like appearance of lesions, by thickening of the bone cortex, and by the dense sclerosis of the pelvic brim (*brim sign*).
D. **Extraosseous extension** of prostate cancer is common. Extension of skull or vertebral lesions can produce neurologic deficits. Extension of rib lesions can produce subcutaneous or pleuropulmonary masses. Retro-orbital and cavernous sinus masses can result in proptosis and visual loss. Extraosseous extension of bony lesions necessitates RT.
E. **Systemic fibrinolysis.** Activators of the fibrinolytic enzyme, plasmin, abound in prostatic tissue. Prostatic disease, especially carcinoma of the prostate, is among the few medical conditions that can produce both significant systemic fibrinolysis and disseminated intravascular coagulation (see Chapter 34, Coagulopathy, section III, for diagnosis and management).

Penile Cancer

I. Epidemiology and etiology

A. **Incidence.** Penile cancer constitutes about 0.5% of all cancers in men in the United States and Europe. The incidence is greatly increased in populations that do not uniformly practice circumcision. The average age of onset is about 60 years, peaking at about 80 years of age.
B. **Etiology.** The etiology of penile cancer is not known. Venereal disease is not a causative factor. The following data suggest that circumcision is preventative:
  1. The disease is almost nonexistent in Jewish men, who are all circumcised shortly after birth.
  2. In Africa and other countries where circumcision is not performed, penile cancer constitutes 20% of all cancers.

3. Moslems have an intermediate risk for penile cancer. Moslem boys are circumcised at puberty.

II. Pathology and natural history

A. **Premalignant lesions**
   1. **Carcinoma *in situ***
      a. **Erythroplasia of Queyrat** occurs on the glans and prepuce of uncircumcised men. The lesions are flat and reddened or are velvety plaques and may progress to invasive cancer in 10% of patients.
      b. **Bowen's disease** appears as a small eczematoid plaque anywhere on the penis. Squamous carcinoma *in situ* is demonstrated by histology. Bowen's disease of the penis, like squamous carcinoma *in situ* in other areas of the skin not exposed to sun, is associated with a high incidence of carcinoma of the gastrointestinal tract and lungs.
   2. **Leukoplakia.** Nonspecific plaques of leukoplakia on the glans are almost always associated with squamous carcinoma. Unlike leukoplakia lesions elsewhere, penile lesions are not white.
   3. **Giant penile condyloma** (Buschke-Löwenstein tumor) grossly resembles a cauliflower-like squamous cell cancer and may have foci of cancer. Surgical excision is mandatory.
B. **Histology.** Squamous cell carcinoma, usually well differentiated, constitutes nearly all penile cancers. Rare penile cancers include melanoma, sarcoma, and metastatic tumor. Squamous carcinoma of the penis may demonstrate variable degrees of keratin formation.
C. **Clinical course.** If left untreated, penile cancers usually cause death within 2 years.
   1. Squamous penile cancer usually starts on the glans or coronal sulcus. As the disease progresses, the corpora cavernosa are invaded. The urethra is usually spared until late in the course.
   2. The rich lymphatic drainage of this region results in metastases to the inguinal nodes (only one third of palpable nodes are involved with tumor by histology). Lymphatic metastases are not common if the tumor is confined to the glans or prepuce.
   3. The tumor disseminates through the lymphatic system and the bloodstream to distant organs in up to 10% of patients, most often to the lungs and less frequently to bone and other sites.
D. **Paraneoplastic syndromes.** Hypercalcemia may develop with no evidence of bony metastasis (20% of patients).

III. Diagnosis is usually delayed substantially because of denial, personal neglect, shame, guilt, or lack of knowledge.

A. **Symptoms and signs**
   1. The earliest lesion of penile carcinoma is described by patients as a nonhealing "sore." There is often an associated foul-smelling discharge. Phimosis may mask penile cancer until erosion through the prepuce occurs. Many patients have a long history of a mass. Urinary tract symptoms, such as pain and hematuria, are signs of locally advanced disease.
   2. Physical examination usually reveals an exophytic mass. Infection of the tumor is usually present when the patient is examined for symptoms. In about 92% of patients, the tumor arises in the glans penis, prepuce, or both.
B. **Laboratory studies**
   1. Routine blood tests, urinalysis, and chest radiographs are obtained.
   2. Biopsy or imprint slides should be done for all patients with a penile mass or with any finding compatible with a precancerous lesion.
   3. Liver and bone scans should be obtained only if abnormalities seen on physical examination or blood studies suggest liver or bone involvement.
   4. MRI and ultrasound of the penis and pelvis are effective in the staging.

IV. Staging system and prognostic factors

A. **Staging system:** TNM classification for squamous cell carcinoma is as follows:

Stage **Extent of disease**

TX	Primary cannot be assessed
T0	No evidence for primary tumor
Tis	Carcinoma *in situ*
Ta	Non-invasive verrucous carcinoma
T1	Subepithelial connective tissue is invaded
T2	Any corpora invasion
T3	Urethra or prostate are invaded
T4	Local extension to adjacent organs beyond T3 definition
NX	Regional lymph nodes cannot be evaluated
N0	No regional nodes involvement
N1	Metastasis to a single superficial inguinal node
N2	Metastasis to multiple or bilateral superficial inguinal nodes
N3	Metastasis to deep inguinal or pelvic nodes, even when unilateral
M0	No distant metastasis
M1	Distant metastasis detected

B. **Prognostic factors.** Poor prognostic features include endophytic and high-grade lesions, invasion of the shaft, and involvement of draining lymph nodes, especially at the iliac level or higher. No more then 10% of patients with clinical stage Tis, Ta, or T1 (Jackson stage I or II) tumors have inguinal node involvement proved by surgery.

V. Prevention and early detection Prevention of penile cancer can be accomplished by routine early circumcision of male babies. Circumcision should be performed in patients with phimosis and penile discharge, inflammation, or induration. Early detection of penile cancer requires regular inspection of the prepuce and glans at physical examination and biopsy of suspected lesions.

VI. Management

A. **Surgery** is the principal modality of therapy for penile cancer in the United States. Partial penectomy is sufficient therapy if there is a 2-cm tumor-free margin.
   1. Total penectomy is necessary for lesions that invade the body of the penis or are very large.
   2. In younger patients with tumor confined to the prepuce, circumcision may be used if close follow-up can be assured; however, the recurrence rate is high.
   3. Dissection or routine sampling of the superficial inguinal nodes for patients with low-stage (up to T2) but high-grade lesions is recommended by some authorities; if the nodes contain tumor, a radical ilioinguinal lymphadenectomy is necessary. Radical lymphadenectomy is routinely performed in patients with stage T3 tumors. The extensiveness of the lymph node dissection (deep versus superficial inguinal versus pelvic node dissection; unilateral versus bilateral; full versus limited) varies according to local and regional disease extension.
B. **RT.** The primary role of RT is to avoid penectomy, especially in younger patients. This modality has been used for treating small primary stage I lesions (less than 3 cm in diameter); the results for RT alone (along with salvage surgery for failures) appear to be the same as those obtained when partial amputation is used as primary therapy.
C. **Chemotherapy**
   1. **Premalignant lesions** may respond to topical therapy with fluorouracil or to laser therapy in selected cases.
   2. **Penile cancer** appears to be responsive to combination chemotherapy: vincristine, bleomycin, and methotrexate (VBM regimen) or cisplatin and 5-fluorouracil. Some authorities use these drugs as an adjunct to surgery or RT for stage T3 and T4 tumors. Response rates of advanced cancer to these drugs may be as high as 50%.

Urethral Cancer

I. Epidemiology and etiology Urethral cancer is extremely rare; fewer than 1500 cases have been reported in the literature. Women are affected three times as often as men. The age of onset is usually older than 50 years. The etiology is not known, but urethral cancer may be associated with gonorrheal urethritis, strictures, or transitional cell carcinoma in the bladder.

II. Pathology and natural history

A. **Histology.** Eighty percent of cases are squamous cell carcinomas, usually arising from the stratified squamous epithelium of the posterior (proximal or bulbous) urethra (60%) or the anterior (distal or penile) urethra (30%). Fifteen percent are transitional cell carcinomas arising in the prostatic urethra. Adenocarcinomas possibly arise from Cowper's glands.

B. **Clinical course.** Urethral cancer is usually diagnosed late and involves inguinal nodes early on. It also spreads hematogenously to distant organs. Lesions of the anterior urethra are less likely to be associated with widespread metastases than are posterior lesions.

III. Diagnosis. Patients have urinary hesitancy, hematuria, palpable mass, urethral discharge, perineal pain, or enlarged inguinal nodes. Transurethral biopsy establishes the diagnosis. The biopsy and imaging studies contribute to TNM staging.

IV. Management. In both female and male patients, the extensiveness of therapy is determined by the stage, location of the tumor (anterior versus posterior urethra), and need for local palliation. In women, treatment varies between total urethrectomy and more extensive surgery that includes cystectomy (with total or partial resection of the vagina), urethrectomy, and pelvic lymph node dissection. In men who have anterior urethral cancer, transurethral resection of the tumor followed by wide local excision is usually enough. If the corpora are infiltrated with tumor, partial or total penectomy is usually required. For posterior urethral disease, the combination of radical cystoprostatectomy, total penectomy, and pelvic lymphadenectomy offers improved results. RT has a limited role in urethral cancer therapy for selected cases. Combination chemotherapy regimens are used for patients with metastases.

Suggested Reading

The National Cancer Institute website for clinical trials is http://cancernet.nci.nih.gov/prot/dismenue.html.

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Chapter 14 Neurologic Tumors

Ellen E. Mack

I. Epidemiology and etiology

A. **Incidence.** Primary brain cancers represent 2% (17,000 cases) of all cancers and 2.5% (10,000 cases) of cancer deaths annually in the United States (Table 14.1). The male-to-female ratio is 3:2. The incidence peaks at 5 to 10 years of age and again at 50 to 55 years of age. Brain cancers are the most common solid tumors in children; brain cancers occurring in childhood are discussed further in Chapter 18, Brain Tumors.

   Table 14.1 Features of common central nervous system tumors

B. **Etiology**
   1. **Environmental factors,** such as tobacco, alcohol, and diet, have not been associated with primary central nervous system (CNS) tumors. Exposure to ionizing radiation, however, can induce the formation of meningiomas, nerve-sheath tumors, sarcomas, and less commonly, astrocytomas. Occupational exposure to vinyl chlorides is a risk factor for astrocytomas; animal studies have shown that exposure to N-nitroso compounds, aromatic hydrocarbons, triazenes, and hydrazines increases the risk for astrocytoma formation.
   2. **Hereditary neurocutaneous syndromes**
      a. **Neurofibromatosis I** is a dominantly inherited condition of multiple neurofibromas, café-au-lait spots, axillary freckling, and Lisch nodules of the iris that confers an increased risk for optic glioma, intracranial astrocytoma, neurofibrosarcoma, neural crest–derived tumors (glomus tumor, pheochromocytoma), embryonal tumors, leukemia, and Wilms' tumor. The gene for this disorder is on chromosome 17, and its product, neurofibromin, is a tumor-suppressor gene that is a major negative regulator of the Ras pathway, which transmits mitogenic signals to the nucleus.
      b. **Neurofibromatosis II** is a condition of multiple schwannomas, especially acoustic neuromas, that is also associated with an increased risk for ependymoma and meningioma. The gene for this disorder is located on chromosome 22, and its product, merlin, encodes a member of the ezrin-radixin-moesin (ERM) family of membrane and cytoskeletal linker proteins thought to be important for cell motility and adhesion.
      c. **Tuberous sclerosis** (Bourneville's disease) is a dominantly transmitted disorder characterized by the development of hamartomas, including subependymal nodules and cerebral cortical tubers, which have abnormal cortical architecture and can be associated with mental retardation, epilepsy, and behavioral disturbances such as autism. Hamartomatous lesions of other organ systems include facial angiofibromas, forehead plaques, shagreen patches, cardiac rhabdomyomas, and renal angiomyolipomas and cysts. This disorder is associated with the formation of giant-cell astrocytomas. Two responsible tumor-suppressor genes, *TSC-1* (chromosome 9) and *TSC-2* (chromosome 16), have been identified.
      d. **Nevoid basal cell carcinoma syndrome** (Gorlin's syndrome) is a dominantly inherited syndrome of multiple basal cell carcinomas that may be associated with the presence of medulloblastoma, meningioma, craniopharyngioma, and some systemic tumors (ovarian tumors, cardiac fibroma, maxillary fibrosarcoma, adrenal cortical adenoma, rhabdomyosarcoma, seminoma). Other features include jaw cysts, palmar and plantar pits, and spine and rib anomalies. The loss of a tumor-suppressor gene on chromosome 9 is responsible for this order. Its gene product, PTCH, is the human homolog of the *Drosophila* patched gene, part of the hedgehog signaling pathway, which is important in embryonic patterning and cell fate.
      e. **Neurocutaneous melanosis** is a developmental rather than inherited condition of large, hairy, pigmented benign nevi of the skin associated with infiltration of the meninges by melanin-containing cells. Although the pigmented lesions of the skin remain benign, the pigmented cells in the meninges often undergo malignant transformation with neural invasion, resulting in primary CNS melanoma.
   3. **Hereditary cancer syndromes**
      a. **von Hippel-Lindau disease** is a dominantly transmitted disorder characterized by hemangioblastomas of the retina, cerebellum, and less commonly, the spinal cord. Other associated tumors include renal carcinoma, pheochromocytoma, islet cell tumors, endolymphatic sac tumors, and benign renal, pancreatic, and epididymal cysts. The disorder is due to the loss of two tumor-suppressor genes on chromosome 3. This loss results in the overexpression of vascular endothelial growth factor and erythropoietin, which are normally induced by hypoxia.
      b. **Turcot's syndrome** is a rare familial syndrome associated with colon cancer, glioblastoma, and medulloblastoma.
      c. **Li-Fraumeni syndrome** is a clinical syndrome of familial breast cancer, sarcomas, and primary brain tumors that is associated with germline *p53* (chromosome 17) mutations.
   4. **Immune suppression.** Transplant recipients and patients with acquired immunodeficiency syndrome (AIDS) have a markedly increased risk for primary CNS lymphoma.

II. Diagnosis

A. **Clinical presentation** depends on the location of the tumor and its rate of growth. In general, slow-growing tumors cause little in the way of focal deficits because the nervous tissue is slowly compressed and compensatory mechanisms appear to occur. After they reach a certain size, cerebrospinal fluid (CSF) pathways may be obstructed, causing evidence of increased intracranial pressure (ICP). Fast-growing tumors tend to be associated with considerable surrounding cerebral edema; the edema, in addition to the tumor mass, is more likely to cause focal deficits. Usually, the deficits caused by edema are reversible, whereas those caused by a mass are much less so. Specific signs and symptoms associated with tumors of the CNS include the following:
   1. **Headaches** are most likely to occur with fast-growing tumors and are typically deep, dull, and not intense or throbbing. They are characteristically worse on arising in the morning and are exacerbated by straining or lifting. Lateralization of headaches occasionally facilitates tumor localization.
   2. **Seizures.** In 20% of patients older than 20 years of age, the onset of seizures is caused by a neoplasm. The seizures may be generalized or partial (focal). Simple partial seizures commonly consist of transient sensory or motor phenomena of a single limb or side. Complex partial seizures, often of temporal lobe origin, consist of changes in the level of consciousness or awareness of surroundings, frequently in conjunction with abnormal olfactory or gustatory phenomena. Speech arrest may also occur. Generalized seizures result in loss of consciousness, bowel and bladder incontinence, and bilateral tonic-clonic movements. In patients with brain tumors, generalized seizures are often partial or focal in onset, and evidence of focality may be found on postictal examination of the patient.
   3. **Increased ICP** may result from a large mass or from obstructive hydrocephalus. Large masses cause progressive obtundation and can lead to transtentorial herniation, which classically presents with a third cranial nerve palsy and hemiparesis. Hydrocephalus causes gait ataxia, nausea, vomiting, headache, and eventually a decrease in level of consciousness. If left untreated, hydrocephalus can lead to central herniation, which is not heralded by a third-nerve palsy. Papilledema is a sign of increased ICP. Unusual signs and symptoms of increased ICP include visual obscurations, dizziness, and the so-called falsely localizing signs. Of these unusual indications, the most classic is diplopia from sixth cranial nerve dysfunction owing to stretching of the nerve from downward pressure caused by a large supratentorial mass.
   4. **Supratentorial lobar** tumors usually present with focal signs and symptoms, including hemiparesis (frontal lobe), aphasia (left frontal and posterior temporal lobes), hemineglect (parietal lobe), and hemianopsia (occipital lobe).
   5. **Hypothalamic** tumors may be associated with disturbance of body temperature regulation, diabetes insipidus, hyperphagia, and, if the optic chiasm is involved, visual-field deficits.
   6. **Brain-stem** tumors, such as brain-stem gliomas, present with multiple cranial nerve deficits and long-tract signs (weakness of the extremities).
   7. **Nerve-sheath** tumors, such as acoustic neuromas, result in deficits of the involved cranial or spinal nerve. As the tumor enlarges, surrounding neural

structures may also be compressed, leading to further symptoms.

   8. **Cerebellar** tumors are associated with dysmetria, ataxia, vertigo, nystagmus, and vomiting.
   9. **Spinal cord** tumors present with spastic paraparesis and sensory loss below the level of the tumor as well as with disturbances of bowel and bladder function.
   10. **Meningeal** involvement by primary CNS tumors is less common than with metastatic tumors and is seen mostly with medulloblastomas, pinealoblastomas, germinomas, primary lymphomas, and to a lesser degree ependymomas. The hallmark for meningeal disease is neurologic dysfunction at multiple levels of the neuraxis. Nonspecific features include seizures and changes in mentation.

B. **Evaluation.** Imaging studies must be performed to evaluate cases of suspected CNS mass lesions.

   1. **Computed tomography** (CT) **and magnetic resonance imaging** (MRI) are the primary imaging modalities for evaluating presumed CNS tumors. MRI is preferable because of its greater sensitivity, especially for mass lesions in the brain stem, posterior fossa, medial temporal lobes, and spinal cord. Contrast studies should always be performed because most tumors show contrast enhancement.
   2. **Lumbar puncture** is almost never a part of the initial evaluation of a suspected CNS tumor and in fact is often contraindicated in this setting. It is used primarily to stage tumors known to disseminate along the neuraxis or to evaluate patients with clinical or radiographic evidence of meningeal dissemination (see section II.A.10). A notable exception is primary CNS lymphoma, which can be diagnosed in some instances by examination of CSF in lieu of biopsy.
   3. **Angiography** is usually not required in the evaluation of suspected CNS tumors. It is most useful in the preoperative evaluation of highly vascular tumors and tumors for which the blood supply may be shared with other neural structures. The need for angiography is determined by the neurosurgical consultant.
   4. **Systemic evaluation.** After a mass lesion is demonstrated on CT or MRI scan, its specific etiology must be determined. The differential diagnosis includes primary tumors of the nervous system, metastatic tumors, stroke, and inflammatory or infectious processes (e.g., multiple sclerosis, cerebral abscess). Radiographic features can help differentiate between these diagnoses; combined with the patient's history and physical examination, they can lead to a presumptive diagnosis with reasonable certainty. Basic screening tests, however, are often performed to exclude an underlying systemic malignancy. A reasonable evaluation includes the following:
      a. Posteroanterior and lateral chest radiographs
      b. Complete blood count, renal and liver function tests, electrolytes, calcium, magnesium, glucose, and thyroid function tests.
      c. Mammogram and pelvic examination, especially if they have not been performed recently or routinely
      d. Stool guaiac for occult blood
   5. **Surgery** is required for definitive diagnosis in most cases of suspected primary nervous system tumors and is usually a cornerstone of treatment as well. Exceptions include tumors not requiring surgical extirpation for therapy that can be diagnosed by other means, including imaging (e.g., neurofibroma, optic nerve glioma) or CSF examination (e.g., primary CNS lymphoma). In addition, patients in whom nonneoplastic processes (e.g., stroke, multiple sclerosis) cannot be excluded may elect to be managed by clinical and radiographic observation.

III. Astrocytoma and glioblastoma multiforme

A. **Pathology.** Astrocytomas are highly infiltrative tumors that are graded by their degree of anaplasia. Well-differentiated tumors are classified as astrocytoma, those with more evidence of atypia as anaplastic astrocytoma, and those with highly malignant features as glioblastoma multiforme (GBM). Glioblastomas with sarcomatous features are referred to as gliosarcomas. The incidence of astrocytomas increases with age, and as the age of the patient increases, the astrocytoma is more likely to be of a higher grade. Astrocytomas are most commonly supratentorial but may occur in the cerebellum, brain stem, and spinal cord. Immunohistochemical phenotypes of neurologic malignancies are shown in Appendix C3.II.

B. **Radiology.** On CT or MRI scans, astrocytomas are usually solitary lesions, appearing as large translucent zones localized to the white matter. The mass is usually solid but may have cystic components. As the tumor grows, it tends to follow white-matter tracts. Most astrocytomas, especially high-grade lesions, enhance after administration of contrast material and are surrounded by focal edema. GBMs often have central necrosis and are described as *ring-enhancing lesions.*

C. **Treatment**

   1. **Dexamethasone** reduces the cerebral edema associated with brain tumors by decreasing vascular permeability through its action on endothelial junctions. Neurologic dysfunction from brain tumors is often due to surrounding edema rather than to the tumor itself. Therefore, treatment with steroids often results in considerable neurologic improvement. Dosing schedules vary, but the typical starting dose is 4 mg PO or IV every 6 hours. After treatment is initiated, patients should be monitored for hypertension and hyperglycemia. Doses should not be reduced until definitive treatment has been undertaken (usually postoperatively or during RT). Thereafter, the drug is gradually tapered off as tolerated.
   2. **Surgical resection** should be performed whenever technically feasible. Not only is surgery necessary for adequate tissue sampling for pathologic diagnosis, but it can also lead to neurologic improvement from reduction of mass effect. The degree of surgical resection has been shown to correlate with survival, especially for higher-grade lesions. The term *gross total resection* refers to removal of all or nearly all tumor visualized radiographically. Based on the infiltrative nature of astrocytomas, however, residual tumor always remains. Postoperative MRI scans should be performed within 2 days of surgery to determine the extent of surgical resection.
   3. **RT** substantially improves survival, and a dose–response relationship has been documented. Astrocytomas are treated with 5400 cGy and anaplastic astrocytomas and GBM with 6000 cGy of radiation to the tumor and surrounding margins. Radiation sensitizers have not been definitively shown to be beneficial in the treatment of astrocytomas.

   The role of adjuvant ("boost") radiation therapy, such as interstitial brachytherapy or radiosurgery, is unclear buy may offer a survival advantage to patients with GBM. Complications of such therapies include steroid dependence and the need for further surgical debulking in half of patients for control of radionecrosis.

   4. **Chemotherapy** used on an adjuvant basis has been shown to provide a modest survival advantage to patients with anaplastic astrocytoma or GBM. Adjuvant chemotherapy is most useful in patients with anaplastic astrocytoma, for which it is now considered to be standard therapy. Patients with GBM and good prognostic factors (young age, high performance status, gross total resection) may also benefit from chemotherapy.

   In general, the most effective agents are the nitrosoureas and procarbazine, often given in combination as the PCV regimen in 42-day cycles:

   Procarbazine, 60 mg/m^2 PO on days 8 through 21
   CCNU, 110 mg/m^2 PO on day 1 of cycle
   Vincristine, 1.4 mg/m^2 IV on days 8 and 29

   Treatment is usually continued until tumor progression is evident or a maximum of six or seven cycles have been administered. Monitoring pulmonary function tests may be necessary in selected patients.

   5. **Treatment at recurrence.** Astrocytomas, including GBM, are responsive to treatment at recurrence, and treatment strategies usually parallel those given at diagnosis. Low-grade astrocytomas are more likely to respond to continued sequential treatments than are high-grade tumors. The decision to treat at recurrence, therefore, depends not only on patient characteristics, such as age and performance status, but also on tumor characteristics, such as histologic grade and surgical accessibility.

   For patients who elect further therapy, dexamethasone should be reinstituted for neurologic symptoms, and further surgical debulking should be performed as much as possible. Postoperatively, either further irradiation using focused techniques, such as radiosurgery or interstitial brachytherapy, or chemotherapy should be employed. Agents other than the nitrosoureas and procarbazine that have activity against astrocytomas include carboplatin, etoposide, interferon- a, and melphalan.

   6. **Patient follow-up.** Patients with astrocytomas require lifelong follow-up. Low-grade astrocytomas can recur, often as higher-grade lesions, as long as 20 years after treatment. Tumor recurrence is usually at the primary site, but occasionally astrocytomas can become multifocal or recur at distal sites within the neuraxis. Metastasis to systemic tissues is exceedingly rare. Monitoring for tumor recurrence can best be achieved with serial neurologic examinations and neuroimaging. The rate of monitoring is individualized and depends on the grade of the tumor, the performance status of the patient, and the intention for further therapy.

D. **Survival.** Median survival is about 5 years for astrocytoma, 2.5 years for anaplastic astrocytoma, and 1 year for glioblastoma. About 5% of patients with GBM survive for 5 years or longer.

IV. Other glial neoplasms

A. **Oligodendroglioma**
1. **Pathology.** Oligodendrogliomas arise from the oligodendrocytes or myelin-producing cells of the CNS and may occur in conjunction with astrocytomas as a mixed tumor. Most are lower-grade lesions, but highly anaplastic forms analogous to GBM also occur.
2. **Clinical features.** Compared with astrocytomas, oligodendrogliomas are more likely to result in seizures and have a higher tendency to hemorrhage and to disseminate to the meninges. Oligodendrogliomas often have a lobar location and are most common in the frontal lobes. Radiographically, they often contain calcifications.
3. **Treatment** is similar to that for astrocytomas and includes dexamethasone for control of symptoms, aggressive surgical resection, and postoperative RT. Oligodendrogliomas are usually more responsive to chemotherapy than astrocytomas, and PCV is often employed. The median survival time is about 5 years.
B. **Juvenile pilocytic astrocytoma** (JPA)
1. **Pathology.** Pilocytic astrocytomas differ in histology and clinical behavior from the astrocytomas discussed in section III. They are less invasive, more circumscribed, and much less likely to progress to a more anaplastic state.
2. **Clinical features.** Pilocytic astrocytomas tend to occur in children and young adults and have a predilection for the cerebellum, hypothalamus, optic chiasm, and thalamus. Radiographically, they are well- demarcated masses that enhance densely and homogeneously and may have cystic components.
3. **Treatment.** Because JPAs tend not to be infiltrative or histologically progressive, and they can often be cured surgically, small residua of subtotally resected tumors may either be electively observed or treated with focal irradiation. Nonresectable tumors are usually treated with RT (54 Gy, focal fields) or, in very young patients, with chemotherapy. JPAs respond to nitrosoureas, procarbazine, cyclophosphamide, vincristine, platinum compounds, and etoposide.
4. **Survival** depends on tumor location and extent of resection. The overall median survival rate is 80% at 10 years and 70% at 20 years.
C. **Ependymoma**
1. **Pathology.** Ependymomas arise from ependymal cells. Therefore, these tumors localize to the ventricular system and spinal canal, most often in the fourth ventricle and in the region of the cauda equina. They are more frequent in children but occur in adults as well. Most are histologically benign, but some types, including anaplastic ependymoma, ependymoblastoma, and myxopapillary ependymoma, can disseminate to the spinal fluid.
2. **Treatment.** Ependymomas can be cured by total resection. Unfortunately, their location often makes them not completely resectable, and RT must often be administered postoperatively. Radiation is usually given to focal fields to a dose of 54 Gy. Anaplastic ependymomas and ependymoblastomas are often treated like medulloblastomas (see section VI). Chemotherapy plays less of a role in the treatment of ependymomas, but when used, platinum compounds are considered most effective.
D. **Brain-stem gliomas** are astrocytomas that arise in the brain stem, usually the pons, and are more common in children than adults. Because their location has a major effect on the clinical course and survival of patients, brain-stem gliomas are classified separately from astrocytomas. Multiple cranial nerve nuclei are usually involved, and therefore patients often have significant neurologic compromise and are at great risk for aspiration and sepsis. Surgical resection is also not possible because of tumor location, and because the radiographic and clinical findings are often characteristic, tissue confirmation by biopsy is often not pursued. Treatment consists of focal RT, usually to 60 Gy. Median survival for patients with diffuse brain-stem gliomas is about 1 year. Patients with more localized, discrete tumors have a longer survival time.

V. Primary CNS lymphoma (PCNSL) is discussed in Chapter 21, Non-Hodgkin Lymphoma, section VI.B and Chapter 37, section II.G. Compared with gliomas, PCNSLs are more likely to cause subcortical dementia, cranial neuropathies, and visual loss and are less likely to cause seizures. These clinical features reflect the tendency of PCNSLs to localize to deep, subcortical midline structures and to involve the meninges. PCNSLs are often elusive in their presentation and occasionally have a relapsing–remitting course similar to that of multiple sclerosis. Radiographically, these tumors tend to be multifocal and enhance homogeneously. They may involve midline structures, such as the corpus callosum or basal ganglia. Radiographic evidence of leptomeningeal enhancement should always be sought. All patients require complete examination of the neuraxis, including the eyes.

VI. Medulloblastoma

A. **Pathology.** Medulloblastomas are embryonal tumors arising from primitive germinal cells in the cerebellum; they most commonly localize to the vermis and fourth ventricle. They are more common in childhood but occur in young adults as well. Other small cell primary malignancies of the brain (e.g., neuroblastoma, pineoblastoma, ependymoblastoma) are similar histologically and clinically and are treated like medulloblastomas.
B. **Clinical features.** Because of their close proximity to CSF pathways, medulloblastomas often cause obstructive hydrocephalus. Patients, therefore, often present with signs of hydrocephalus (e.g., gait ataxia, headache, nausea and vomiting) rather than signs localizing to the site of their tumor.
C. **Staging and treatment.** Patients require full staging of the neuraxis, that is, contrast-enhanced MRI of the head and full spine and cytologic examination of CSF. Spinal imaging can often be performed preoperatively. CSF should be obtained intraoperatively or not until 2 weeks after surgery to avoid false-positive results.
1. **Surgery.** The extent of surgical resection correlates with survival in patients with medulloblastoma, and gross total resection should be attempted. Patients with persistent hydrocephalus may require placement of a shunting device. Dexamethasone is used to control cerebral edema, especially in the perioperative period.
2. **RT,** consisting of craniospinal irradiation, is the cornerstone of therapy, even for patients with negative staging studies. Doses range from 30 to 36 Gy to the whole brain and spine with an additional boost to the tumor to 60 Gy.
3. **Chemotherapy** is administered to patients with evidence of tumor dissemination on staging studies. There is no established first-line chemotherapeutic regimen, but active agents include the nitrosoureas, procarbazine, cyclophosphamide, and cisplatin.
D. **Prognosis.** Patients with medulloblastomas who have had a gross total resection and who show no evidence of tumor dissemination have a 5-year survival rate of 60% to 75%. In cases of disseminated tumor, the addition of chemotherapy has increased the median survival to about 5 years.

VII. Germ cell tumors

A. **Pathology.** Germ cell tumors arising in the nervous system are usually localized in the pineal and suprasellar regions. They are of two basic types: germinomas and nongerminomas. The former are highly sensitive to radiation and are analogous to systemic seminomas and dysgerminomas. The latter, including teratomas, choriocarcinomas, endodermal sinus tumors, and some tumors of mixed histology, are resistant to radiation. All germ cell tumors except mature teratomas are malignant. They are more common in male patients and in Japanese people, and they occur mostly in the first three decades of life.
B. **Evaluation.** Because germ cell tumors can readily disseminate in the neuraxis, all patients require complete staging, including contrast MRI of the brain and full spine, CSF cytologic examination, and determination of serum and CSF a-fetoprotein and b-human chorionic gonadotropin levels.
C. **Treatment.** Previously, patients with pineal tumors underwent a trial of RT; if the tumor responded rapidly, the diagnosis of germinoma was inferred. With improved surgical techniques and the advent of histology-directed therapy, however, surgical resection or biopsy should be performed first. Resection constitutes complete therapy for benign tumors (mature teratomas). Germinomas with no evidence of neuraxis dissemination and with negative tumor markers are subsequently treated with irradiation of the tumor and surrounding ventricular system. Nongerminoma, tumors with positive markers, and tumors with evidence of neuraxis dissemination are treated with craniospinal irradiation and chemotherapy. Regimens are similar to those used for systemic germ cell tumors. The 5-year survival rate approaches 80% for germinomas but is less than 25% for nongerminomas, which are relatively resistant to therapy.

VIII. Benign nervous system tumors

A. **Meningiomas** are tumors arising from arachnoidal cells. Their incidence increases with age, and they are more common in female patients. The location of meningiomas may be over the convexities, parasagittal along the falx, along the sphenoid wing, retroclival, or along the thoracic spine. Although most of these tumors are benign, some are histopathologically classified as aggressive or malignant. The tumors are recognized radiographically by their extraaxial location and their dense, homogeneous pattern of contrast enhancement.

Treatment is by surgical resection, which is often curative. Recurrent or incompletely resected tumors may be treated with RT. These tumors have not been shown to respond to chemotherapy. Receptors for estrogen, androgens, and especially progesterone have been demonstrated in meningiomas; they may be responsive to hormones.

B. **Craniopharyngiomas** are congenital suprasellar tumors thought to arise from epithelial remnants of Rathke's pouch. They present clinically with dysfunction of the optic chiasm or hypothalamic-pituitary axis as a result of tumor compression. The tumor may contain calcifications and an oily, cellular debris that causes a

severe chemical meningitis if introduced into the spinal fluid. The tumor is histologically benign and can be cured by total resection. Unfortunately, this is often not possible, and RT is eventually required for tumor control.

C. **Pituitary adenoma.** Adenomas of the pituitary gland can either be secreting or nonsecreting tumors. Secretory tumors can cause acromegaly, infertility, galactorrhea, amenorrhea, or Cushing's disease. These tumors, especially those secreting adrenocorticotropic hormone, are often small and may be difficult to demonstrate radiographically, even with MRI. In such cases, venous sampling of the petrosal sinuses may be required to help localize the tumor. Nonsecretory tumors can result in bitemporal hemianopsia because of mass effect, pituitary apoplexy resulting from hemorrhage into the tumor, or hypopituitarism. Treatment usually consists of surgical resection, usually by the transsphenoidal route, except in the case of prolactinomas, which are initially treated with a trial of bromocriptine. Incompletely resected tumors may require RT as well.

D. **Schwannoma and acoustic neuroma.** Schwannomas, which are tumors arising from Schwann's cells in spinal nerve roots, are referred to as *acoustic neuromas* when present in the cerebellopontine angle, where they usually arise from the vestibular nerve. Acoustic neuromas lead to sensorineural hearing loss, tinnitus, and vertigo that can progress to involve adjacent neural structures, causing facial weakness, facial numbness, dysphagia, and ataxia. On contrast-enhanced MRI scans, these tumors are seen as a homogeneous, densely enhancing mass that follows the eighth cranial nerve into the internal acoustic canal. Brain-stem evoked potentials are also useful for early diagnosis and monitoring. Management depends on the extent of hearing loss and whether bilateral tumors are present, but therapeutic options include surgical resection and focal irradiation with radiosurgery. Bilateral acoustic neuromas constitute the diagnosis of neurofibromatosis II. Spinal schwannomas cause a radiculomyelopathy and can be cured by total resection. Rarely, these tumors can have sarcomatous degeneration.

IX. Special clinical problems

A. **Seizures.** The prophylactic use of anticonvulsants is controversial in the setting of brain tumors. Because these drugs are often administered perioperatively, they are frequently continued, even in the absence of a history of seizures. Information regarding possible seizures, such as unexplained, transient neurologic events that could represent partial or focal seizures, should always be sought. Several anticonvulsants are available; the choice of a specific agent depends mostly on the side-effect profile, the desired route of administration, and the urgency for treatment. If seizures have been multiple, prolonged, or generalized, a loading dose of anticonvulsants may be required. Otherwise, patients can be started on maintenance therapy and monitored until therapeutic levels are achieved. Commonly used agents include the following:

1. **Phenytoin (Dilantin)**
   a. **Loading dose** is 18 mg/kg (usually 1 g for adults). Maintenance doses are 5 mg/kg per day (usually 300 mg/day for adults). Phenytoin given orally is usually administered in a long-acting formulation, such that once-a-day administration is adequate. For intravenous or intramuscular administration, phenytoin is given in the form of fosphenytoin in *phenytoin-equivalent* (PE) doses (18 mg PE/kg loading; 5 mg PE/kg per day in divided doses maintenance) at a rate not to exceed 150 mg PE/min. Parenteral loading of phenytoin should be performed with electrocardiogram, blood pressure, and respiratory monitoring.
   b. **Therapeutic levels** are 10 to 20 μg/mL. Dose adjustments should be made gradually, because phenytoin has zero-order kinetics, and small increases in the dose can sometimes result in large increases in serum levels.
   c. **Side effects** of phenytoin include gingival hypertrophy, hirsutism, megaloblastic anemia, leukopenia, and hepatic dysfunction. Allergic reactions manifesting as eosinophilia and a rash are not uncommon and can proceed to a Stevens-Johnson reaction. Toxicity is progressively manifested by nystagmus, ataxia, and lethargy.
2. **Phenobarbital** is often the second-line agent in the emergent setting because an intravenous formulation is available. The loading dose is 20 mg/kg and may be administered up to a rate of 100 mg/min. Maintenance doses are 1 to 5 mg/kg/day, usually 90 to 120 mg/day in adults, and may be given before bedtime as a single dose. Therapeutic levels are 15 to 40 μg/mL. Sedation is the primary side effect.
3. **Carbamazepine** is often a first-line agent in the nonemergent treatment of seizures. It is available only in an oral form, and doses must be slowly increased to maintenance levels because rapid loading is not tolerated. Doses range from 7 to 15 mg/kg per day, divided into twice-daily or three times daily fractions, typically 600 to 1000 mg/day for an adult. Therapeutic serum levels range from 6 to 12 μg/mL. Side effects include granulocytopenia, diplopia, nystagmus, fatigue, hepatic dysfunction, and allergic dermatitis. Monitoring of blood counts is required.
4. **Valproate** is administered orally at a dose of 15 mg/kg per day divided into three times daily doses and elevated by 5 mg/kg per day as needed to control seizures; the therapeutic dose is 50 to 100 μg/mL. Side effects include hepatic and pancreatic toxicity, thrombocytopenia, nausea, tremor, and alopecia. Monitoring of LFTs is required.
5. **Newer anticonvulsants,** such as felbamate, gabapentin, lamotrigine, topiramate, and vigabatrin, can be used at the discretion of the treating physician.

B. **Hydrocephalus** can result from obstruction of CSF pathways, especially with intraventricular tumors or tumors in the upper brain stem. Patients with hydrocephalus present with headaches, nausea, vomiting, gait ataxia, urinary incontinence, and progressive lethargy. Large ventricles above the level of obstruction can be diagnosed with a noncontrast CT scan. Treatment consists of placement of a ventriculoperitoneal shunt.

C. **Radiation necrosis** can result from RT and is not uncommon after high-dose and interstitial irradiation. Clinically and radiographically, it is often indistinguishable from tumor recurrence. Position emission tomography is useful in distinguishing tumor recurrence from radiation necrosis. Radiation necrosis can be treated with dexamethasone, but surgical debulking is often required to relieve mass effect and to provide a definite tissue diagnosis.

D. **Deep-vein thrombosis** occurs in about 20% of patients with high-grade gliomas. Ideal treatment consists of placement of an inferior vena cava filter. Although some physicians have expressed concern that anticoagulation poses increased risk for intracranial hemorrhage in patients with primary brain tumors, most studies have not substantiated this risk. Anticoagulation should therefore be used as therapy for patients with brain tumors and deep-vein thrombosis or pulmonary embolism in whom a filter cannot be placed.

E. **Herniation** results from progressive mass effect in patients with large, edematous tumors. Herniation can be central in the case of midline tumors and hydrocephalus, uncal in the case of hemispheric lesions, or tonsillar in the case of posterior fossa tumors. Once recognized, herniation is an emergency that must be treated with methods to decrease intracranial pressure. These include the following:
1. Elevation of the head of bed
2. Hyperventilation to a Pco_2 of about 30 mm Hg
3. Creation of an osmotic gradient by administration of mannitol at 1 g/kg IV (usually 50 to 100 g in adults)
4. Dexamethasone, up to 100 mg IV

Suggested Reading

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Chapter 15 Endocrine Neoplasms

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I. General considerations. Cancers of endocrine glands constitute less than 1% of all malignancies. Most malignant neoplasms derived from endocrine organs are not associated with clinical endocrinopathies, although several do produce unique syndromes and biochemical markers.

A. **Steroid hormones** are never ectopic tumor products. They are always produced by the tissue that normally produces them, such as the adrenal cortex and gonads, whether that tissue is healthy or cancerous. The mechanism of action for most steroid hormones depends on specific receptors in the target cell cytoplasm or nucleus.

B. **Peptide hormones and catecholamines** appear to act at the cell surface, where they attach to specific receptors and modify intracellular concentrations of cyclic nucleotides, calcium, and kinases.

 1. **Amine precursor uptake and decarboxylation (APUD) cells** are theoretically derived from embryonic neuroectoderm (melanocytes, thyroid C cells, adrenal medulla, paraspinal ganglia, argentaffin cells of the intestine). These cells produce hormone mediators such as serotonin, catecholamines, histamine, and kinins. Neoplasia of these tissues gives rise to carcinoid tumors, pheochromocytoma, and medullary thyroid cancer; these tumors may also produce peptide hormones (e.g., adrenocorticotropic hormone [ACTH] and vasoactive intestinal polypeptide [VIP]) in addition to their natural products. Other peptide-producing endocrine tissues (e.g., parathyroid, pancreatic islet) demonstrate some APUD characteristics, even though they may not be derived from neuroectoderm.

 2. **Peptide hormones,** such as ACTH, human chorionic gonadotropin (HCG), and calcitonin, are produced by a wide variety of neoplastic tissues that may or may not normally synthesize detectable amounts of these hormones. Many of these peptides are synthesized as a *prehormone.* A segment of prehormone is enzymatically cleaved to form a storage molecule, a *prohormone.* The prohormone is further cleaved into the active hormone, which is secreted into the blood.

 3. **Gastrointestinal hormones,** such as insulin, glucagon, somatostatin, VIP, and gastrin, are normally produced by gut endocrine cells and the pancreatic islets. Neoplasms of these tissues commonly produce one or more of these hormones; gut hormones are also normally produced in the brain and may be products of a wide variety of other neoplasms.

C. **Multiple endocrine neoplasias (MEN)** are inherited mendelian-dominant endocrine tumor syndromes. Two categories of the syndrome are recognized.

 1. **MEN-I** (Wermer's syndrome; menin gene located at chromosome 11q13)

 a. **Pituitary tumors** (acromegaly, nonfunctioning adenoma, prolactinoma, or ACTH-producing adenoma)

 b. **Pancreatic islet cell tumors,** including gastrinoma, VIPoma, glucagonoma, and insulinoma

 c. **Parathyroid hyperplasia**

 2. **MEN-II.** Medullary carcinoma of the thyroid is present in all patients with this syndrome. Cushing's syndrome may develop as a consequence of ectopic ACTH production by medullary carcinoma or pheochromocytoma.

 a. **MEN-IIA** (Sipple's syndrome; *ret* oncogene located at chromosome 10q11)

 1. Medullary carcinoma of the thyroid

 2. Pheochromocytomas (bilateral)

 3. Parathyroid hyperplasia

 b. **MEN-IIB** (also called MEN-III; *ret* oncogene located at 10q11)

 1. Medullary carcinoma of the thyroid

 2. Pheochromocytoma (bilateral)

 3. Multiple mucosal ganglioneuromas (lips, tongue, eyelids)

 4. Marfanoid body habitus, high-arched palate, pes cavus, diverticulae, and sugar-loaf skull often accompany the endocrine abnormalities in MEN-IIB.

II. Carcinoid tumors

A. **Epidemiology and etiology.** Carcinoid cancers represent less than 1% of visceral malignancies. The cause of these tumors is unknown, but they may be associated with MEN-I.

B. **Pathology and natural history**

 1. **Primary tumor.** Carcinoid tumors belong to the APUD system of tumors (see section I.B.1). The primary tumors are usually small and most commonly arise in the small intestine. They also develop in the stomach, colorectum, lung, ovary, and rarely other organs. Appendiceal carcinoids are common but are usually of no clinical significance.

 2. **Metastases** tend to develop primarily in the liver. Bone metastases, which are often osteoblastic, also occur. Carcinoid metastases are indolent or slowly progressive and evolve over many years. Carcinoid tumors tend to produce desmoplastic responses, which can result in mesenteric fibrosis and bowel obstruction ("parachute intestine"). Hormonally inactive tumors usually cause death by replacing hepatic tissue, which leads to liver failure.

 3. **Tumor products.** Hormonally active tumors occur in 30% to 50% of patients and produce a variety of potentially lethal complications (*carcinoid syndrome*).

 a. **Small intestine carcinoids** never produce the carcinoid syndrome in the absence of liver metastases; the responsible hormonal mediators are degraded in their first pass through the liver.

 b. **Benign and malignant lung carcinoids** occur with about equal frequency; those that produce the carcinoid syndrome are malignant. Lung carcinoids can potentially produce hormonal effects without metastasizing; active tumor products pass directly into the circulation without being filtered by the liver. Most patients with endocrinologically active lung carcinoids, however, also have liver metastases. Bronchial carcinoids that produce ACTH or growth hormone–releasing factor (GRF) may be benign, and Cushing's syndrome or acromegaly may be the only endocrine manifestation.

 c. **Symptomatic ovarian carcinoids** are rarely associated with liver metastases.

 d. **Humoral mediators** of the carcinoid syndrome are serotonin, histamine, kinins, prostaglandins, and other hormonally active tumor products.

 1. The major source of serotonin is dietary tryptophan, which normally is mostly metabolized to nicotinic acid. In carcinoid syndrome, tryptophan metabolism is directed to the production of serotonin (Fig. 15.1). Most patients with carcinoid syndrome develop chemical evidence of niacin deficiency, and some may develop clinically recognizable pellagra.

Figure 15.1 Hepatic metabolism of tryptophan and serotonin in carcinoid syndrome. The normal pathway (thin arrow) of tryptophan metabolism is impaired in carcinoid syndrome, resulting in excessive production of serotonin. Monamine oxidase inhibitors interfere with the metabolism of serotonin and are contraindicated in patients with carcinoid syndrome. 5-HIAA, 5-hydroxyindoleacetic acid.

 2. Other hormones and hormone metabolites that are found in some patients with carcinoid include calcitonin, gastrin, GRF, and ACTH. These substances may or may not produce clinical syndromes, but they should be searched for in patients with serum calcium abnormalities, peptic ulcer, or Cushing's syndrome.

C. **Diagnosis**

 1. **Symptoms: endocrinologically inactive carcinoids.** Most carcinoid tumors are endocrinologically inactive. Patients who have these tumors may have appendicitis, bowel obstruction, or a painful, enlarged liver that results from metastases.

 2. **Symptoms: endocrinologically active carcinoids**

a. **Humoral mediators** produce attacks of flushing, diarrhea, hypotension, light-headedness, and bronchospasm in various combinations. Attacks may be spontaneous or precipitated by emotional stress, alcohol ingestion, exercise, eating, or vigorous palpation of a liver that contains metastatic deposits.

b. **Heart failure** from valvular lesions commonly occurs in patients with long-standing carcinoid symptoms. Ileal carcinoids produce tricuspid valve stenosis and insufficiency and pulmonary valve stenosis. Bronchial carcinoids with venous drainage into the left atrium can produce mitral valve disease.

3. **Physical findings**

   a. **The characteristic flush** differs somewhat according to the site of the primary tumor.

      1. **Ileal carcinoid.** Purple flush involves the upper trunk and face and usually lasts less than 30 minutes.
      2. **Bronchial carcinoid.** Deep, dusky purple flush over the entire body.
      3. **Gastric carcinoid.** Generalized urticaria-like, pruritic, and painful wheals, probably related to histamine production

   b. **Chronic skin changes** involve repeated episodes of flushing, especially with bronchial carcinoids, which cause thickening of the facial features, telangiectasis, enlargement of the salivary glands, and leonine facies. A pellagrous skin rash characterized by photosensitivity, atrophy of the lingual mucosa, and thickened skin may develop.

   c. Right heart failure with evidence of tricuspid valve disease

   d. Hepatomegaly

   e. Cushing's syndrome and occasionally, acromegaly

4. **Laboratory studies in all patients**

   a. Routine blood tests, particularly liver function tests (LFTs)
   b. Liver ultrasound or CT scan if hepatomegaly is present or if LFTs are abnormal
   c. Chest radiograph to search for bronchial carcinoids
   d. Upper barium series
   e. Nuclear scanning using a radiolabeled somatostatin analogue
   f. A histologic diagnosis is essential for management. Biopsy the site that is associated with the least morbidity and that has been determined by noninvasive tests to be probably affected.

5. **Laboratory studies** in patients with symptoms consist of 24-hour urine collections for 5-hydroxyindoleacetic acid (5-HIAA). Serotonin is a product of tryptophan metabolism and is metabolized to 5-HIAA (Fig. 15.1). The normal value for 5-HIAA excretion is less than 9 mg per 24 hours.

   a. **Causes of elevated 5-HIAA excretion** include the following:

      1. Carcinoid syndrome
      2. Other tumors that produce 5-HIAA include biliary, pancreatic islet, and medullary thyroid cancers.
      3. Dietary intake of nuts, bananas, avocados, or pineapples within 48 hours of urine collection
      4. Medications that must be stopped 1 day before urine collection include mephenesin and guaifenesin.
      5. Malabsorption syndromes (celiac disease, Whipple's disease, and tropical sprue) rarely increase 5-HIAA urine excretion above 20 mg per 24 hours.

   b. **Causes of falsely low 5-HIAA excretion.** Phenothiazines interfere with the color reaction of the test and must be stopped 2 to 3 days before the collection of urine.

   c. **Interpretation.** A level of 5-HIAA greater than 9 mg per 24 hours in patients without malabsorption or greater than 30 mg per 24 hours in patients with malabsorption is pathognomonic for carcinoid unless interfering foods or drugs have been ingested. The magnitude of 5-HIAA excretion in the urine roughly corresponds to the tumor volume; 5-HIAA excretion can also be used to monitor therapy.

D. **Management.** The most important principle of management of metastatic carcinoid tumors is therapeutic restraint. These patients often survive for more than 10 years without antitumor treatment. Patients with endocrinologically active tumors are at especially high risk for complications from any procedure requiring anesthesia. Therapy should be focused on controlling the endocrine symptoms.

   1. **Surgery** is useful for patients with localized primary carcinoids or metastatic tumors that produce obstruction. For patients with incidental appendiceal carcinoids that are 2 cm or less in diameter (rarely metastasize), appendectomy is adequate treatment.

      Partial hepatectomy has been recommended by some physicians, particularly if the metastases are confined to one lobe of the liver. The 20% mortality rate of hepatectomy and the long natural history of the disease, however, often dissuade the physician from recommending the procedure.

   2. **Hepatic artery occlusion** performed surgically or by catheterization and embolization of hepatic metastases has been successfully used to palliate endocrine symptoms or pain. Objective regression of manifestations occurs in 60% of patients for a median of 4 months. Side effects of arterial occlusion include fever, nausea, and LFT abnormalities. Both the response rate and median duration of response appear to improve when occlusion is followed by sequenced chemotherapy (see section II.D.4).

   3. **Radiation therapy** (RT) is used to palliate liver pain caused by far-advanced metastatic disease unresponsive to other treatments. However, carcinoid tumors are relatively radioresistant.

   4. **Chemotherapy** is used late in the course of disease for treatment of symptomatic metastases and for patients with severe endocrine symptoms that do not respond satisfactorily to pharmacologic maneuvers (see section 5). There is no general agreement on when (or even if) chemotherapy should be started in patients with malignant carcinoid. Single-agent therapy with 5-fluorouracil (5-FU), streptozocin, cyclophosphamide, doxorubicin (Adriamycin), dacarbazine, or interferon-a (IFN-a) has been associated with response rates of about 25%, with variable median durations of response. Endocrine symptoms may be palliated, but the effect of chemotherapy on survival is not known.

      a. **Combination chemotherapy regimens** have not clearly had a beneficial effect compared with single agents. The largest experience in the treatment of metastatic carcinoid tumors has been gained with the combination of 5-FU and streptozocin administered every 42 days (see section 4.b for dosages). Cisplatin in combination with etoposide is useful for anaplastic forms of neuroendocrine carcinomas. Combinations of IFN- a (3 to 10 million U three times weekly) and octreotide have been more effective than monotherapy with either agent alone; however, antithyroid antibodies develop in most patients on long-term treatment with IFN, and its associated flu-like syndrome may be problematic.

      b. **Sequenced chemotherapy after hepatic arterial occlusion** is initiated about 3 weeks after the procedure, which is performed for symptomatic hepatic metastases from carcinoid tumors or islet cell carcinomas. Substantial or complete relief from the endocrine syndromes is achieved in about 80% of selected patients, with a median duration of 18 months.

      The following two regimens are alternated every 4 to 5 weeks until the patient has stabilized with maximum tumor regression (usually about 6 months):

      1. Doxorubicin (60 mg/m^2 IV on day 1) and dacarbazine (250 mg/m^2 IV daily for 5 days)
      2. Streptozocin (500 mg/m^2) and 5-FU (400 mg/m^2), both given daily IV for 5 days

   5. **Pharmacologic management.** It is probably not possible to control the symptoms of carcinoid syndrome completely with aggressive dietary tryptophan restriction and high-dose antiserotonin drugs alone.

      a. **Octreotide,** a somatostatin analogue, reduces the secretion of 5-HIAA and ameliorates symptoms in about 90% of patients. The drug may have a tumorostatic effect as well. The dosage is usually 100 to 600 µg SC daily in two to four divided doses. A long-acting depot form of octreotide is now available; the dose is 10 to 30 mg every 28 days, often supplemented by SC injections.

      b. **Hypotension,** the most life-threatening complication of carcinoid syndrome, is mediated by kinins (and perhaps prostaglandins) and can be precipitated by catecholamines. b-Adrenergic drugs (e.g., dopamine, epinephrine) must be strictly avoided because they may aggravate hypotension. Pure a-adrenergic (methoxamine, norepinephrine) and vasoconstrictive (angiotensin) agents are preferred for treating hypotension in carcinoid syndrome.

         1. Methoxamine (Vasoxyl) is given IM at a dose of 0.5 mL (10 mg), or IV at a dose of 0.25 mL (5 mg) over 1 to 2 minutes (using a tuberculin syringe). The dose is repeated as necessary to maintain the blood pressure.
         2. Angiotensin amide (Hypertensin), rather than methoxamine, is recommended by some anesthesiologists.
         3. Corticosteroids may prevent episodes of hypotension.

      c. **Flushing** is mediated by kinins and histamine and may respond to several agents, including the following:

         1. Prochlorperazine (Compazine), 10 mg PO four times daily
         2. Phenoxybenzamine (Dibenzyline), 10 to 20 mg PO twice daily
         3. Cyproheptadine (Periactin), 4 to 6 mg PO four times daily
         4. Prednisone, 20 to 40 mg PO daily, is useful for flushing as a result of bronchial carcinoids and occasionally for patients with other kinds of carcinoids.
         5. The combined use of H$_1$- and H$_2$-receptor antagonists has been effective in patients with carcinoid flush and documented hypersecretion of histamine. Diphenhydramine hydrochloride (Benadryl), 50 mg PO four times daily, plus cimetidine (Tagamet), 300 mg PO four times daily, has been used with success in some patients.
         6. Methyldopa (Aldomet) is useful in some patients.
         7. Monoamine oxidase inhibitors *are contraindicated* in carcinoid syndrome because they block serotonin catabolism and can aggravate symptoms (Fig. 15.1).

      d. **Bronchospasm** is mediated by histamine and managed with aminophylline. Adrenergic agents, such as isoproterenol, do not appear to worsen

bronchospasm for carcinoid and may also may be used.

   e. **Diarrhea** is mediated by serotonin and is often difficult to control. A recommended sequence for treatment before the use of octreotide is as follows:
      1. Belladonna alkaloids and phenobarbital combination (Donnagel-PG), 15 mL every 3 hours as needed
      2. Loperamide (Imodium) or diphenoxylate and atropine (Lomotil) as needed.
      3. Cyproheptadine (Periactin), 4 to 6 mg PO four times daily
      4. Methysergide maleate (Sansert), started at 8 to 12 mg/day and gradually increased to 20 to 22 mg/day if needed
   f. **Preparation for anesthesia.** Patients with carcinoid syndrome are at high risk for the development of flushing and hypotensive episodes during surgery. Stimulation of adrenergic hormone release and use of drugs that induce hypotension (morphine, succinylcholine, and curare) must be minimized.
      1. **Preoperative period.** Patients should be premedicated with cyproheptadine, 4 to 8 mg PO. Methotrimeprazine, 10 mg IM, is given 1 hour before surgery. Methotrimeprazine is a phenothiazine with amnesic, analgesic, antihistaminic, and catechol blocker properties. This drug permits the use of lower doses of anesthetics and allows the avoidance of morphine.
      2. **During surgery.** Aminophylline can be used for bronchoconstriction, methotrimeprazine for flushing, and methoxamine for hypotension. Rapid, dramatic improvement has been reported after administration of intravenous somatostatin.

E. **Special clinical problems associated with carcinoid syndrome**
   1. **Bowel obstruction** may result from dense fibrosis of the mesentery. Surgical relief is impossible. Patients may improve with simple nasogastric decompression and fluid replacement.
   2. **Right ventricular failure** results from tricuspid and pulmonic valve lesions. These lesions develop with far-advanced carcinoid syndrome, which has a poor prognosis independent of the heart lesions. Because of the high surgical risk in these patients, valve replacement is usually not warranted. Heart failure should be medically managed with diuretics.
   3. **Pellagrous skin lesions** may be treated with daily oral vitamin preparations containing 1 to 2 mg of niacin.

III. Thyroid cancer

A. **Epidemiology and etiology**
   1. **Incidence.** Thyroid cancer accounts for less than 1% of visceral malignancies; there are 14,000 new cases and 1000 cancer deaths in the United States annually. The risk increases with age. Women are affected more than men in a ratio of 3:2.
   2. **Radiation exposure.** Radiation fallout and RT given over the neck region in intermediate doses (less than 2000 cGy) for benign conditions (such as acne in teenagers, or enlarged tonsils or thymus glands in children) increase the risk for thyroid cancer, particularly the papillary type.
      a. The lag time between radiation exposure and the onset of thyroid cancer averages 25 years but ranges from 5 to 50 years. Most patients younger than 20 years of age with thyroid cancer have a history of neck irradiation.
      b. About 4% of patients with thyroid cancer have a history of radiation to the neck. Between 5% and 10% of patients who have a history of neck irradiation develop thyroid cancer; 25% have an abnormal thyroid by palpation.
      c. Thyroid cancers after neck irradiation are often multifocal but have an indolent course and a prognosis similar to that of spontaneous tumors.
      d. Neck irradiation also increases the risk for hyperparathyroidism and parotid gland tumors.
   3. **Hereditary factors.** Medullary cancer of the thyroid may arise sporadically or as a dominantly inherited syndrome of MEN-II (see section I.C.2). Thyroid tumors (including papillary and follicular carcinomas), as well as breast neoplasms, also occur frequently in Cowden's multiple hamartoma syndrome. Several oncogenes and tumor-suppressor genes have been implicated in the pathogenesis of thyroid neoplasms.
   4. **Thyroid-stimulating hormone** (TSH). An increased risk for thyroid cancer may be present in patients with chronic TSH elevation, such as patients with congenital defects in thyroid hormone formation.

B. **Pathology and natural history.** The more aggressive histologic subtypes of thyroid cancer tend to affect older patients. Immunohistochemical phenotypes of thyroid cancers are shown in Appendix C.3.V.
   1. **Papillary cancers** (70% of thyroid cancers in adults) affect younger patients. Psammoma bodies are usually present in histologic sections. Regional lymph nodes that drain the thyroid are involved in half of patients. Mixed papillary and follicular cancers behave like pure papillary cancer. All combinations of papillary and follicular carcinoma have indolent courses. Distant metastases to lungs, bone, skin, and other organs occur late, if at all.
   2. **Follicular cancers** (20% of thyroid cancers) have a peak incidence at 40 years of age. They tend to invade blood vessels and to metastasize hematogenously to visceral sites, particularly bone. Lymph node metastases are relatively rare, especially compared with papillary cancers.
   3. **Anaplastic giant and spindle cell cancers** (2% of thyroid cancers) occur most often in patients older than 60 years of age. Anaplastic thyroid cancers are aggressive cancers, which rapidly invade surrounding local tissues and metastasize to distant organs.
   4. **Medullary thyroid cancers** (5% to 10% of thyroid cancers) secrete calcitonin. ACTH, histaminase, and an unidentified substance that produces diarrhea may also be secreted by these tumors. Large amounts of amyloid are evident by histologic examination. Metastases are mostly found in the neck and mediastinal lymph nodes and may calcify. Widespread visceral metastases occur late.
   5. **Hürthle cell cancer** is a variant of follicular carcinoma and has a relatively aggressive metastatic course.
   6. **Other tumors** found in the thyroid include Hodgkin lymphomas, a variety of soft tissue sarcomas, and metastatic cancers of lung, colon, and other primary sites. Small cell cancers of the thyroid are rare, are histologically similar to lymphoma, and spread to both lymph nodes and distant sites.

C. **Diagnosis**
   1. **Symptoms and signs**
      a. **Symptoms.** Some patients with thyroid cancer complain of an enlarging mass in the neck. Hoarseness may be the result of recurrent laryngeal nerve paralysis. Neck pain or dysphagia occasionally is a complaint. Patients without symptoms may have thyroid cancer discovered at thyroidectomy done for other reasons or as an incidental finding in the course of radiologic examinations of the neck (see section III.C.3.a).
      b. **Physical findings.** Thyroid cancer may be found on routine physical examination as a mass in the thyroid or in the midline up to the base of the tongue (thyroglossal duct remnant). Thyroid masses less than 1 cm in diameter often are not palpable. Most patients have a single palpable nodule; others have a normal, multinodular, or diffusely enlarged thyroid gland. Anaplastic cancer is often manifested by obvious masses infiltrating the skin of the neck or by respiratory distress. Cervical lymph nodes are frequently palpable.
   2. **Laboratory studies**
      a. **Routine studies.** Chest radiographs and serum alkaline phosphatase levels should be obtained to look for evidence of metastatic disease in the lung, liver, or bone. Liver and bone scans and selected skeletal radiographs are indicated when the alkaline phosphatase level is elevated.
      b. **Thyroid scans** may be obtained in nonpregnant patients with palpable abnormalities of the thyroid. Nonfunctional "cold" nodules are found in 90% of patients with palpable nodules, both benign and malignant, but only about 10% of cold nodules prove to be cancer.
      c. **Thyroid ultrasonography** may be obtained in patients with palpable abnormalities of the thyroid but are unreliable for excluding cancer. Purely cystic lesions, found in about 10% of patients with palpable nodules, are reported to be malignant in less than 1% of cases. Benign and malignant lesions cannot be distinguished by ultrasonography if they are mixed with solid and cystic components or are entirely solid.
      d. **Diagnostic use of thyroxine.** Some clinicians treat cold nodules with thyroid hormones at physiologic doses for 3 months or longer to try to distinguish benign from malignant lesions. Although most thyroid cancers remain unchanged or enlarge during this treatment, some cancers may partially regress temporarily.
      e. **Thyrocalcitonin assay.** Patients with a family history of medullary thyroid cancer should be given a pentagastrin or calcium infusion test for thyrocalcitonin. Patients with positive tests require neck exploration regardless of findings on physical examination or thyroid scan.
   3. **Thyroid gland biopsy**
      a. **Needle aspiration biopsy** is invaluable for cytologic diagnosis of thyroid nodules and for preventing unnecessary thyroidectomies. Many authorities recommend needle biopsy as the first step in evaluation of any thyroid lump, even before A thyroid scan is done, because 90% of all thyroid nodules are cold. The accuracy of needle biopsy of the thyroid is more than 90% for benign lesions; the false-negative rate is 5% to 10%. Only about 10% of cold nodules are cancerous. Roughly, if 100 patients with cold nodules underwent needle biopsy rather than thyroidectomy, and if patients with benign histopathology were excluded from surgery, one cancer would be missed, nine cancers would be appropriately resected, and 10 patients would have undergone unnecessary surgery. Therefore, the needle biopsy saves 80 of 100 patients from unnecessary surgery at the expense of missing one cancer, which is usually indolent and can be detected later. Patients with nonpalpable nodules larger than 1.5 cm in diameter found on radiologic examinations should undergo guided needle aspiration biopsy.
      b. **Open biopsy.** Nodules interpreted as suspicious on needle biopsy should undergo open biopsy. Solid nodules that grow during suppressive therapy should be excised despite negative cytology.

D. **Survival and prognostic factors**
   1. **Papillary and papillary–follicular adenocarcinomas.** Decreased survival is not noted when compared with age-matched populations until 12 years after the diagnosis. Only 3% to 12% of patients die as a result of thyroid cancer. Even with distant metastases, patients often survive many years without therapy. The raw 10-year survival rate is 95% for patients younger than 40 years of age and 75% for patients older than 40 years of age.
      a. **Factors that have no adverse effect on prognosis**
         1. Sex

2. Radiation-related neoplasms

3. Regional lymph node metastases (increased recurrences, but normal survival)

b. **Factors that adversely affect prognosis,** which both increase the recurrence rate and decrease the survival rate

1. Age older than 40 years

2. Size of nodule greater than 5 cm (compared with less than 2.5 cm)

3. Tumor extends through the thyroid capsule

4. Presence of symptoms, such as hoarseness or dysphagia

5. Distant metastases

6. Residual tumor fails to take up ^{131}I

7. Subtotal thyroidectomy (compared with "near-total" thyroidectomy) for tumors greater than 1.5 cm in diameter

8. Probably, postoperative therapy with thyroid hormone alone (compared with thyroid hormone and ^{131}I)

2. **Follicular adenocarcinoma** without vascular invasion has essentially the same survival rate as papillary carcinoma for age-matched populations. With significant vascular invasion, the 10-year survival rate drops to 35%.

3. **Medullary carcinoma** without lymph node involvement is nearly always cured with surgery. With lymph node involvement, the 5-year survival rate decreases to 45%.

4. **Anaplastic carcinoma.** Nearly all patients die within 6 to 8 months.

E. **Management.** No uniform opinion exists regarding the management of indolent varieties of thyroid cancer.

1. **Surgery.** Total or near-total thyroidectomy is the treatment of choice for all types of thyroid cancer. Subtotal thyroidectomy is associated with double the recurrence rate and a lower survival rate than total thyroidectomy for papillary and follicular cancers. Subtotal thyroidectomy may be sufficient, however, for low-risk patients with small tumors. Medullary cancer of the thyroid is often bilateral, and total thyroidectomy is imperative.

a. **Neck nodes** that are involved clinically should be removed. Neck dissection, however, does not improve the rate of survival or relapse, except in medullary carcinoma, and is responsible for increasing the rate of major complications.

b. **Complications.** The major complications of thyroidectomy are hypoparathyroidism and vocal cord paralysis; death is rare. Combinations of these problems and other complications occur in 10% to 15% of patients subjected to total thyroidectomy; the incidence is doubled to tripled if neck dissection is added to the procedure.

2. **Thyroxine.** TSH suppression after thyroidectomy is essential because TSH stimulates most papillary and follicular tumors. Thyroxine is given in a dose sufficient to suppress serum TSH to low-normal or subnormal levels. Patients must be monitored for signs of hyperthyroidism and the dose of thyroxine decreased to keep the patient clinically euthyroid. If ^{131}I is given, thyroxine is begun afterward.

3. **Radioactive iodine.** Fears of the leukemogenic potential of ^{131}I have abated because little increase in the incidence of acute leukemia has been found in many long-term studies. ^{131}I given postoperatively (usually about 30 to 100 mCi) to ablate thyroid remnants may improve survival in patients with papillary, follicular, and mixed papillary–follicular tumors. Thyroid tumors that do not take up ^{131}I are not ablated by the isotope. See Chapter 2, section IV.A.

a. **Indications for ^{131}I.** The true value of ^{131}I is not known and is difficult to determine because the isotope has been given to patients with thyroid cancer as part of standard practice for many years. Radioactive iodine may not be necessary in all patients. Clear indications for postoperative ^{131}I in patients in whom the residual tissue demonstrates uptake include the presence of the following:

1. Multiple tumors of the thyroid gland

2. Tumors larger than 2.5 cm

3. Locally invasive tumors

4. Remote metastases

b. **Administration.** ^{131}I may be given either when the patient demonstrates biochemical evidence of hypothyroidism or after treating the patient with TSH. Both methods are based on the principle that TSH stimulates ^{131}I uptake in both residual thyroid tissue and residual carcinoma and that it permits ablation of both.

1. **Waiting for hypothyroidism** means postponing treatment for 3 to 6 weeks after thyroidectomy. Hypothyroidism is defined as serum TSH levels greater than 30 µU/mL by radioimmunoassay.

2. **Giving TSH.** The patient is treated with bovine TSH (10 units IM for 3 or 4 days) and then given ^{131}I in therapeutic doses. A thyroid and body scan is obtained 72 hours later to look for areas of residual thyroid tissue or metastatic disease. Exogenous bovine TSH may be allergenic. Recombinant human TSH is available, but its use is limited to diagnostic scanning only; recombinant human TSH appears to be less effective in stimulating ^{131}I uptake than endogenous TSH.

4. **Patient follow-up.** Patients may need to be retreated with ^{131}I. Thyroxine therapy is discontinued for 3 to 6 weeks, and the TSH level is checked weekly until it exceeds 30 µU/mL. The ^{131}I body scan is repeated, and ^{131}I therapy is given if needed. Thyroxine maintenance is then resumed. Withdrawal of thyroxine and performance of ^{131}I scans are repeated every 6 to 12 months until a negative scan is obtained. In most patients with papillary and follicular cancers, serum levels of thyroglobulin correlate with residual thyroid tissue (either normal or neoplastic) and can be used as a tumor marker after all normal thyroid remnants have been ablated.

5. **Relapsing disease** develops in about 12% of patients who have no evidence of disease after primary therapy. Tumors that are not treatable by the combination of surgery, thyroxine therapy, and repeat doses of ^{131}I respond poorly to external-beam RT and chemotherapy.

a. **External-beam RT** is probably indicated as adjuvant therapy after surgery for anaplastic thyroid cancer and for all patients with known residual cancers that do not take up ^{131}I.

b. **Chemotherapy** for symptomatic, widespread metastatic thyroid cancer that is unresponsive to ^{131}I can occasionally produce short-range palliation. Doxorubicin as a single agent produces up to a 30% tumor response rate. Doxorubicin is the most active agent in anaplastic thyroid cancer as well. The effect of chemotherapy on survival is uncertain.

F. **Special clinical problems associated with thyroid cancer**

1. **Hypoparathyroidism** complicates total thyroidectomy in 10% to 15% of patients; it is rare after ^{131}I therapy. Hypoparathyroidism is transient in 5% to 10% of cases; blood calcium levels normalize in 1 or 2 weeks.

a. **Acute therapy.** Blood calcium levels and clinical evidence of hypocalcemia are checked daily. If the blood calcium level is below 8 mg/dL, oral calcium lactate (2 g four times daily) or calcium carbonate (2.5 g/day) is given. If the patient manifests tetany or the blood calcium is 6 mg/dL or less, intravenous calcium gluconate or lactate is given (1 g every 4 to 6 hours), and calcium blood levels are monitored more frequently.

b. **Chronic therapy.** Patients with persistent hypocalcemia 1 week after thyroidectomy usually require chronic calcium supplements. If hypocalcemia recurs after 2 more weeks of therapy that has been followed by weaning off supplements, vitamin D therapy is necessary as well. Calcitriol is started at a dose of 0.25 µg/day PO; calcium lactate or carbonate is continued. Calcium level measurements are repeated weekly; if less than 8 mg/dL, the calcitriol is increased in 0.25-µg increments weekly until the calcium level has normalized. Ergocalciferol may also be used; it is much less expensive than calcitriol but may cumulate and cause vitamin D intoxication. Serum calcium should be maintained in the low-normal range (8.5 to 9.5 mg/dL) to avoid hypercalciuria.

2. **History of neck irradiation.** Patients who have a history of neck radiation exposure and no palpable abnormalities should be followed by careful annual physical examination. Repeated radionuclide scans are potentially carcinogenic, especially in young adults. Radiation-induced thyroid cancer typically has an indolent course and does not necessitate anxiety-provoking management.

IV. Pheochromocytoma

A. **Epidemiology and etiology.** Pheochromocytomas (PCCs) are very rare tumors; they belong to the APUD system and produce symptoms by elaborating catecholamines. Certain hereditary syndromes are associated with an increased risk for PCC.

1. Dominantly inherited MEN-II (see section I.C)

2. Dominantly transmitted PCC

3. Neurofibromatosis (von Recklinghausen's disease)

4. von Hippel-Lindau disease of cerebellar hemangioblastoma with retinal angiomas and polycythemia

B. **Pathology and natural history**

1. **PCC originates** in the adrenal medulla (90% of patients) or in the paraganglia of the sympathetic nervous system. The paraganglia range from the organ of Zuckerkandl at the aortic bifurcation to the carotid bifurcation. Bilateral PCC frequently occurs in inherited syndromes and in 10% of noninherited cases.

2. **Metastases** to bone, liver, and lung occur in 10% of cases of PCC despite a historically benign appearance. Metastases have an indolent growth pattern but are lethal because they often produce cardiovascular complications.

3. **Hyperglycemia** is common in patients with PCC. Patients also have an increased incidence of gallstones.

4. **Paraneoplastic complications of PCC**

a. Polycythemia

b. Hypercalcemia

c. Cushing's syndrome
C. **Diagnosis**
1. **Symptoms and signs**
    a. **Symptoms.** The most common symptoms of PCC are episodes of various combinations of the following: headache, sweating, tachycardia, palpitations, pallor, nausea, and feeling of impending death. Episodes may be triggered by exercise, emotional upset, alcohol ingestion, physical examination in the area of the tumor, or micturition. Vague complaints of anxiety, tremulousness, fever, dyspnea, or angina are often mistaken for psychosomatic illness or thyrotoxicosis. Weight loss is common, but one third of patients are overweight.
    b. **Hypertension** is present in 90% of patients. The hypertension is fixed (66% of patients) or paroxysmal (33%). Orthostatic hypotension occurs in 70% of patients.
    c. **Catechol cardiomyopathy.** Patients may have cardiovascular collapse after a vague history of arrhythmias and anxiety.
2. **Selection of patients for study.** Young patients without hypertension but with documented atrial arrhythmia, evidence of an unexplained hypermetabolic state, or cardiomyopathy should be screened for PCC and thyrotoxicosis. The presence of PCC should be sought in patients with hypertension and any of the following:
    a. Age less than 45 years (PCC is a remediable, although rare, cause of hypertension)
    b. A family history of a hereditary PCC syndrome
    c. Episodic attacks typical of the syndrome
3. **Chemical tests**
    a. **Catecholamine metabolites.** A 24-hour urine collection for vanillylmandelic acid (VMA) or total metanephrines (TMN) collected during a hypertensive episode is the best screening test for PCC (more than 90% sensitivity). Plasma assays and plasma catecholamine assays are also available but require meticulous technique in sample collection and handling. The upper limit of normal is 6.8 mg for VMA and 0.9 mg for TMN per 24-hour urine specimen. Elevated levels suggest the presence of PCC and mandate further studies. A large number of drugs affect either the metabolism or assay of catecholamines. All drugs, except perhaps mild tranquilizers, sedatives, and analgesics, should be discontinued 72 hours before urine collection if possible.
        1. **Misleading elevations in urinary catecholamine metabolites.** Phenothiazines and tricyclic antidepressants increase levels during acute therapy but may decrease catecholamine excretion during chronic therapy. Increased excretion of metabolites is commonly found with drugs that are catecholamines (e.g., isoproterenol) or catecholamine releasers (e.g., ephedrine, amphetamines, methylxanthines). Other agents include l-dopa, nalidixic acid, or paraaminosalicylic acid (which affect the VMA level) and methyldopa, buspirone, and monoamine oxidase inhibitors (which affect the TMN level).
        2. **Misleading low values** may result from incomplete urine collections or the following drugs:
            a. a-Methylparatyrosine, clonidine, reserpine, guanethidine, monoamine oxidase inhibitors, clofibrate, and methenamine mandelate (Mandelamine) affect the VMA level.
            b. a-Methylparatyrosine, clonidine, reserpine, and guanethidine affect the TMN level.
    b. **Fasting hyperglycemia** is almost always present in patients with PCC; its absence makes the diagnosis doubtful.
    c. **Pharmacologic tests** (e.g., production of a vasodepressor response with phentolamine) are hazardous, have a poor predictive value, and no longer have a role in the diagnosis of PCC. Failure to suppress plasma catecholamines by clonidine, however, may be useful in diagnosis.
4. **Radiographic techniques** are used for localization of tumor in patients with a chemical diagnosis of PCC.
    a. **Chest radiographs** may reveal a paraganglionic tumor.
    b. **CT scan** may identify PCC.
    c. **MRI scan** shows a characteristic bright, hyperintense image on T2-weighted images in PCC.
    d. **Selective venography.** During this procedure, blood catecholamines can be sampled from several areas of the venous system to help locate small tumors. Venography is useful in the following circumstances:
        1. When less-invasive studies fail to show the tumor
        2. To search for multiple primary sites, especially in patients with MEN syndromes
    e. **Isotope scanning** with ^{131}I-metaiodobenzylguanidine may be useful in demonstrating PCC, especially in extraadrenal sites.
D. **Management**
1. **Pharmacologic control** of PCC is essential before invasive diagnostic tests or surgery is done.
    a. Phenoxybenzamine (Dibenzyline), 10 to 20 mg PO given twice daily, is a pure a-adrenergic blocker that controls both episodic and fixed hypertension.
    b. Propranolol (Inderal), 10 to 40 mg PO given four times daily, is a b-adrenergic blocker that is useful for treating sweating, hypermetabolism, and arrhythmias. Propranolol should be used only after adequate a-adrenergic blockade is established to avoid hypertension.
    c. a-Methylparatyrosine (Demser) blocks catecholamine synthesis in doses of 2 to 4 g/day PO.
    d. Labetalol, a combined a- and b-adrenergic blocker, can also be used in doses of 200 to 600 mg given twice daily.
2. **Surgery**
    a. **Before surgery**
        1. Long-acting a- and b-adrenergic blockers should be continued preoperatively and throughout surgery.
        2. Close attention should be paid to maintaining fluid and electrolyte balance. Preoperative volume expansion may be useful.
        3. Central venous and arterial catheters should be placed to monitor blood volume and pressure changes closely.
    b. **During surgery**
        1. Close ECG monitoring is necessary to manage arrhythmias.
        2. Hypertensive episodes, which may occur while the tumor is being manipulated, are managed with nitroprusside infusion or rapid intravenous boluses of phentolamine (Regitine, 1 to 2 mg IV).
        3. Hypotensive episodes, which occur after the tumor's blood supply has been isolated, should be treated with intravenous fluids and norepinephrine.
        4. Obvious tumors and paraspinal ganglia should be carefully inspected. All visible tumor is removed. In patients with metastatic PCC, as much tumor as possible is removed to reduce catecholamine secretion.
    c. **After surgery**
        1. Hypertension may develop as a result of fluid overload during surgery and is treated with intravenous furosemide and fluid restriction until the blood pressure is controlled.
        2. If hypertension persists for 2 or 3 days postoperatively, residual PCC must be suspected.
        3. All patients should have 24-hour urine studies for VMA and TMN repeated about 1 week after surgery. Unsuspected residual tumors and tumor recurrences should be surgically removed.
3. **Metastatic disease**
    a. **RT is useful** for palliating locally symptomatic metastases.
    b. The usefulness of chemotherapy for unresectable disease is not established, although the combination of cyclophosphamide, vincristine, and dacarbazine produces objective responses in most patients. Symptoms of catecholamine excess are managed pharmacologically (see section D.1).
    c. Some patients may respond to therapeutic doses of ^{131}I-metaiodobenzylguanidine.

V. Adrenal carcinoma

A. **Epidemiology.** Adrenal cancer causes 0.2% of cancer deaths. The average age at diagnosis is 40 years, but the tumor occurs at all ages. Two thirds of the patients are women.
B. **Pathology and natural history.** Adrenal cancers are highly aggressive; they frequently metastasize to lungs, liver, and other organs and are large and bulky at the time of diagnosis. About half of these tumors produce functional corticosteroids, including cortisol, aldosterone, androgens, and estrogens.
C. **Diagnosis**
1. **Symptoms and signs**
    a. **Hormonally inactive tumors** are discovered as large abdominal masses in patients with abdominal pain, weight loss, or evidence of metastases.
    b. **Hormonally active tumors** present with the following:
        1. Rapid virilization (hirsutism, clitoromegaly, oligomenorrhea, or amenorrhea) in women
        2. Gynecomastia in men
        3. Precocious puberty
        4. Cushing's syndrome with hypertension and glucose intolerance
2. **Adrenal function tests.** Patients with clinical or laboratory evidence (hypokalemic alkalosis) of hypercortisolism should have the dexamethasone suppression test and 24-hour urine collection for 17-ketosteroids or serum DHEA-sulfate measured. The differential diagnosis of causes of Cushing's syndrome is shown in Table 15.1.

Table 15.1 Differential diagnosis of causes of Cushing's syndrome

       a. **Dexamethasone suppression test.** Before and after 2 days of treatment with dexamethasone, 0.5 mg PO every 6 hours, plasma cortisol and ACTH levels are obtained at 8:00 am. Dexamethasone dose in increased to 2 mg PO every 6 hours for 2 days, and 8:00 am cortisol and ACTH levels are measured again. Both doses suppress the plasma cortisol to below 5 μg/dL in healthy subjects; failure of the 8-mg/day dose to suppress cortisol blood levels suggests an adrenal source (adenoma or adenocarcinoma) of the hypercortisolism if ACTH levels are low. Nonadrenal tumors that produce ectopic ACTH also demonstrate failure of dexamethasone to suppress cortisol, but these patients have high levels of ACTH in the plasma.

       b. **24-hour urine collection** is obtained for urinary free cortisol (upper limit of normal is less than 100 μg per 24 hours) and 17-ketosteroids (upper normal limit is less than 14 to 26 mg per 24 hours, depending on the age and sex of the patient). The levels of both substances are elevated in Cushing's syndrome, no matter what the cause. Levels of 17-ketosteroids in excess of 50 mg in 24 hours make the diagnosis of adrenal carcinoma likely; levels higher than 100 mg in 24 hours are diagnostic. Serum DHEA-sulfate can be measured as an alternative to urine 17-ketosteroids; DHEA-sulfate is elevated in most cases of adrenal carcinoma.

   3. **Further studies**

       a. **Chest radiograph** to search for metastases.

       b. **Abdominal CT scan** to look for abdominal masses not clinically evident. Small (less than 6 cm) benign adrenal masses are common incidental findings on CT examination; laboratory findings and follow-up CT scans may help in the differential diagnosis.

       c. **Biopsy**

         1. In patients with metastatic disease, biopsy is performed on the most readily accessible site (e.g., superficial lymph nodes or liver with evidence of metastases).

         2. If only intra-abdominal disease is evident, laparotomy is necessary for biopsy proof of the diagnosis.

  D. **Management.** The median survival for untreated patients is 3 months. Treated patients may survive up to 5 years, depending on the extent of disease.

   1. **Surgery** should be used to resect as much tumor as possible. The contralateral adrenal gland should be inspected and removed if there is evidence of tumor.

   2. **RT** is used to palliate symptoms from local metastatic sites.

   3. **Chemotherapy** may be useful for reducing tumor bulk and controlling endocrine symptoms. Mitotane (o,p'-DDD) produces objective tumor regression or improvement of endocrine symptoms in 30% of cases. The use of mitotane as an adjuvant to surgery in localized disease does not appear to improve results. Pharmacologic management of hypercortisolism is discussed in Chapter 27, section VIII.C.

VI. Islet cell tumors

  A. **General aspects.** Islet cell tumors of the endocrine pancreas are uncommon. In addition to the specific endocrine manifestations associated with each kind of tumor, some have been associated with ectopic production of ACTH (Cushing's syndrome) and other hormones. Many of these tumors are malignant and metastasize to the liver.

   1. **Diagnosis.** The diagnosis of islet cell tumor is usually suspected because of endocrine or biochemical abnormalities. Signs and symptoms of islet cell tumors are described according to the specific type. After abnormal hormonal products are detected, the following studies are done in all patients to determine the tumor's location and extent:

       a. LFTs; liver imaging if there is hepatomegaly or abnormal LFTs

       b. Liver biopsy is the diagnostic method of choice if liver imaging suggests the presence of tumor.

       c. CT scan of the pancreas may reveal isolated tumors. Selective angiograms have less than a 50% yield. Endoscopic ultrasonography also appears to be useful in localizing tumors in the pancreas or duodenal wall.

       d. Somatostatin receptor scanning using radioiodinated octreotide frequently demonstrates primary and metastatic islet cell tumors. More than 90% of PETs (pancreatic endocrine tumors) possess somatostatin receptors. Detection of somatostatin receptors by this method correlates well with response to treatment with octreotide.

       e. Exploratory laparotomy is indicated if there is clinical or laboratory evidence of an islet cell tumor, even if preoperative localization is unrevealing.

   2. **Management**

       a. **Surgery.** Intra-operative pancreatic ultrasonography is used to localize tumors. Benign tumors are excised. Cytoreductive surgery should be performed in all patients with malignant tumors when feasible. Partial hepatectomy in patients with metastases confined to one lobe of the liver, however, is hazardous and is generally not recommended. Hepatic artery embolization is helpful in carefully selected patients, with or without postocclusion chemotherapy (see section II.D.2).

       b. **Chemotherapy** has been useful in half of patients with metastatic disease, by both decreasing tumor mass and ameliorating otherwise refractory endocrine symptoms. The presence of metastases to the liver or other sites does not justify instituting cytotoxic therapy in itself because such patients can still survive several years (e.g., a median of about 4 years for gastrinomas with liver metastases if gastric acid secretion is controlled). Chemotherapy is generally reserved for patients with documented progressive liver metastases or without control of symptoms by octreotide and other medical measures.

         1. **Octreotide,** a somatostatin analogue, inhibits hormone release in gastrinomas, insulinomas, VIPomas, glucagonomas, and GRFomas and often relieves the symptoms of the associated clinical syndrome but usually has no effect on tumor mass.

         2. **Streptozocin** is the drug of choice for islet cell tumors and is associated with a 40% to 50% response rate. Other single chemotherapeutic agents are much less effective.

         3. **Combination chemotherapy** with streptozocin and doxorubicin or 5-FU achieves a 65% response rate for an average duration of 18 months. These combinations appear to be the combinations of choice. Alternatively, the combination of 5-FU and streptozocin can be sequenced with the combination of doxorubicin and dacarbazine after hepatic artery occlusion (see section II.D.4).

         4. **IFN-**a in doses of about 5 million U three times weekly controls symptoms and biochemical abnormalities in 45% of patients with little effect on tumor mass.

  B. **Gastrinoma (Zollinger-Ellison syndrome).** About 60% of these tumors are malignant, 90% are multiple, and about 50% are associated with MEN syndromes.

   1. **Diagnosis**

       a. **Symptoms** include severe peptic ulcer disease refractory to medical management and often, severe diarrhea.

       b. **Laboratory studies**

         1. **Upper GI contrast radiographic studies** show severe ulceration and hypertrophic gastric folds.

         2. **Fasting serum gastrin level** (normal value is less than 150 pg/mL) is usually elevated to more than 500 pg/mL. If gastrinoma is suspected but serum gastrin levels are not elevated, gastrin stimulation with calcium or secretin may be attempted. Calcium infusion (12 mg/kg of calcium gluconate over 3 hours) causes the gastrin level to more than double in patients with gastrinoma; the paradoxic increase in gastrin after secretin stimulation is used by some authorities to diagnose gastrinoma. Other causes of increased gastrin levels (atrophic gastritis, vagotomy, retained antrum after Billroth II gastrojejunostomy, and G-cell hyperplasia) must be differentiated from gastrinoma. Atrophic gastritis is differentiated by gastric acid studies.

         3. **Gastric secretory studies.** After an overnight fast, a nasogastric tube is placed, and four 15-minute aliquots are removed for analysis. Acid secretion of more than 10 mEq/hour and a volume of more than 100 mL/hour suggest gastrinoma. These studies clearly distinguish gastrinoma from atrophic gastritis.

       c. **Tumor location and extent.** See section VI.A.1.

   2. **Management**

       a. Therapy with H$_2$-antihistamines, proton-pump inhibitors, and liquid antacids controls symptoms in many patients.

       b. Surgery is necessary in cases refractory to medical therapy. Total gastrectomy is usually the procedure of choice to control peptic ulcer symptoms because of the multiplicity of tumors. Tumor excision may be possible in patients without hepatic metastases.

       c. Chemotherapy is used for metastatic disease (see section VI.A.2.b).

  C. **Insulinomas** are most likely to occur between the ages of 40 and 60 years. About 80% are benign, 10% are malignant, and 10% are multifocal; 80% are hormonally functional. Insulinomas are sometimes found in association with gastrinomas. A family history of diabetes mellitus is present in 25% of patients.

Insulinomas occur with equal frequency in the head, body, and tail of the pancreas; less than 1% develop outside the pancreas. Malignant tumors are more frequent in male patients. When malignant, they metastasize to the liver primarily.

   1. **Diagnosis.** The differential diagnosis of hypoglycemia is discussed in Chapter 27, section XII.A.

a. **Symptoms.** Fasting hypoglycemia, often alleviated by meals, is usually the presenting feature of insulinoma. Symptoms include diaphoresis, nervousness, palpitations, hunger pangs, anxiety, asthenia, confusion, weakness, seizures, and coma. Many patients have personality or other psychiatric changes noticed by the family. Weight gain is occasionally reported. Weight loss and liver failure may develop with metastases to the liver.

b. **Laboratory studies.** Measurements of fasting blood glucose and insulin levels are the cornerstone for diagnosis of insulinoma.

1. **Fasting hypoglycemia.** An overnight fast is begun at 10:00 pm. Blood glucose and insulin assays are obtained at 6:00 am, noon, 6:00 pm, and midnight. An inappropriately elevated plasma insulin level (greater than 10 µU/mL) in the presence of hypoglycemia usually is diagnostic of insulinoma. A ratio of glucose (mg/dL) to insulin (µU/mL) of less than 2.5 is also strongly suggestive of insulinoma. If symptoms of hypoglycemia develop at any time, blood glucose and insulin levels should be measured; if the glucose concentration is less than 40 mg/dL, the test should be terminated by giving the patient food or a 50-mL intravenous bolus of 50% dextrose.

2. **Other insulin assays.** Proinsulin and C peptide are absent from commercial insulin preparations; their measurement by radioimmunoassay determines the role of exogenous insulin administration in the causation of hypoglycemia. In fasting patients, proinsulin levels are normally less than 20% of total insulin; a higher percentage of proinsulin is indicative of insulinoma.

c. **Tumor location and extent.** See section VI.A.1.

2. **Management**

a. **Surgery.** Surgical removal of the tumor is the treatment of choice for insulinoma.

b. **RT** as an adjuvant to surgery has not been shown to be helpful.

c. **Chemotherapy** may be used for advanced disease (see section VI.A.2.b).

d. **Treatment of hypoglycemia**

1. Diazoxide, 150 to 600 mg PO daily, is effective in managing hypoglycemic symptoms. The drug can induce hyperglycemia, hyperosmolar coma, or ketoacidosis; urine sugar and ketones should be monitored daily. A mild diuretic, such as hydrochlorothiazide, 50 mg daily, should be given to counteract the sodium retention properties of diazoxide. Other complications of diazoxide therapy include cytopenias, lanugo hair growth, rashes, eosinophilia, and hyperuricemia.

2. Corticosteroids (prednisone, 40 mg/day, or hydrocortisone, 100 mg/day) may be given to patients who do not respond to diazoxide.

3. Patients with unresponsive hypoglycemia and unresectable insulinoma may be approached with several other, usually unsatisfactory alternatives, including: continuous intravenous infusion of 10% dextrose solutions through a Broviac or Hickman catheter, hepatic irradiation, or infusion of 5-FU into the hepatic artery.

4. Subcutaneous injections of a long-acting somatostatin preparation (octreotide) can be used to inhibit insulin secretion and restore euglycemia.

D. **Glucagonomas** are usually malignant, and most have metastasized at the time of discovery. The disease is suspected in patients who have diabetes mellitus that is moderately resistant to insulin and who have the following abnormalities:

1. **Diagnosis**

a. **Symptoms and physical findings**

1. *C*ermatosis: A peculiar erythematous migratory skin rash that had waxed and waned over many years (often more than 6 years), especially involving perioral and perigenital regions (also the fingers, legs and feet), occurs in 80% of patients.

2. *D*epression or other personality changes reported by family members

3. *D*iarrhea; abdominal pain

4. *D*eep-vein thrombosis (half of patients)

5. Oral cavity ulcerations and sore tongue are common.

6. Weight loss

b. **Laboratory studies**

1. Hyperglycemia (usually mild)

2. Normocytic anemia

3. Elevated fasting blood glucagon levels (normal range, less than 150 pg/mL)

c. **Tumor location and extent.** See section VI.A.1.

2. **Management.** See section VI.A.2. Prophylactic measures to prevent venous thrombosis during the perioperative period are mandatory.

E. **Pancreatic cholera syndrome** (VIPoma). These islet cell tumors are manifested by the release of VIP; half are malignant.

1. **Diagnosis**

a. **Symptoms** include severe watery diarrhea, muscle weakness due to hypokalemia, psychosis, and hypotension.

b. **Laboratory studies**

1. Serum chemistry studies show hypokalemia and often, hypercalcemia.

2. Gastric secretory studies show achlorhydria or hypochlorhydria.

3. Serum levels of VIP are elevated (normal is less than 70 pmol/mL).

c. Tumor location and extent. See section VI.A.1.

2. **Management**

a. **Surgery.** Removal of solitary tumors controls manifestations of the pancreatic cholera syndrome, including hypercalcemia. Debulking of extensive tumor may palliate the diarrhea.

b. **Chemotherapy** (see section VI.A.2.b) is useful for controlling symptoms in patients with metastatic tumor. Prednisone (80 mg/ day PO) may reduce the diarrhea in some patients. Refractory diarrhea may respond to trifluoperazine (Stelazine), up to 38 mg per 24 hours, or lithium carbonate, 300 mg PO every 12 hours. A long-acting somatostatin preparation (octreotide) may lower VIP levels and reduce diarrhea.

F. **Other pancreatic endocrine tumors**

1. **Somatostatinoma.** Somatostatin (somatotropin-release inhibiting factor) inhibits numerous endocrine and exocrine secretory functions. Half of patients with somatostatinoma have other endocrinopathies as well. This rare tumor produces diabetes mellitus, diarrhea, steatorrhea, gastric achlorhydria, weight loss, and in many cases, gallstones. Metastases are present in most cases at presentation. Cases are discovered by accident; symptoms are investigated, the tumor is found, and then the assays to confirm the diagnosis of somatostatinoma are performed. No definite procedure for diagnosis has been established. Evaluation of diabetic patients for somatostatinoma is not worthwhile unless severe malabsorption is present. See section VI.A.2 for treatment recommendations.

2. **PPoma.** Pancreatic polypeptide (PP) inhibits gallbladder contraction, and thus PPomas are usually silent biochemically. It appears that many cases of so-called nonfunctional islet cell tumors are actually PPomas. These tumors are usually found unsuspectedly while evaluating the patient for abdominal symptoms. Caution must be exercised in interpreting elevated PP levels because they can occur in other conditions, such as with the MEN-I syndrome. Benign tumors should be excised. Malignant PPomas respond to octreotide and streptozocin.

3. **GRFomas** are large tumors that excessively produce growth hormone– releasing hormone. About one third of these rare tumors originate in the pancreas, and more than half originate in the lung. The diagnosis can be suspected in patients with acromegaly but without an imaged pituitary tumor or with an abdominal mass. The diagnosis can be confirmed with elevated plasma GRF levels. Surgical resection is performed if possible. Octreotide effectively lowers plasma GRF levels.

VII. Other endocrine cancers

A. **Parathyroid carcinoma** is extremely rare. Patients present with a neck mass and hypercalcemia. Tumor growth is slow and tends to involve the neck and upper mediastinum; widespread metastases are uncommon.

1. **Diagnosis**

a. Patients with parathyroid cancer usually have stigmata of hypercalcemia, including polyuria, polydipsia, constipation, mental status changes, bone disease, and hypercalciuria.

b. High blood calcium levels are typical (15 to 16 mg/dL). Patients appear to tolerate these high levels relatively well, although hypercalcemic nephropathy and progressive bone disease ultimately complicate the course.

c. The diagnosis is established by biopsy of obvious neck masses in patients with evidence of hyperparathyroidism.

2. **Management**

a. **Surgery.** Surgical extirpation of as much tumor as possible is necessary. Periodic repeated surgical debulking is warranted to try to control both the local effects of tumor and hypercalcemia.

b. **Hypercalcemia** may be difficult to manage unless the tumor can be removed. Attempts should be made to normalize blood calcium levels; because this may be impossible, however, the alternative therapeutic goal is to reduce blood levels to the asymptomatic range. The management of patients with hypercalcemia is discussed in Chapter 27, section I. Chronic therapy with mithramycin (10 to 15 µg/kg every 4 to 5 days) or pamidronate (30 to 90 mg every 5 to 10 days) may be necessary.

B. **Pineal gland neoplasms** are extremely rare and are usually found in boys and young men. Dysgerminoma is the most common tumor of the pineal gland, although gliomas, choriocarcinoma, and melanomas also occur. Most tumors are localized, but spreading along the flow tract of cerebrospinal fluid often occurs.

See Chapter 14, for diagnosis and management.

VIII. Metastases to endocrine organs

A. **Adrenal gland metastases.** The adrenal gland is frequently the site of metastatic tumors, particularly from lung cancer, breast cancer, and melanomas. Addison's disease, although rare, can develop with bilateral adrenal metastases.
  1. **Diagnosis**
     a. **Symptoms and signs.** Patients develop malaise, asthenia, weakness, decreased ability to taste salt, and salt craving. Hyperpigmentation of the skin and mucous membranes, particularly the gums, and orthostatic hypotension may occur.
     b. **Laboratory findings** include hyponatremia, hyperkalemia, and elevated blood urea nitrogen. Diagnosis is established by the following steps:
        1. Obtaining a baseline serum cortisol level that is low (less than 5 µg/dL)
        2. Repeating the serum cortisol 1 hour after administering 0.25 mg of cosyntropin IV. Failure of the cortisol level to rise by at least 7 µg/dL to a peak value of at least 19 to 20 µg/dL is diagnostic of adrenal insufficiency.
  2. **Management.** Patients should be treated with fludrocortisone acetate (0.1 mg once or twice a day) and hydrocortisone (30 mg/day) or prednisone (5 mg daily). The correct dose of fludrocortisone is determined by measuring orthostatic blood pressure changes and blood electrolyte levels. If the orthostatic drop in blood pressure is more than 10 mm Hg, the fludrocortisone is increased by 0.1-mg increments every few days until orthostasis is corrected. If the patient develops hypertension, hypokalemia, or alkalosis, the fludrocortisone dose is decreased.
B. **Thyroid gland metastases.** The thyroid gland is rarely involved with metastases and rarely the presenting site for metastatic tumors. Non-Hodgkin lymphomas, and carcinomas of the breast, ovary, cervix, kidney, esophagus, colon, and lung have been reported to produce thyroid metastases. Diagnosis is established, if necessary, by needle biopsy of the thyroid masses. Therapy depends on the presence of local symptoms and the nature of the primary tumor.
C. **Testicular metastases.** Acute leukemia, melanoma, and carcinomas of the lung, prostate, bladder, and occasionally, kidney can metastasize to the testes. A peritesticular mass, intratesticular mass, or stony-hard enlarged testis (particularly characteristic of leukemic infiltration) is found on physical examination. Biopsy is necessary to establish the diagnosis; a transinguinal approach is mandatory.
D. **Ovarian metastases.** Ovarian metastases may complicate melanomas and primary tumors of the breast, stomach, colon, lung, and occasionally, other organs. Ovarian metastases are usually asymptomatic but occasionally are the presenting feature of the primary tumor. An ovarian mass is palpable on pelvic examination. Biopsy must be done to determine the diagnosis if no other sites of cancer are evident.
E. **Pituitary metastases** cannot be distinguished on clinical or biochemical grounds from pituitary adenomas. Patients with known cancers have about a 3% incidence of sellar or suprasellar metastases and a 1.5% incidence of pituitary adenomas. Radiologic discrimination is not possible. Primary cancers of the breast account for more than half of the cases; lung cancer accounts for 20% of cases; the remainder are caused by other carcinomas, melanomas, sarcomas, and leukemias. The triad of headache, extraocular nerve palsy, and diabetes insipidus is highly suggestive of sellar metastases whether or not the patient has a known cancer. Surgical exploration and decompression are essential unless precluded by progressive widespread metastases.

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Chapter 16 Skin Cancers

Richard F. Wagner, Jr., and Dennis A. Casciato

Basal Cell and Squamous Cell Carcinomas

I. Epidemiology and etiology

A. **Incidence.** At least 1 million new cases of cutaneous basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) are diagnosed annually in the United States. Men are more frequently affected than women. Although the most common of all malignancies, skin cancers account for less than 0.1% of patient deaths due to cancer.

B. **Risk factors**
   1. **Actinic (sun) damage** appears to be a major carcinogenic factor. Ninety percent of these cancers develop in sun-exposed areas of the body. The incidence in white populations rises dramatically near the equator and is greater at higher altitudes than at sea level. Blue-eyed, fair-skinned, blond and red-haired people and those who are easily sunburned are at increased risk. The incidence in blacks is much lower than in whites.
   2. **Other carcinogens**
      a. **Arsenic.** Arsenical exposure predisposes to the development of Bowen's disease, multiple BCC, and SCC, and is also associated with a higher incidence of intestinal carcinoma. Hard, yellowish hyperkeratotic plaques on the palms and soles provide a clue that the patient was exposed to arsenic.
      b. **Irradiation** given for benign conditions (such as acne or hirsutism) or resulting from occupational exposure is associated with up to a 20% risk for skin cancer. The tumor develops many years after the initial exposure; latent periods may extend up to 50 years. About two thirds of these cancers are BCC, and one third are SCC. Radiation-associated SCC tends to be aggressive and has a 10% mortality rate.
      c. **Coal tar and quinacrine** exposures appear to be risk factors for SCC.
      d. **Immunosuppression,** such as with renal transplantation, predisposes patients to an increased incidence of cutaneous SCC. Cyclosporine is associated with cutaneous SCC and lymphoma.
   3. **Chronic inflammation and trauma**
      a. **Chronic draining osteomyelitis** predisposes to the development of SCC. The local tumor is usually evident but may first be manifested by metastases to a draining lymph node.
      b. **Fistulas, stasis dermatitis, and areas of irritative leukoplakia** can also give rise to skin cancers.
      c. **Thermal or electrical burns and chronic heat exposure** are associated with increased risk for high-grade, aggressive SCC. Certain ethnic groups are burned from hot coals used as bed or clothing warmers.
      d. **Atrophic skin lesions** of discoid lupus or epidermolysis bullosa give rise to SCC.
   4. **Hereditary factors**
      a. **Xeroderma pigmentosum** is an autosomal recessive disease with one or more defects in DNA repair enzymes. Patients sunburn and freckle easily. Young children with xeroderma pigmentosum are at high risk for BCC, SCC, or malignant melanoma before their teenage years. Disturbances in speech, mentation, and convulsive disorders may also be present. A severe form (De Sanctis-Cacchione syndrome) includes microcephaly, mental deficiency, dwarfism, and failure of gonadal development.
      b. **Basal cell nevus syndrome** appears to be inherited as an autosomal dominant trait. Multiple BCC lesions appear over the face, arms, and trunk during the late teenage years. A large variety of associated lesions can occur and include jaw cysts, palmar pits, bifid ribs, kyphoscoliosis, spina bifida, short metacarpals, and hyporesponsiveness to parathyroid hormone. Patients with this syndrome also appear to be at increased risk for medulloblastoma and ovarian fibroma.
   5. **Infection**
      a. **Epidermodysplasia verruciformis** is primarily caused by human papillomaviruses (HPV) types 5 and 8 and results in *in situ* and invasive SCC synergistically with other carcinogens, such as sunlight.
      b. **SCCs** of the genitals and anal regions are strongly associated with HPV types 16 and 18. Infection, usually through sexual transmission, increases the risk for regional SCC.
      c. **Periungual SCC** is associated with HPV type 16.
   6. **Oncogene** (*Ha-ras, Ki-ras, N-ras, c-myc,* and others) mutation and amplification, as well as anti-oncogene *p53* mutations, have been reported for BCC and SCC.

II. Pathology and natural history

A. **SCC** nearly always arises in skin that is visibly damaged. Lesions most commonly are ulcerative but may be exophytic.
   1. **Aggressive squamous cell cancers** are unlikely to arise from actinic keratosis or actinic skin damage. The lower extremities are frequently involved and may have to be amputated to effect cure. Aggressive SCC also develops from burn scars, radiation dermatitis, erythroplasia of Queyrat (see Chapter 13, Penile Cancer, section II.A), and Bowen's disease.
   2. **Bowen's disease** consists of small eczematoid plaques. By histology, the plaques demonstrate intraepithelial carcinoma *in situ*. Invasion may occur; thus, treatment is necessary. Although historically suspected, Bowen's disease is not associated with an increased risk for internal cancer.
   3. **Bowenoid papulosis** is characterized by multiple genital papules that are histologically indistinguishable from Bowen's disease. They are usually caused by HPV type 16 and, when present on the female patient or her sexual partner, may indicate increased risk for cervical carcinoma.
   4. **Metastases.** Tumors that metastasize are usually poorly differentiated. The incidence of metastasis is less than 3% for actinically induced SCC and 35% for nonactinically induced SCC. The draining lymph nodes are the most frequent sites of metastases, although distant organs are eventually involved.

B. **BCC** is the most common type of skin cancer. It has several recognized subtypes.
   1. **Nodular-ulcerated BCC,** the most common type, usually appears on the face as a waxy papule with pearly or waxy borders. Some lesions are pigmented and clinically indistinguishable from melanoma. They spread both over the surface and deeply into the tissues to invade cartilage and bone. Ulceration is common ("rodent ulcer"). Inadequately treated BCC can result in severely deforming facial ulcerations and death through invasion of the vital structures of the head and neck. Distant metastases from BCC are extremely rare.
   2. **Superficial BCC** lesions usually arise on the trunk, are often multiple, and appear as red, scaly patches with areas of brown or black pigmentation. They

spread over the skin surface and may have areas of nodularity.

3. **Sclerosing BCC** usually affects the face. The tumors closely resemble scars and may have an ivory-colored and ill-defined border. Histologically, the cancer cells are surrounded by a dense bed of fibrosis ("morphea-like"). Considering all types of BCC, they have the highest recurrence rate after treatment.
4. **Cystic BCC** is uncommon. The tumor undergoes central degeneration to form a cystic lesion.
5. **Linear BCC** is a recently recognized morphologic clinical entity characterized by an increased risk for aggressive histopathologic pattern and increased subclinical tumor extension.
6. **Micronodular BCC** is defined histopathologically by small tumor nests and often exhibits covert subclinical growth.

III. Diagnosis. Skin biopsy is necessary to confirm the clinical suspicion of skin cancer. A shave or curette biopsy is usually adequate to diagnose BCC or SCC. If the first biopsy is negative and the tumor is still suspected, a deeper biopsy is necessary.

IV. Staging system and prognostic factors

A. **TNM system** for classification of cutaneous carcinomas uses NX, N0, or N1 for unassessed, absent, or present regional lymph node metastasis, respectively, and MX, M0, or M1 for unassessed, absent, or present distant metastasis, respectively.
   1. **Primary tumor stage**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis, pTis	Carcinoma *in situ*
T1, pT1	Tumor 2 cm or smaller in greatest dimension
T2, pT2	Tumor 2 to 5 cm in greatest dimension
T3, pT3	Tumor more than 5 cm in greatest dimension

   2. **The histopathologic grades** for cutaneous carcinomas are as follows:

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

B. **BCC** does not ordinarily require staging because of the rarity of metastases. However, the clinician should record the diameter and location of the lesion and whether the tumor is primary or recurrent. The prognosis for BCC is worsened if the tumor is morpheaform, linear, micronodular, recurrent, or greater than 2 cm in diameter; has poorly defined clinical borders; or is located in areas associated with high recurrence rates (see section VI.B.2.a).
C. **Cutaneous SCC** is clinically staged based on clinical examination of the lesion and regional lymph glands. No other metastatic workup is indicated. The prognosis for SCC is worsened if the tumor is recurrent, arises in a scar, occurs in immunocompromised patients, is greater than 4 mm thick or greater than 2 cm in diameter, is poorly differentiated, has perineural invasion, or appears in high recurrence areas (see section VI.B.2.a). Metastases to regional lymph nodes portend increased morbidity and mortality; visceral metastases are lethal.

V. Prevention. *Primary prevention* is largely achieved by encouraging patients and other responsible parties to minimize sunlight exposure and other reducible risk factors. *Secondary prevention* is provided by lesional treatment.

Skin erythema from solar exposure, even from ultraviolet light on cloudy days, represents skin damage that is cumulative over the years. The "healthy tan" represents the body's reaction to skin damage, and freckling should be recognized as an early sign of skin injury. Sunscreens with a sun protective factor (SPF) of 15 or greater and protective clothing, including hats, are helpful. Solumbra clothing that provides high SPF is manufactured by Sun Precautions in Everett, Washington.

VI. Management

A. **Actinic keratoses** may become SCC (1% risk). Lesions may be treated by liquid nitrogen or by curettage with electrical cautery of the base. The use of topical applications of fluorouracil or masoprocol can be successful in highly motivated patients.
B. **BCC and SCC** are treated by several techniques, which have various cure rates.
   1. **Traditional surgical resection** requires a surgical margin of 4 to 6 mm for primary tumors less than 2 cm in diameter (more margin for bigger primary tumors, tumors in high-risk areas, or recurrent tumors). Lack of complete visualization of tumor margins because of sampling error may result in tumor recurrence.
   2. **Mohs micrographic surgery** has the highest cure rates, maximally spares uninvolved tissue, and is less costly than radiation therapy (RT) or traditional excision surgery with frozen-section control. With this method, the tumor is microscopically mapped after it is excised. Mohs surgery is indicated for the following lesions:
      a. **Primary BCC or SCC** with the following characteristics:
         1. Located in regions at high risk for tumor recurrence (i.e., the periorbital area, nasolabial fold, nose–cheek angle, posterior ear sulcus, pinna, ear canal, nose, forehead, and scar tissue)
         2. Located in regions where tissue conservation is mandated
         3. Poorly defined clinical borders
         4. Diameter greater than 2 cm
         5. Perineural invasion
         6. Morpheaform, sclerotic, infiltrating, micronodular, or basosquamous histopathologic features or linear clinical presentation
      b. **Recurrent BCC or SCC.** Of all therapeutic modalities for recurrent tumors, Mohs surgery has the greatest success rate (95%) and should ordinarily be considered the preferred treatment.
   3. **Curettage** of the tumor with electrodesiccation of the apparently normal base to an additional depth of 3 or 4 mm is particularly useful for superficial BCC of the trunk or Bowen's disease.
   4. **Cryosurgery** using liquid nitrogen to freeze the tumor to −40°C should be considered for patients who refuse surgery or are poor surgical candidates. A probe to monitor freezing must be used for all tumors with the possible exception of superficial BCC. Cryosurgery is contraindicated for sclerosing BCC and cold-induced diseases.
   5. **RT** has the same indications as cryosurgery. It is relatively contraindicated in patients with xeroderma pigmentosa, epidermodysplasia verruciformis, or the basal cell nevus syndrome because RT may induce more tumors in the treated field. RT may have adjuvant use for unusually aggressive SCC and is used with or without surgery when metastasis involves regional lymph glands.
   6. **Large, deeply eroding tumors** can partially or totally destroy the face. These far-advanced cancers often cannot be cured. Computed tomography (CT) or magnetic resonance imaging (MRI) scans are useful for determining the extent of disease resulting from local invasion. Often, extensive reconstructive surgery is necessary after a surgical intervention. In the most severe cases, the patient may elect to wear a prosthesis.
   7. **Chemotherapy.** Chemotherapy has no adjuvant use for BCC or SCC. Experience in treating metastatic skin cancers is extremely limited. Fluorouracil, cisplatin, methotrexate, bleomycin, retinoids, and cyclophosphamide given singly and in combination have produced temporary tumor regression. Excellent response rates have been reported for advanced cases of SCC and BCC treated with cisplatin in combination with either a 5-day infusion of 5-fluorouracil (dosages similar to those used for head and neck cancers) or doxorubicin.

Malignant Melanoma

I. Epidemiology and etiology

A. **Incidence**
   1. **Geography.** About 40,000 new cases of melanoma are diagnosed in the United States annually, and the incidence continues to rise.
   2. **Sex.** The risk for melanoma is the same for men and women. Men are more likely to develop melanoma on the trunk, and women are more likely to develop lesions on the lower extremities.

3. **Age.** Melanoma is rare in young children. The incidence begins to rise with puberty, increases until 65 to 70 years of age, and then decreases.
4. **Race.** The incidence of melanoma is low in people of color.
5. **Multiplicity.** About 5% of patients with a primary cutaneous melanoma have or will develop another primary melanoma or multiple primary melanomas.

B. **Risk factors**
1. **Sun exposure** appears to increase the risk for cutaneous and ocular melanoma.
2. **Hereditary factors.** About 10% of melanomas occur in family clusters.
   a. **"Melanoma families"** appear to have a dominant mode of inheritance with incomplete penetrance. Ocular or cutaneous melanoma occurs in several members of these families. Members of melanoma families who get melanoma do so at a younger age and have a higher incidence of multiple primary tumors than do patients with sporadic melanomas.
   b. **Atypical mole syndrome** (AMS), **or dysplastic nevus syndrome** (DNS), is a recently described clinical syndrome of acquired atypical-appearing nevi that are associated with melanoma. Inheritance appears to be autosomal dominant with incomplete expression and penetrance.
3. **Nevi**
   a. About 70% of patients with melanoma have had a preexisting nevus at the primary tumor site. Congenital nevi may engender increased risk for melanoma. Giant congenital nevi have an extremely high incidence of malignant transformation. When feasible, removal is advised.
   b. White men have 20 to 40 moles by the third decade of life. Nevi continue to form throughout adult life; however, only 1 mole out of 500,000 becomes malignant.
4. **Other melanoma risk factors** include chemical exposure, physical agents (i.e., nonsolar ultraviolet radiation, ionizing radiation, trauma, burns), immunosuppression, and profession.
5. **Oncogene mutations** (*N-ras, Ha-ras, Ki-ras*) and amplifications (*N-ras, Ha-ras*), as well as *p53* antioncogene mutation, have been described.

II. Pathology and natural history

A. **Melanocytes** are believed to migrate from the embryonic neural crest to the dermal-epidermal junction of the skin. The number of melanocytes per unit of skin surface appears to be the same for all races, even albinos. Pigmentary differences between races are dependent on how the melanin is "packaged" in each cell.

B. **Histopathologic types of melanoma**
1. **Superficial spreading melanoma,** or radial spreading melanoma (70% of melanomas), is more common in women and is most frequently located on the back. The lesion is a pigmented macule or a barely palpable plaque with variegated colors (black, tan, red, brown, or white). Irregularity of the margins, especially the presence of a notch, is a suspicious feature. These tumors mostly manifest radial growth but eventually enter a vertical growth phase.
2. **Nodular melanoma** (15% of melanomas) occurs more frequently in men. Most of these lesions are jet-black or dark-blue with a distinct border. Occasionally, no pigment is present, and electron microscopy or special tissue stains are needed to determine the diagnosis. These tumors grow rapidly and vertically from the onset.
3. **Lentigo maligna melanoma** (10% to 15% of melanomas) has no sexual predilection. The lesion appears as a large, flat, tan-to-black macule of up to 4 cm in diameter, developing in sun-exposed areas of older, light-skinned people, most commonly on the face and neck. The *in situ* lentigo maligna lesion (or *Hutchinson's freckle*) shows a horizontal growth phase for up to 20 years and eventually a vertical growth phase anywhere in the involved area. The vertical phase resembles superficial spreading melanoma rather than nodular melanoma.
4. **Acral lentiginous melanoma** is melanoma involving the palms, fingers, soles, and toes.
5. **Unclassified** and rare desmoplastic variants also exist.

C. **Natural history**
1. **Mode of spread.** Most cutaneous melanomas are believed to arise near the basal lamina.
   a. **Radial growth.** The superficial spreading and lentigo maligna melanomas grow horizontally along the lamina (radial growth phase) before penetrating the deep skin structures (vertical growth phase). The radial phase may last as long as 20 years in lentigo maligna and 5 years in superficial spreading melanoma.
   b. **Vertical growth.** Nodular melanomas have a vertical growth phase from the outset. The vertical phase is associated with invasion of dermal blood and lymphatic vessels.
   c. **Lymphatics.** Local lymphatic spread results in satellite nodules of melanoma appearing near the site of the primary tumor (*satellitosis*). Draining lymph nodes are frequently involved after the vertical growth phase develops. The first lymph node to become involved is termed the *sentinel node.*
   d. **Distant metastases.** Metastatic melanomas can involve any organ in the body, including the placenta and fetus. About 5% of patients with melanoma present with symptoms of distant metastases without an apparent primary site.
2. **Unusual primary sites of melanoma**
   a. Melanomas can occur on the soles of the feet and under fingernails, especially of the thumbs and large toes. These sites are more likely to be affected in people of color.
   b. Ocular melanoma can develop in the choroid, ciliary body, or uvea. Melanomas occurring in the eye itself have been divided into a variety of histologic subtypes, which have different prognoses. These tumors have a peculiar tendency of metastasizing to the liver, sometimes many years after diagnosis of the primary site, giving rise to the "syndrome" of hepatomegaly, unilateral scleral icterus, and a prosthetic glass eye.
   c. Melanomas may rarely arise in the palate or gingiva, usually in a site in which increased pigmentation was previously noted.
   d. The anus and vulva are also potential sites for development of melanoma; 5% of melanomas in women occur on the vulva and 5% to 10% of vulvar cancers are melanomas, even though the vulva accounts for less than 2% of the body surface area.
   e. Internal sites with a melanocyte population, such as the foregut or central nervous system, may rarely be the site of a primary melanoma.
3. **Metastatic melanoma from an unknown primary site** accounts for 4% to 5% of all cases. To further complicate the problems of diagnosis and management, amelanotic melanoma may be mistaken for undifferentiated carcinoma. Patients usually have lymphatic metastases, but any organ may be involved. The occult primary site may have disappeared spontaneously or may have been excised or cauterized years before the appearance of the metastasis. The prognosis for these patients depends on the stage of disease and appears to be the same as for patients with clinically evident primary sites. This important clinical problem is discussed further in Chapter 20.
4. **Paraneoplastic syndromes** associated with melanoma have a wide scope and include vitiligo, dermatomyositis, melanosis, gynecomastia, ectopic Cushing's syndrome, and neurologic abnormalities.

III. Diagnosis

A. **Symptoms**
1. **Change in a preexisting pigmented lesion** is the first sign of melanoma in 70% of patients. The lesion becomes lighter, darker, or variegated in color; increases in size; or may be associated with an itching sensation. Ulceration or bleeding usually represents advanced disease.
2. *De novo* **melanomas,** not associated with previously observed skin lesions, occur in about 30% of patients.
3. **Symptoms of distant metastases** depend on the anatomic site involved.

B. **Physical examination.** Patients should be viewed completely for skin lesions. Special attention is given to areas not usually inspected, such as axillae, scalp, interdigital webs, mouth, genitals, and anal and oral regions. Palpation may reveal lymph node enlargement or organomegaly.

C. **Differential diagnosis**
1. **Pigmented skin lesions.** There are many pigmented skin lesions to consider in the differential diagnosis of melanoma. Common dark skin lesions include atypical mole, pigmented BCCs, seborrheic keratoses, and sclerosing hemangiomas. It is often difficult to distinguish early melanoma from a benign lesion clinically. Epiluminescence microscopy has not gained widespread acceptance in the United States.
2. **Signs that suggest melanoma** are variegated color and irregular borders. The presence of hair in the lesion does not assist in the differentiation of a benign lesion from melanoma. Specific findings that may indicate melanoma include the following:
   a. Changes in size, color, sensation, or surface characteristics of a preexisting nevus
   b. Lesions with variegated color (shades of brown, black, red, white, or blue)
   c. Lesions that contain bluish coloration even if not variegated
   d. Lesions with angular indentations or notches
   e. Other signs of possible malignancy include the following:
      1. Lesions that do not contain skin creases
      2. Lesions that ulcerate or bleed

D. **Laboratory studies**
1. **Biopsy of the lesion** is the first diagnostic procedure to be undertaken. Suspected melanoma should not be observed for further signs. An excision may be desirable based on the size and location. Excisional margins should only be a few millimeters in order not to interfere with future possible sentinel node mapping. An incisional biopsy may be performed when excision is not desired. There is no reliable evidence that incisional biopsies for melanoma result in increased morbidity or mortality.

2. **Patients with many small atypical nevi** (AMS, DNS). Several nevi should be excised and examined microscopically. Baseline total-body photographs are recommended. Significantly changed lesions should prompt excision. Monthly skin self-examination is recommended for the purpose of monitoring the atypical moles for malignant changes, with interim physician examination as indicated. Lifetime physician follow-up is recommended for early melanoma diagnosis.

3. **Immunohistochemistry.** S100 protein (more sensitive) and HMB-45 (more specific) may help distinguish poorly differentiated amelanotic malignant melanoma from tumors of obscure histologic origin. See Appendix C-1 and Appendix C-3.

IV. Staging system and prognostic factors

A. **Staging systems.** Several systems are in common use. The reader is referred to current staging manuals for the TNM classification, which is complicated. Another staging system developed by the American Joint Committee on Cancer (AJCC) is gaining popularity because of its applicability and simplicity. The AJCC system is as follows:

Stage Criteria

IA   Cutaneous melanoma £ 0.75 mm thick
IB   Cutaneous melanoma 0.76 to 1.50 mm thick
IIA   Cutaneous melanoma > 1.5 to 4.0 mm thick
IIB   Cutaneous melanoma > 4.0 mm thick
III   Nodal metastases
IV   Distant metastases

B. **Prognostic factors.** Depth of invasion, presence of positive lymph nodes, and presence of distant metastases greatly affect prognosis. Women have a better prognosis than do men when matched by age and stage of disease.
   1. **Clark's levels** by depth or invasion into the skin (Fig. 16.1) are as follows:

Figure 16.1 Clark's levels of invasion for malignant melanoma.

Level	Tumor extent	Five-year survival (%)
I	Tumor is confined to epidermis (*in situ*)	100
II	Tumor extends beyond basal lamina into papillary dermis	85
III	Tumor extends into papillary dermis and abuts onto, but does not invade, the reticular dermis	65
IV	Tumor extends into reticular dermis	50
V	Tumor extends into subcutaneous fat	15

   2. **Breslow's system** by depth of tumor invasion from the basal lamina (measured with an ocular micrometer). Tumors with less than 0.85 mm of invasion have a low metastatic potential.

Depth of tumor invasion	Five-year survival (%)
<0.5 mm	99
>3 mm	30

   3. **Survival according to regional lymph node involvement**.

Node involvement	Five-year survival (%)
Negative nodes	75
1–3 positive nodes	50
4 or more positive nodes	25

   4. **Survival according to metastatic spread**

Stage	Extent	Five-year survival (%)
II	Local recurrences within 3 cm of primary site	30
III	Satellitosis	<20
IV	Distant metastases	<10

C. **Recommended staging evaluation**
   1. Breslow's or Clark's level should be determined in all instances when a primary tumor is identified.
   2. Regional lymph nodes should be palpated and any suspicious finding should undergo biopsy. Lymph nodes containing melanoma require treatment.
   3. Sentinel node dissection after lymphoscintigraphy is offered at some centers to patients who have primary melanomas that are 1 to 4 mm thick but no palpable lymph nodes.
   4. For melanomas thicker than 1 mm, chest radiographs, liver function tests, and lactate dehydrogenase levels should be followed periodically. CT or MRI scans are performed if clinical or laboratory evidence suggests that specific organs are involved.

V. Prevention.
Primary prevention of melanoma involves the avoidance of sun and other reducible risk factors. *Secondary prevention* depends on careful physical examination and biopsy of all suspicious skin lesions.

VI. Management

A. **Surgery**
   1. **Management of the primary tumor**
      a. **Cutaneous melanoma.** Local excision of early melanoma is the only proven method of curative therapy. The extent of tumor-free margins that is necessary remains controversial. Current required surgical margins are 5 mm for *in situ* lesions, 1 cm for thin melanomas (1 mm or smaller), and 2 to 3 cm for lesions thicker than 1 mm.

      Mohs micrographic surgery should be considered for facial melanoma and other areas where tissue conservation is desired because of its equivalent cure rate. Tumor margin is often influenced by site. Large defects may require skin grafting or skin flaps.

      b. **Choroidal melanomas of the eye** were treated historically by enucleation. Small tumors have been successfully treated with high-dose irradiation and local surgical measures; this treatment avoids removal of the eye.
   2. **Management of lymph nodes.** Prophylactic resection of clinically uninvolved draining lymph nodes for intermediate-thickness stage I disease is controversial because it may not affect survival. Palpable nodes should be excised.
   3. **Management of metastases.** Highly selected patients may benefit from resection of metastases, particularly if they are solitary and completely excised.
      a. **Solitary brain metastases.** The brain is the third most frequent site of metastases. Operable solitary metastases may be excised, but prolonged survival is rare.
      b. **Gastrointestinal problems.** Melanoma has a tendency to metastasize to the gastrointestinal tract, where it may cause bleeding, intussusception, or obstruction. Endoscopy should be an early study done on patients who have upper gastrointestinal tract bleeding. The characteristic "bull's eye" appearance on contrast studies of small bowel lesions is highly suggestive of melanoma. Patients with obstruction or uncontrolled bleeding from an apparently isolated intestinal lesion may temporarily benefit from resection of the tumor.
      c. **Pulmonary metastases** from melanoma are rarely beneficially resected, even if they appear to be solitary.
B. **RT** is occasionally useful as a primary or adjuvant modality for treating melanoma patients who are debilitated or who refuse surgery.

C. **Systemic therapy.** Caution must be used when interpreting responses of metastatic melanoma to systemic therapies of any kind because melanoma is a capricious neoplasm that is associated with spontaneous regressions. Responses may be temporally but not causally related to treatment.

1. **Adjuvant therapy.** The use of traditional chemotherapy as an adjuvant to surgery failed to improve survival. Interferon- a (IFN-a), however, has clearly demonstrated effectiveness in melanoma, particularly for patients with lymph node involvement. Treatment should be started shortly after surgery. IFN- a2a and IFN-a2b differ in only one amino acid.

    a. **AJCC stage III: intravenous IFN-a2b** improved the 5-year relapse-free survival rate (67% reduction in relapses) and the overall 5-year survival rate for stage III melanoma (pathologically positive nodes) in a large Eastern Cooperative Oncology Group study (#1684). IFN- a2b is given as an IV bolus at a dose of 20 MIU/m^2 for 5 days per week for 4 weeks, followed by SC injections three times weekly of 10 MIU/m^2 for 48 weeks. Toxicity of this therapy is substantial, constitutional, hematologic, hepatic, neurologic, and financial. The dose of IFN is withheld until toxicity improves and then reduced by 33% to 50% if the neutrophil count falls to below 500/μL, if the transaminase levels are 5 to 10 times normal, or if the bilirubin is 2 to 5 times normal. IFN therapy is discontinued if the neutrophil count falls to below 250/μL, if the ALT or AST is more than 10 times normal, or if the bilirubin is more than 5 times normal.

    b. **AJCC stage IIB: IFN-a2b** by the protocol, in section 1.a, is also being offered to patients with stage IIB melanoma (more than 4 mm thick).

    c. **AJCC stage IIA: IFN-a2a,** 3 MIU (not per m^2) given SC three times weekly for 18 months, has significantly improved relapse-free interval but has not yet been shown to improve overall survival in these patients. The toxicity and cost of this regimen is substantially less than that of the intravenous regimen described earlier.

2. **Limb perfusion.** Patients with melanoma of the extremity and "in-transit" or "satellite" cutaneous metastases may be treated by limb perfusion with cytotoxic agents. Although excision can be considered for a few small satellites, perfusion is considered when the satellites are multiple, recurrent, or unresectable. The arterial and venous blood supplies of the involved extremity are isolated, and heated solutions of melphalan or other drugs are injected. Limb perfusion permits the administration of high doses of drugs while minimizing drug toxicity. Local tumor response rates are reported to be high, but whether the survival rate is affected is unclear.

3. **Cytotoxic agents** can be used in patients with distant metastases. Dacarbazine (DTIC) is the most effective drug. Response rates are 20% for skin and lymph node metastases but less than 5% for visceral or skeletal metastases. The combination of dacarbazine with a vinca alkaloid and an alkylating agent (cisplatin or lomustine) appears to improve the response rate to 30% to 40%. The addition of IFN increases the toxicity but not the response or survival rates. The traditional BOLD regimen (described subsequently) is given to suitable patients every 28 days, as follows:

    Bleomycin, 15 units IV on days 1 and 4
    Vincristine (**O**ncovin), 1 mg/m^2 IV on days 1 and 5
    Lomustine (CCNU), 80 mg/m^2 PO on day 1 (maximum, 150 mg)
    DTIC, 200 mg/m^2 IV on days 1 through 5

4. **Tamoxifen** was shown in small studies to have effectiveness and improved response rate in melanoma for women only. Subsequent studies have not validated those observations.

5. **Immunotherapy.** The use of bacillus Calmette-Guérin (BCG) does not affect survival of patients with malignant melanoma. The use of IFN in melanoma was discussed previously.

    a. **Satellite lesions** injected with BCG may regress in 40% of treated patients. This treatment can leave chronic, draining BCG infections or scabs on the skin, result in disseminated BCG infection (e.g., granulomatous hepatitis) that requires therapy with isoniazid, and produce a shocklike syndrome.

    b. **Interleukin-2** (IL-2), with or without lymphokine-activated killer cells, is associated with response rates of about 25% at the expense of high cost and considerable toxicity. Only a small proportion of patients achieves a durable remission.

    c. **Sequential chemobiotherapy** using standard cytotoxic drugs with IFN, IL-2, or both is investigational.

    d. **Tumor cell vaccines and gene therapies** are investigational.

VII. Special clinical problems associated with malignant melanoma

A. **Cardiac metastases** frequently occur with melanoma and can occasionally result in arrhythmia or cardiac rupture. Antemortem diagnosis is difficult in the absence of malignant pericardial effusion. Patients should be treated with appropriate antiarrhythmic agents. RT to the heart is probably of little benefit.

B. **Breast metastases.** Poorly differentiated or undifferentiated melanoma metastatic to breast can be confused with primary breast cancer.

C. **Slate-gray skin discoloration** (melanosis syndrome) results from widespread melanoma, which causes high blood and urinary melanogens. Affected patients often have urine that is dark or darkens on exposure to air.

D. **Black sputum,** similar to that seen in coal miners, may occur in patients who have pulmonary melanoma lesions that have eroded into the airways.

Kaposi's Sarcoma

I. Epidemiology. Historically, Kaposi's sarcoma (KS) was a rare cutaneous tumor that mostly affected southern African black children and elderly whites. The occurrence of the malignancy in the United States has now been well described as part of the acquired immunodeficiency syndrome (AIDS); see Chapter 37, section IV. Human herpesvirus type 8, has been strongly associated with KS.

A. **Older patients** with KS are usually older than 65 years of age, and most have ancestry from the Mediterranean region. Lesions tend to be multifocal on the lower extremities and occasionally involve the hands, ears, and nose. The disease affects men 10 to 15 times more frequently than women and is relatively indolent.

B. **Black children** with KS in southern Africa tend to have tumors that involve the lymph nodes. This form of KS is generalized and aggressive.

C. **Patients with AIDS,** particularly homosexual men in the third or fourth decades of life, develop a widely disseminated, aggressive, and usually fatal form of the disease. Generalized cutaneous involvement, generalized lymphadenopathy, and visceral or gastrointestinal involvement are typical.

D. **Others with a increased risk for KS** include renal transplant recipients, immunosuppressed nontransplantation patients, and Eskimos.

II. Pathology and natural history This spindle cell tumor appears to originate in the dermis; the cell of origin is controversial. The tumor has vascular channels with variable fibrotic and lymphocytic components. The classic disease has a protracted indolent course, predominantly cutaneous manifestations, and expected survival of more than 15 years. Metastases may occur, but the rate of spread is variable. In African children and in AIDS patients, the median survival time appears to be less than 5 years.

III. Diagnosis

A. **Signs.** KS typically presents as purplish blotches or nodules on the feet, which resemble venous stasis. Because of the pleomorphic nature of this disease and of opportunistic infections in AIDS patients, however, any new skin lesion in this population should be investigated. Other skin sites, mucosa, or visceral organs may be involved. The lesions may be painful or pruritic. Tumor nodules may regress if thrombosis occurs. Edema is associated with involvement of the deep lymphatic system and veins.

B. **Biopsy** of masses or of what appear to be chronic, progressive venous stasis ulcers reveals the diagnosis. Lymph node biopsy is necessary for evaluating the African form of the disease.

C. **Staging.** No system is in widespread use, and no specific staging evaluation is universally accepted.

IV. Management

A. **Local therapy.** A topical treatment for cutaneous KS, 0.1% alitretinoin gel (Panretin), should be tried first for local control. However, local erythema, scaling, and dermatitis may limit the use of alitretinoin. Liquid nitrogen can be used for the destruction of localized nodular lesions.

B. **RT** is useful for local disease. KS is very radiosensitive.

C. **Chemotherapy** is inconsistently effective. Vinblastine appears to be the most active agent. Responses have also been reported for nitrosoureas, actinomycin D, and bleomycin. Response rates and effects on survival are unknown. The treatment of KS in AIDS is discussed in Chapter 33, section IV.

Suggested Reading

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Ross MI. Surgical management of stage I and stage II melanoma patients: approach to the regional lymph node basin. *Semin Surg Oncol* 1996;12:394.

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Chapter 17 Sarcomas

Charles A. Forscher and Dennis A. Casciato

I. Epidemiology and etiology Primary mesenchymal tumors localized outside the skeleton, parenchymatous organs, or hollow viscera are generally designated as soft tissue sarcomas (STSs). Sarcomas of the mediastinum, heart, and blood vessels are discussed in Chapter 19.

A. **Incidence.** Sarcomas constitute about 1% of all cancers and accounted for 8000 new cases in the United States in 1999. STSs outnumber bone sarcomas by a ratio of 3:1. In children, most STSs are rhabdomyosarcomas or undifferentiated tumors originating in the head and neck regions. In adults, STSs occur most frequently on the extremities or retroperitoneum and least frequently in the head and neck region. Bone sarcomas occur mostly between 10 and 20 years of age (osteogenic sarcoma) or between 40 and 60 years of age (chondrosarcoma). Most sarcomas show no sexual predilection. Incidence peaks during childhood and in the fifth decade.

B. **Etiology.** Certain kinds of sarcomas are associated with exposure to specific agents or with underlying medical conditions.
   1. **Lymphangiosarcoma.** Prolonged postmastectomy arm edema (Stewart-Treves syndrome)
   2. **Angiosarcoma and other STSs.** Polyvinyl chloride, thorium dioxide, dioxin, arsenic, and androgens
   3. **Osteosarcoma.** Radium (watch dials) exposure; postmastectomy irradiation; Paget's disease of bone
   4. **Fibrosarcoma.** Postirradiation: Paget's disease of bone
   5. **Kaposi's sarcoma.** Cytomegalovirus and human immunodeficiency virus type 1 (HIV-1; discussed in Chapter 16, Kaposi's Sarcoma, and Chapter 37, section IV)
   6. **Leiomyosarcoma.** HIV-1 in children
   7. **Genetically transmitted diseases**
      a. **Li-Fraumeni syndrome.** Various sarcomas (especially rhabdomyosarcoma) and carcinomas of breast, lung, and adrenal cortex (*p53* gene)
      b. **Beckwith-Wiedemann syndrome.** Wilms' tumor, genitourinary anomalies, aniridia, and hemihypertrophy
      c. **Neurofibromatosis.** Schwannomas (*NF1* gene)
      d. **Familial retinoblastoma.** Osteosarcoma (*RB1* gene)
   8. **Chromosomal aberrations** are found in nearly all sarcomas. Characteristic translocations, particularly involving DNA transcription factors, are being defined (e.g., the X; 18 translocation in synovial sarcoma and 11;22 translocation in Ewing's sarcoma).

II. Pathology and natural history

A. **Histology and nomenclature.** Sarcomas are given a bewildering variety of names that do not indicate biologic behavior and usually do not influence therapeutic approach. The multipotential capacities of the mesenchymal tissue and the appearance of several histologic elements in the same tumor often make clear-cut histologic diagnosis difficult.
   1. Sarcomas are named for the **tissue of origin** (e.g., osteosarcoma, chondrosarcoma, schwannoma, liposarcoma). These names may be combined to describe multicomponent tumors (e.g., fibrous histiocytoma).
   2. Tumors are also named for **special histologic characteristics** or given a nondescriptive name because the tissue of origin is unknown (alveolar soft parts tumor, Kaposi's sarcoma, Ewing's sarcoma).
   3. **The degree of cellular differentiation (grade) and amount of necrosis** within the tumor are absolutely the most important factors in predicting tumor behavior and in determining treatment modalities for sarcomas. The other descriptive terms for the tumor are far less important. Expert pathologic evaluation is crucial.
   4. **The presence of osteoid formation** by the tumor cells suggests the diagnosis of osteogenic sarcoma. This must be distinguished from reactive or metaplastic bone formation by the pathologist.
   5. **Immunohistochemistry** may be helpful in confirming the diagnosis of rhabdomyosarcoma and leiomyosarcoma. Expected immunophenotypes for the various sarcomas are shown in Appendix C3.IV.
   6. **Cytogenetics** can be useful in the diagnosis of Ewing's sarcoma, synovial sarcoma, and rhabdomyosarcoma. Newer techniques, such as FISH analysis, are also becoming increasingly useful.

B. **Natural history.** Generally, sarcomas arise *de novo* and not from preexisting benign neoplasm. Tumors occasionally "dedifferentiate," however, from benign to malignant forms or from a lower grade to a higher grade. Sarcomas spread without interruption along tissue planes; they invade local nerve fibers, muscle bundles, and blood vessels. Histologic sections usually show much greater local extension than is apparent on gross examination.
   1. **Histologic grade.** The biologic behavior of sarcomas can usually be predicted by their histologic grade. Low-grade tumors tend to remain localized; high-grade tumors (especially those with a marked degree of necrosis) metastasize early. Virtually all osteogenic sarcomas, rhabdomyosarcomas, and synovial sarcomas are high grade.
   2. **Site of origin.** The site of origin of the sarcoma may suggest the cell type, as follows:
      a. **Head and neck**
         1. Rhabdomyosarcoma (in a child)
         2. Angiosarcoma (in an elderly person)
         3. Osteogenic sarcoma (jaw)
      b. **Distal extremity**
         1. Epithelioid sarcoma
         2. Synovial sarcoma
         3. Clear cell sarcoma
         4. Osteogenic sarcoma (femur)
      c. **Proximal tibia or humerus.** Osteogenic sarcoma
      d. **Mesothelium**. Mesothelioma
      e. **Retroperitoneum and mesentery**
         1. Leiomyosarcoma
         2. Liposarcoma
         3. Malignant fibrous histiocytoma
      f. **Genitourinary tract**
         1. Rhabdomyosarcoma (in a child)
         2. Leiomyosarcoma (in an adult)
      g. **Skin**
         1. Angiosarcoma, lymphangiosarcoma
         2. Kaposi's sarcoma
         3. Epithelioid sarcoma
         4. Dermatofibrosarcoma protuberans (on trunk)
   3. **Metastases.** Sarcomas typically spread hematogenously. Lung metastases occur most commonly. Hepatic metastases can be seen from primary gastrointestinal or gynecologic sarcomas. The retroperitoneum can be a site of metastasis for extremity liposarcomas. Other sites, such as bone, subcutaneous tissue, and brain, are less common and are often detected only after pulmonary metastases have developed (tertiary metastases).
      a. **Sarcomas that metastasize to lymph nodes**
         1. Rhabdomyosarcoma
         2. Synovial sarcoma

3. Epithelioid sarcoma
   b. **Sarcomas that rarely metastasize** and are associated with a favorable survival
      1. Liposarcoma (myxoid and well-differentiated types)
      2. Fibrosarcoma (infantile and well-differentiated types)
      3. Malignant fibrous histiocytoma (superficial type)
      4. Dermatofibrosarcoma protuberans
      5. Parosteal sarcoma
      6. Kaposi's sarcoma (not related to acquired immunodeficiency syndrome [AIDS])
   4. **Paraneoplastic syndromes** associated with sarcomas
      a. Hypoglycemia (particularly with retroperitoneal fibrosarcoma)
      b. Hypertrophic osteoarthropathy (sarcoma of pleura or mediastinum)
      c. Hypocalcemia
      d. Oncogenic osteomalacia
C. **Clinical aspects of specific STSs**
   1. **Alveolar soft-part sarcoma**
      a. **Tissue of origin (incidence).** Unknown (rare)
      b. **Features.** Unique histology with no benign counterpart; often indolent even with lung metastases, which are common. The sarcoma most associated with brain metastases. Commonly affects the thigh in adults and the head and neck in children. The 5-year survival rate exceeds 60%.
   2. **Angiosarcoma (hemangiosarcoma, lymphangiosarcoma)**
      a. **Tissue of origin (incidence).** Blood or lymph vessels (2% to 3%)
      b. **Features of hemangiosarcoma.** Affects the elderly; aggressive. Arises in many organs, notably the head and neck region, breast, and liver; especially affects the skin and superficial soft tissues (whereas most STSs are deep). Dedifferentiation from a hemangioma is rare. The 5-year survival rate is less than 20%.
      c. **Features of lymphangiosarcoma.** Affects older adults; aggressive. Arises in areas with chronic lymphatic stasis (especially postmastectomy). The 5-year rate survival is 10%.
   3. **Clear cell sarcoma**
      a. **Tissue of origin (incidence).** Now recognized as a form of malignant melanoma (rare).
      b. **Features.** Affects adults younger than 40 years of age; painless, firm, spherical masses on tendon sheaths and aponeurotic structures of distal extremities. The 5-year survival rate is about 50%.
   4. **Epithelioid sarcoma**
      a. **Tissue of origin (incidence).** Unknown (rare)
      b. **Features.** Affects young adults; aggressive; typically appears on distal extremities. Epithelioid sarcoma and synovial sarcoma are the most common tumors of the hand and foot. Differs from other STSs by having a greater tendency to spread to noncontiguous areas of skin, subcutaneous tissue, fat, draining lymph nodes, and bone. The 5-year survival rate is about 30%.
   5. **Fibrosarcoma**
      a. **Tissue of origin (incidence).** Fibrous tissue (5% to 20%)
      b. **Features.** Affects all age groups; arises in many mesenchymal sites; usually involves the abdominal wall or extremities. Ninety percent are well-differentiated (desmoid). Dermatofibrosarcoma protuberans (rare) develops on the skin of the trunk and almost never metastasizes. Fibromyxosarcoma affects any soft tissue site but usually develops on the extremities. Ten percent are poorly differentiated (high-grade). Survival is directly related to tumor grade (also see section D.5).
   6. **Malignant fibrous histiocytoma (MFH)**
      a. **Tissue of origin (incidence).** Fibrous tissue and histiocytes (10% to 23%)
      b. **Features.** Age older than 40 years (less than 5% of affected patients are younger than 20 years of age). MFH has become a popular histologic diagnosis, often encompassing tumors that were previously classified as pleomorphic rhabdomyosarcoma or undifferentiated fibrosarcoma; it is the most common STS in some series. MFHs range from benign to atypical to frankly malignant. Develops in extremities (especially legs), trunk, and retroperitoneum. Superficial MFH develops close to the skin surface and is often low grade; the 5-year survival rate is 65%. Deep MFH usually is high grade; the 5-year survival rate is 30% to 60%.
   7. **Hemangiopericytoma**
      a. **Tissue of origin (incidence).** Blood vessels (less than 1%)
      b. **Features.** Affects all ages. Develops under finger tips (glomus tumors), on lower extremities or pelvis, in the retroperitoneum, and elsewhere. Benign and malignant versions. The 5-year survival rate is about 50%.
   8. **Kaposi's sarcoma**
      a. **Tissue of origin (incidence).** Controversial (varied)
      b. **Features.** Classically affects older adults; extremely indolent lesions arise on lower extremities and rarely cause death. The epidemic and aggressive variety is associated with AIDS and Africans (see Chapter 16, Kaposi's Sarcoma, and Chapter 37, section IV).
   9. **Leiomyosarcoma, gastrointestinal stromal tumors, and metastasizing leiomyoma**
      a. **Tissue of origin (incidence).** Smooth muscle (7% to 11%)
      b. **Features.** Affects all age groups. Develops in gastrointestinal tract, uterus, retroperitoneum, and other soft tissues. Generally refractory to chemotherapy and radiotherapy. The 5-year survival rate is 30%.
      c. **Gastrointestinal stromal tumors** (GISTs) are morphologically similar to leiomyosarcoma but have different immunohistochemical staining characteristics. GISTs do not stain for actin (as leiomyosarcomas do) and do express SC117 (c-kit protein).
      d. **Leiomyoma peritonealis disseminata** (LPD). A condition in women, usually in reproductive years. Myriads of asymptomatic benign leiomyomas are usually scattered throughout the peritoneal cavity and range from 1 to 10 cm in size; they are stimulated by estrogen. LPD causes occasional mechanical problems with bowel or pain. Generally, no treatment is required; when symptomatic, treatment is with estrogens or antiestrogens.
      e. **Leiomyoma, benign metastasizing.** Histologically benign, these leiomyomas are typically discovered as persistent pulmonary nodules and possibly as a variant of LPD. Associated nodules in the pelvis are mostly in round ligaments of uterus and not as diffuse as in LPD. Treatment is surgical for symptomatic or progressive lesions.
   10. **Liposarcoma**
      a. **Tissue of origin (incidence).** Fat tissue (15% to 18%)
      b. **Features.** Affects middle and older age groups, mostly men. Develops in thigh, groin, buttocks, shoulder girdle, and retroperitoneum. Does not arise from benign lipomas. The 5-year survival rate is 80% for low-grade liposarcomas and 20% for high-grade liposarcomas.
   11. **Mesenchymoma**
      a. **Tissue of origin (incidence).** Two or more distinct types of mesenchymal tissue (less than 1%).
      b. **Features.** Affects children. Tumors are composed of combinations of smooth or striated muscle, nerve sheath, vascular stroma, reticulum cells, osteoblasts, chondroblasts, or fat cells. Often low grade with high survival rates; the 5-year survival rate is greater than 80%.
   12. **Mesothelioma**
      a. **Tissue of origin (incidence).** Mesothelium
      b. **Features.** Age older than 50 years. Asbestos exposure is etiologic. Involves pleura and peritoneum; aggressively encases viscera. Highly lethal; the 5-year survival rate is less than 10%. (See Chapter 8, section II.C.4.)
   13. **Myxoma**
      a. **Tissue of origin (incidence).** Mesenchymal tissues
      b. **Features.** Usually found on extremities; has histologic appearance of umbilical cord. The 5-year survival rate is about 80%.
   14. **Neurofibrosarcoma (schwannoma, neurilemoma)**
      a. **Tissue of origin (incidence).** Nerve (5% to 7%)
      b. **Features.** Affects young and middle-aged adults and patients with von Recklinghausen's disease (about 10% develop sarcomatous changes during lifetime). Histologically resembles fibrosarcoma. Presents with thickening of nerves and without anatomic predilection. Superficial variety is low-grade, spreads extensively along nerve sheaths without metastasizing, and has a 5-year survival rate of more than 90%. Penetrating variety is high grade with nodular growth, vascular invasion, and lung metastases and has a 5-year survival rate of less than 20%.
   15. **Polyhistiocytoma** (see section D.10)
   16. **Rhabdomyosarcoma**
      a. **Tissue of origin (incidence).** Striated muscle (5% to 19%)
      b. **Features.** By definition in the G-TNM staging system, all are grade 3. All types can occur in any age group, but the typical onset and distribution is noted below (see Chapter 18, Rhabdomyosarcoma).

c. **Features of embryonal rhabdomyosarcoma.** Affects infants and children; sites are head and neck (70%) and genitalia (15% to 20%). Includes sarcoma botryoid. The 5-year survival rate is about 70%.

d. **Features of alveolar rhabdomyosarcoma.** Affects teenagers at any site; highly aggressive; histology resembles lung alveoli. The 5-year survival rate is about 50%.

e. **Features of pleomorphic rhabdomyosarcoma.** Affects patients older than 30 years of age; is rare; develops in extremities. Often is highly anaplastic; microscopically confused with MFH. The 5-year survival rate is about 25%.

17. **Synovial sarcoma**

a. **Tissue of origin (incidence).** Tenosynovial mesothelium (5% to 20%)

b. **Features.** Affects young adults, but may occur from the second to fourth decade. Monophasic and biphasic subtypes are distinguished. Presents with hard masses, often painful, near tendons in the vicinity of joints of the hands, knees, or feet. Synovial and epithelioid sarcoma and epithelioid sarcoma are the most common tumors of the hand and foot. Often calcified, with characteristic radiographic appearance. By definition in the G-TNM staging system, virtually all are grade 3. Relatively high rates of local recurrence and lymph node metastases. The 5-year survival rate is about 30%.

D. **Clinical aspects of specific bone sarcomas**

1. **Adamantinoma**

a. **Tissue of origin (incidence).** Unknown; nonosseous (less than 1%)

b. **Features.** Osteolytic tumor; often develops on upper tibia; resembles ameloblastoma of mandible. Indolent behavior; the 5-year survival rate is greater than 90%.

2. **Chondrosarcoma**

a. **Tissue of origin (incidence).** Cartilage (30%)

b. **Features.** Age, 40 to 60 years; fewer than 4% of patients are younger than 20 years of age. Usually develops in shoulder girdle (15%), proximal femur (20%), or pelvis (30%). Chondrosarcomas are the most common malignant tumors of the sternum and scapula. Most tumors are grade 1 or 2; higher-grade tumors metastasize frequently; however, tumor grade does not appear to affect prognosis. Local recurrence is a major problem in management. Usually refractory to both radiation therapy (RT) and chemotherapy. Dedifferentiated chondrosarcomas may, however, respond to chemotherapy. Complete surgical removal is the main determinant of recurrence and survival. The 5-year survival rate is about 50%.

1. Central chondrosarcomas (75%) arise within a bone; peripheral chondrosarcomas (25%) arise from the surface of a bone. Peripheral lesions can become quite large without causing pain; central lesions present with a dull pain but rarely with a mass. Pain means that the apparently "benign" cartilage tumor on radiographs is probably a central chondrosarcoma.

2. About 25% of chondrosarcomas represent malignant transformation of a preexisting endochondroma or osteocartilaginous exostosis. The presentation of multiple benign cartilaginous tumors has a higher rate of malignant transformation than the corresponding solitary lesions.

3. **Chordoma**

a. **Tissue of origin (incidence).** Primitive notochord cells (5%)

b. **Features.** Develops in the midline of the neural axis at base of skull or sacrococcygeal area. The physaliferous cells are pathognomonic histologically. Indolent tumor with almost universal tendency for local recurrence. Low grade but eventually fatal after many years because of complications associated with invasion into neural tissues. Treated with surgery and RT. The 5-year survival rate is 50%.

4. **Ewing's sarcoma**

a. **Tissue of origin (incidence).** Unknown; nonmesenchymal elements of bone marrow (15%)

b. **Features.** Affects children 10 to 15 years of age; rare in blacks; highly aggressive; arises in many bones, but especially the femoral diaphysis (see Chapter 18, Ewing's Sarcoma).

5. **Fibrosarcoma of bone**

a. **Tissue of origin (incidence).** Fibrous tissue (2%)

b. **Features.** Affects middle-aged patients in major long bones; develops occasionally in conjunction with an underlying disease (bone infarcts, osteomyelitis, benign giant cell tumor, Paget's disease, after RT). Resembles fibrosarcoma, but osteoid is detected in parts of the lesion. Often high grade, which correlates with metastatic potential and survival (see section C.5).

6. **Fibrous histiocytoma of bone**

a. **Tissue of origin (incidence).** Fibrous and primitive mesenchymal tissue (5%)

b. **Features.** Affects older patients; arises *de novo* or as a complication of Paget's disease. Most common sites are metaphyses of long bones, especially around the knee. In contrast to osteogenic sarcoma, serum alkaline phosphatase levels are normal. Pathologic fracture is often the first manifestation. Aggressive with high rate of dissemination to lungs (also see section C.6)

7. **Malignant giant cell tumor of bone**

a. **Tissue of origin (incidence).** Unknown (less than 1%)

b. **Features.** Affects older patients, particularly women; develops predominantly in long bones, especially around the knee. Aggressive, locally recurrent tumor with low metastatic potential. Local recurrence is determined by the adequacy of surgical removal rather than the histologic grade. The entity is distinct from the tumor that arises from the transformation of a benign giant cell tumor, which occurs in 10% to 20% of cases.

8. **Osteogenic sarcoma**

a. **Tissue of origin (incidence).** Bone (40% to 50%)

b. **Features of classic osteogenic sarcoma.** Affects any age, but the onset is usually between 10 and 20 years; more common in boys and men. Most tumors originate in the metaphysis of long bones, the region of highest growth velocity. Tender, bony masses in the distal femur, proximal tibia, and proximal humerus account for 85% of cases. Nearly always high-grade

c. **Features of low-grade osteogenic sarcoma.** Rare; central lesions can occur.

d. **Features of osteogenic sarcoma of the jaw.** Affects patients between the ages of 20 and 40 years; men are more commonly affected; frequently detected during dental examinations. High- and low-grade varieties are treated with hemimaxillectomy or hemimandibulectomy and reconstruction. Local control can often be a major problem if less than radical surgery is performed.

e. **Features of telangiectatic osteogenic sarcoma.** Affects younger patients; a purely lytic tumor that can be confused with an aneurysmal bone cyst. Highly malignant; metastasizes early

f. **Features of multifocal sclerosing osteogenic sarcoma.** Rare; affects children younger than 10 years of age. Develops multiple simultaneous primary sites in metaphyses; rapidly metastasizes to lung and soft tissues.

g. **Features of periosteal osteogenic sarcoma.** Rare. Affects patients between the ages of 15 and 25 years; arises on external bone surface growing into the overlying soft tissues as an enlarging painless mass with minimal involvement of medullary canal. Histologically confused with chondrosarcomas. More than 50% metastasize (also see section D.9).

9. **Parosteal (juxtacortical) sarcoma**

a. **Tissue of origin (incidence).** Bone surface (less than 2%)

b. **Features.** A distinct clinical entity (see section D.8.g). Onset from 20 to 30 years of age. Characteristic exophytic lesion that is often on the posterior aspect of the distal femur or medial aspect of the proximal humerus. Presents as a fixed painless mass. Usually low grade with an indolent course; rarely involves medullary canal. Infrequently metastasizes; the 5-year survival rate is 80%.

10. **Polyhistiocytoma**

a. **Tissue of origin (incidence).** Mixed (less than 1%).

b. **Features.** Typically affects patients in the first and second decades. Undifferentiated cells resembling Ewing's sarcoma are combined with differentiated mesenchymal elements. Any bone (e.g., ankle, skull) or soft tissue (e.g., orbit, meninges, heart valve) may be involved. Variable grade; the 5-year survival rate is about 50%.

11. **Sarcomas of bone associated with other conditions**

a. **Paget's disease of the bone.** Affects patients older than 60 years of age; the risk for sarcoma is 1000-fold greater than in the general population at this age. Sarcomatous transformation occurs in 0.7% of patients with Paget's disease and accounts for 5% to 14% of osteogenic sarcomas. The histologic form varies among reported series but is usually osteogenic sarcoma, MFH, or fibrosarcoma; chondrosarcoma, giant cell tumor, and other forms occur infrequently. Tends to affect the pelvis and proximal femur; frequently presents as pathologic fracture of the femur. Highly malignant

b. **After high-dose RT.** Sarcoma develops within the irradiated field (bone or adjacent soft tissue structures) about 10 years after treatment. Highly malignant

c. **Familial or bilateral retinoblastoma.** A tumor-suppressor gene (*RE*) has been identified on the 13q chromosome in some patients with retinoblastoma. Patients who have a 13q deletion are at increased risk for later development of osteogenic sarcoma, not only in the irradiated field but also in long bones distant from irradiated sites about 10 to 20 years later. Highly malignant

III. Diagnosis

A. **Symptoms and signs** are summarized in section II.C and section II.D. Patients with STS typically present with a painless, progressive swelling in an extremity;

all such swellings are suspect for malignancy. Head and neck sarcomas manifest as proptosis, masses, or neurologic abnormalities. Retroperitoneal sarcomas present with back pain, lower extremity edema, and abdominal masses. Bone sarcomas usually result in visible enlargement of bone and pathologic fractures.

B. **Biopsy.** An accurate biopsy diagnosis is always essential. An open biopsy that does not adversely affect subsequent resection is the gold standard for diagnosis. Computed tomography (CT)-guided biopsies can often be done and are especially useful in evaluating areas for possible recurrence. Fine-needle aspiration is not usually the initial diagnostic procedure at our institution.

C. **Radiographic studies**
   1. **Plain radiographs** of soft tissues may demonstrate bone involvement. Stippled calcification may be present within the mass. Patients with painful or enlarged bones should have radiographic study of these areas. The following findings are helpful for making the diagnosis of osteogenic sarcoma:
      a. Mixed sclerotic or lytic areas
      b. Periosteal reaction with elevated periosteum forming a triangle (*Codman's triangle*) with bone cortex. Any periosteal elevation in an apparent bone lesion is an indication for biopsy.
      c. Sunray-like spiculation of bones
      d. Onion-skin appearance (an uncommon finding in Ewing's sarcoma)
   2. **CT scans** are most useful for evaluating retroperitoneal or head and neck regions. CT scanning of the extremities appears to be effective in delineating the extent of the tumor.
   3. **Magnetic resonance imaging** (MRI) is comparable to CT scans in defining the relation of the tumor to neurovascular and skeletal structures, but MRI might be better for predicting resectability.
   4. **Arteriography** may be useful in certain cases to plan surgical resection.
   5. **Bone scan** is performed in patients with STS to evaluate periosteal reaction, which may be helpful in planning resection.
   6. **CT of the thorax** is necessary for all patients with sarcoma to detect lung metastases, which may be resected after the primary tumor is managed. An "old calcified granuloma" is an untenable radiologic diagnosis in a young person with sarcoma.
   7. **Serum alkaline phosphatase** levels are elevated in 60% of patients with osteogenic sarcoma and rarely in other bone sarcomas. When elevated at the time of diagnosis, this result is an important tumor marker to evaluate response to therapy.

IV. Staging system and prognostic factors

A. **Staging system.** Tumor grade is the single most important prognostic factor in sarcomas and is incorporated into the G-TNM staging system.
   1. **Grade (G).** All rhabdomyosarcomas and synovial sarcomas are grade 3 by definition.
      G1 Well differentiated
      G2 Moderately differentiated
      G3 Poorly differentiated
      G4 Undifferentiated
   2. **Primary tumor (T)**
      a. **Bone sarcomas**
         T1 Tumor confined within the cortex
         T2 Tumor invades beyond the cortex
      b. **Soft tissue sarcomas (adults)**
         T1 Tumor 5 cm or smaller in greatest dimension
         T2 Tumor larger than 5 cm in greatest dimension
   3. **Regional lymph nodes (N)**
      N0 No regional lymph node metastases
      N1 Regional lymph node metastases present
   4. **Distant metastases (M)**
      M0 No distant metastases
      M1 Distant metastases present

B. **Prognostic factors**
   1. **Histologic grade** (the degree of differentiation, the amount of necrosis, and the number of mitoses per high-power microscopic field) is the single most important prognostic factor, especially for STS. The shortcoming of this system is the less than ideal reproducibility of grading among pathologists.
   2. **Local recurrence** predisposes to further recurrences. The absence of clear surgical margins, with or without postoperative RT, increases the rate of local recurrence in patients with STS but does not affect survival. The development of distant metastases after local recurrence may be either directly related to the recurrence or only a reflection of the more aggressive tumor biology.
   3. **Site of disease.** Half of deaths in patients with STS occur in the 8% of patients with retroperitoneal lesions.
   4. **Tumor-suppressor gene *p53*** is located on the short arm of chromosome 17. Nuclear accumulation of p53 protein appears to be a marker of tumor aggressiveness and may be a useful prognostic factor for STS.

C. **Stage groupings and survival for STS** are shown in Table 17.1.

Table 17.1 Stage groupings and survival for soft tissue sarcoma

D. **Cure.** About 80% of all STSs that recur do so within 2 years. Patients with osteogenic sarcoma who survive 3 years without evidence of disease appear to be cured.

V. Prevention and early detection
The physician must suspect and biopsy all soft tissue masses, *de novo* bony abnormalities, and periosteal elevations with an apparent bone lesion.

VI. Management

A. **Treatment of STS.** Wide, adequate surgical resection with pathologically proven clear margins is the most effective therapeutic approach. Soft- part resection can be accomplished without amputation in at least 80% of patients.
   1. **Extent of resection.** Surgical exploration of the tumor demonstrates apparent encapsulation; this is actually a *pseudocapsule*. Local recurrences develop in 80% of patients treated only by enucleation of the pseudocapsule. The surgeon must remove the localized sarcoma *within a complete envelope of normal tissue*; normal structures must be sacrificed if necessary to encompass the tumor. The biopsy site, skin, and most of the subcutaneous tissue, fibrous tissue, and (often) the adjacent muscle group should be included in the resection.
   2. **Regional lymph node dissection.** Only angiosarcomas and synovial sarcomas are commonly treated with regional node dissection because of the frequency of nodal metastasis with these tumors. Node dissection is usually not performed for other STSs.
   3. **RT** is administered to the tumor bed before or after surgery (depending on the treatment center) for high-grade or large STSs to improve local control rates.
      a. **Microscopically positive surgical margins** increase the risk for local failure. The presence of microscopically positive surgical margins or the occurrence of local failure, however, does not affect overall survival. Adjuvant RT may be most important when achieving clear margins would require amputation or significant functional compromise of the extremity.
      b. **For lesions distal to the elbow or knee,** postoperative RT raised the ability rate to perform limb-salvage surgery to 95% and reduced the local recurrence rate to 10%. These results were the same as if radical amputation or muscle group excision were performed.
   4. **Treatment of STS for specific presentations**
      a. **Grade 1 and small grade 2 lesions** are treated with surgery alone; the relapse rate is less than 10% with surgery alone. Adjuvant RT is not required.
      b. **Grade 2 lesions that are proximal and large** are treated with surgery and postoperative RT.
      c. **Grade 3 or 4 lesions.** RT is advisable before or after surgery.
      d. **Head and neck STS.** Appropriate therapy is not defined. Wide surgical excision and RT before or after surgery is advisable.
      e. **Childhood rhabdomyosarcoma** is treated intensively with chemotherapy, RT, and surgery (see Chapter 18, Rhabdomyosarcoma).
      f. **Retroperitoneal STS** (mostly leiomyosarcomas and liposarcomas) must be radically extirpated. Complete resection is possible in about 65% of patients and strongly predicts outcome. Median survival with complete resection is 80 months for low-grade STS and 20 months for high-grade disease. Median survival with incomplete resection for all STSs is only 24 months. The survival rate is not affected by tumor type or size.

5. **Adjuvant chemotherapy** is standard practice in the management of rhabdomyosarcoma in children. Adjuvant chemotherapy for STS in adults with high-grade tumors remains controversial.

A metaanalysis of randomized trials of adjuvant doxorubicin for STS demonstrated a reduction in local and distant recurrence rates and a trend toward improved overall survival; this survival benefit was most clear for those with extremity sarcomas. More recent trials using the combination of ifosfamide with an anthracycline (either epirubicin or doxorubicin) showed an advantage in both disease-free survival and overall survival for those receiving chemotherapy. Additionally, preoperative treatment with both RT and chemotherapy that includes ifosfamide has shown higher rates of complete pathologic response at the time of surgery than prior preoperative regimens using either RT alone or RT with intravenous or intraarterial doxorubicin.

Useful chemotherapy regimens are shown in Table 17.2. At our institutions, patients with STS who are candidates for adjuvant chemotherapy typically are given two cycles of ifosfamide plus mesna and one cycle of doxorubicin plus cisplatin both before and after RT to the affected part.

Table 17.2 Combination chemotherapy regimens for sarcoma

B. **Treatment of osteogenic sarcomas** results in a 65% to 80% 10-year, disease-free survival. Relapse after 3 years of disease-free survival is unusual.
   1. **Limb-salvage surgery** is now the standard treatment for most patients with osteogenic sarcomas of the extremities, where nearly 90% of these tumors originate. Only occasional patients require amputation. The widespread, successful use of limb-salvage therapy has been made possible by the following advances:
      a. **Significant progress in the development of modern prostheses** that are available immediately after surgery. For example, young children who would have had unacceptable leg-length discrepancy with limb-salvage procedures can now be given a prosthesis that can be lengthened while the patient grows ("expandable prosthesis").
      b. **Major advances in orthopedic surgical techniques.** Furthermore, the historical fear of "skip metastases" (within the same bone of involvement) has proved excessive; the occurrence rate of "skip metastases" appears to be less than 10%.
      c. **The use of preoperative (neoadjuvant) chemotherapy**
         1. Preoperative chemotherapy can result in enough tumor shrinkage to permit the use of prostheses and can allow time for fabrication of the prosthesis.
         2. Preoperative chemotherapy provides an *in vivc* drug trial to determine the drug sensitivity of an individual tumor and to customize postoperative chemotherapy regimens. Patients who respond to preoperative chemotherapy are destined to do well, and vice versa.
   2. **Amputation** provides definitive surgical treatment in patients in whom a limb-sparing resection is not a prudent option. The procedures include hip disarticulation, hemipelvectomy, and forequarter resection. Although these procedures were once used for technically difficult resections and proximal tumors, most sarcomas of the shoulder girdle or knee can now be resected rather than amputated with the extremity.
   3. **Adjuvant RT** is usually not necessary for osteogenic sarcomas of the extremities. Tumors of the jaw, facial bones, and axial skeleton require combined RT and limited surgery.
   4. **Preoperative (neoadjuvant) chemotherapy** provides a response rate of 60% to 85% with combination regimens, including high-dose methotrexate (HDMTX) with leucovorin rescue. Response to preoperative chemotherapy is the single most important prognostic variable in predicting relapse-free survival.
   5. **Adjuvant chemotherapy** is standard practice in the management of all patients with osteogenic sarcoma. Prospective, randomized, controlled studies demonstrated improvement in relapse-free survival for patients treated adjuvantly with chemotherapy compared with those treated with surgery alone (17% versus 65% to 85% at 2 years). A steep dose–response curve has been repeatedly observed for chemotherapy of sarcomas: the higher the dose, the higher the response rate.
      a. **HDMTX** with leucovorin rescue (given with attention to blood methotrexate levels and urine alkalinization) is clearly the most effective drug treatment for this disease; doses of 12 g/m^2 are associated with a 50% response rate. Patients who responded to this therapy have continued to do well.
      b. **Other single-agent chemotherapies** for osteogenic sarcoma have produced the following response rates: doxorubicin (90 mg/m^2), 30%; ifosfamide (6 to 10 g/m^2 given over several days), 20% to 30%; and cisplatin (120 mg/m^2), 20%. Ifosfamide given in doses of 14 to 18 g/m^2 (over several days) is reported to be associated with a 65% response rate.
      c. **Combination chemotherapy.** Doxorubicin, cisplatin, and etoposide are being given in combination with HDMTX and with hematopoietic growth factor support in an attempt to improve the already impressive cure rate.
C. **Treatment of other bone sarcomas**
   1. **Chondrosarcoma.** Complete surgical excision with limb-sparing procedures where applicable. Adjuvant RT or chemotherapy is not helpful, but may be tried in cases of dedifferentiated chondrosarcoma.
   2. **MFH of bone.** Radical surgical resection. Because of the poor prognosis, adjuvant chemotherapy is justified, but its efficacy has not been proved.
   3. **Fibrosarcoma of bone.** Surgery alone
   4. **Chordoma.** The first surgical procedure has the best chance for cure. Inadequate surgery results in local recurrence and ultimate death. RT is also used adjuvantly with disappointing results. Heavy-particle irradiation appears promising for improving local control.
   5. **Ewing's sarcoma** is discussed in Chapter 18, Ewing's Sarcoma.
   6. **Giant cell tumor of bone.** Surgical removal cures 90% of these tumors when benign. Amputation is reserved for massive recurrence or malignant transformation.
   7. **Cryosurgery,** using liquid nitrogen after curettage of a tumor cavity, can decrease local recurrence for aggressive benign bone tumors and low-grade sarcomas.
D. **Treatment of metastatic or advanced sarcomas**
   1. **Surgery**
      a. **Painful extremities.** Removal of a painful, functionless extremity that is the site of an eroding, necrotic tumor may be palliative, even in patients with metastatic disease. Surgery may be attempted after chemotherapy and RT have failed to control progressive disease.
      b. **Resection of pulmonary metastasis** is a reasonable measure in selected patients with resectable pulmonary metastasis and no other evidence of disease (see Chapter 29, section II). The best results of this approach are observed in patients with sarcomas, as compared with patients with carcinomas or melanomas.
   2. **RT**
      a. **Palliation.** The heterogeneity of sarcomas is reflected in their variable responses to RT. This group of tumors is only moderately sensitive to RT at doses that can be tolerated by most patients. Liposarcoma and the embryonal variety of rhabdomyosarcoma are the only STSs in which an objective response to RT is the rule. Objective tumor regression occurs in less than half of patients with other types of sarcomas.
      b. **Inoperable disease.** RT for patients who have inoperable lesions or who refuse surgery is of marginal value.
      c. **Local hyperthermia** used with chemotherapy or RT is an experimental modality that occasionally induces tumor responses.
   3. **Chemotherapy**
      a. **Effective agents.** The combination of vincristine, actinomycin D, and cyclophosphamide in children with rhabdomyosarcoma produces a response rate of 90% even with disseminated disease. Responses to these agents in other sarcomas are usually minimal and brief.

   The response rates of STS to doxorubicin, ifosfamide, or dacarbazine used as single agents are 30%, 30%, and 15%, respectively. Dacarbazine is the only effective agent in the treatment of leiomyosarcoma, but that advantage is associated with minor improvement. Other drugs have minor activity (15% response rates or lower) in the treatment of STS. See section B.5 for the activity of single agents in osteogenic sarcoma.

      b. **Combination chemotherapy regimens** (e.g., CyVADic, as defined in Table 17.2) appear to provide no advantage over single agents for palliation or survival but are more toxic. Pulmonary and soft tissue metastases are more responsive than liver and bone metastases. Intraarterial administration is not superior to intravenous administration.
      c. **Dose intensity** probably correlates with response rates in the treatment of sarcomas. Currently used combination chemotherapy regimens for sarcoma are shown in Table 17.2. High-dose combinations of ifosfamide (with mesna uroprotection), doxorubicin (Adriamycin), and dacarbazine (MAID regimen) results in a higher response rate (45%) than single agents but at the expense of substantial myelosuppression. Very high doses of ifosfamide (14 to 18 g/m^2) given over several days with precautions for the development of renal tubular acidosis reportedly give much better responses to STSs that were previously considered to be resistant to chemotherapy (e.g., synovial sarcoma). These dose-intensive regimens must be given with caution because of

their substantial toxicity and the lack of corroborating evidence of efficacy.

Suggested Reading

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Chapter 18 Cancers in Childhood

Carole G. H. Hurvitz

Incidence, Leukemia, and Lymphoma

I. Incidence and overview. Although cancer is the second leading cause of death in children, it is still relatively uncommon. The incidence of cancer is increasing, however. Fortunately, with modern aggressive multidisciplinary therapy, most children with cancer survive.

    A. **Cooperative groups.** The treatment of children with cancer is highly specialized. Whenever possible, patients younger than 18 years of age should be treated in specialized centers related to one of the major pediatric cooperative groups, such as the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG). More than 90% of children younger than 10 years of age are treated in such centers, and their mortality has decreased proportionally. Only about 30% of teenagers are enrolled in such centers, however, and the mortality rates in this group have not shown the same improvement.

    B. **Incidence.** Leukemia and lymphoma make up almost half the cases of malignancy in childhood, followed by central nervous system (CNS) tumors. The mortality rate for CNS cancers now exceeds that for acute lymphocytic leukemia. The incidence of malignant tumors in children in the United States is as follows (cases per 1 million population):

Leukemia—42	Neuroblastoma—8	Bone tumors—6
CNS tumors—24	Wilms' tumor—8	Retinoblastoma—3
Lymphomas—13	Soft tissue sarcomas—8	

II. Acute leukemia (see Chapter 25)

    A. **Pathology.** Acute lymphoblastic leukemia (ALL) accounts for 80% to 85% of leukemias in childhood. Acute myelogenous leukemia (AML) accounts for 15% and chronic myelogenous leukemia for 5% of cases.

    In ALL, 25% of cases are T-cell, 5% are B-cell, and the remainder are precursor B-cell leukemias. Of the precursor B-cell leukemias, 70% possess the common acute lymphoblastic leukemia antigen (CALLA, CD-10). They are usually also terminal deoxynucleotidyl transferase–positive. Almost all are also CD-19 positive.

    B. **Treatment** of acute leukemias in childhood involves induction of remission, prophylaxis to the CNS, and maintenance therapy. Standard treatment for ALL leads to long-term remission in more than 70% of cases. Induction therapy employs vincristine, prednisone, and l-asparaginase. Intensification therapy includes CNS prophylaxis. During maintenance therapy, oral mercaptopurine is given daily and methotrexate weekly for 2 to 3 years. Often one or two cycles of a reinduction regimen are added in ALL.

    Certain prognostic factors at diagnosis affect the outlook of children with ALL, and their treatment is modified accordingly. Children with poorer prognostic features require more intensive treatment than standard therapy.

        1. **Average risk factors** include initial white blood cell count of less than 50,000/μL; age, 1 to 9 years; non–T-cell, non–B-cell leukemia; L1 morphology; hyperploidy; probably CALLA positivity; lack of organomegaly; and low bone marrow blasts on day 7 of induction therapy.

        2. **Poor prognostic factors** include WBC greater than 50,000/μL, age more than 10 years, massive organomegaly, lymphoma-like features, CNS involvement at diagnosis, mediastinal mass, and certain chromosomal translocations. Failure to achieve remission by day 14 or 28 is unfavorable.

        3. **AML** requires intensive therapy, often followed by allogeneic bone marrow transplantation (BMT), if possible. BMT (allogenic, autologous, or matched unrelated) is also often recommended for patients with ALL and AML who relapse.

    C. **Survival.** The 5-year survival rate is more than 80% in children with "good-prognosis" ALL following standard therapy. Even children with poorer risk factors who receive intensive therapy have an overall long-term survival of at least 70%. Sites of relapse include the CNS, testes, and bone marrow. The risk for relapse after 2 years of therapy is very low. The 5-year survival rate with the best available regimens in children with AML is about 50%.

III. Lymphoma

A. **Non-Hodgkin lymphoma** (see Chapter 21). In pediatrics, lymphomas can be considered to be lymphoblastic or nonlymphoblastic and localized or nonlocalized. Lymphoblastic lymphomas are usually T cell and, when nonlocalized, may be the same entity as T-cell leukemia; these illnesses are usually treated in the same way. Nonlymphoblastic lymphomas are usually B cell and are frequently Burkitt (or Burkitt-like) lymphoma.

Different combination chemotherapeutic regimens are necessary for the subtypes of lymphoma. Localized lymphomas respond very well to chemotherapy even when bulky and have a cure rate of more than 90%. The prognosis for disseminated T-cell lymphomas is the same as for T-cell ALL. The outlook for disseminated nonlymphoblastic or B-cell lymphoma is about 50%.

B. **Hodgkin lymphoma** (see Chapter 21). There is no consensus on the treatment of Hodgkin lymphoma in children, with the exception of stage IV disease, which is primarily treated with chemotherapy. Chemotherapy is used for all stages of disease. Most physicians no longer perform staging laparotomy, and splenectomy is contraindicated in young children because of fatal infectious complications and increased risk for leukemia. The alternation of the MOPP and ABVD regimens (defined in Chapter 21 and Appendix A-1) is frequently recommended rather than either regimen alone. In children, local-field rather than extended-field radiation is preferred in an effort to reduce long-term side effects, such as growth retardation and second cancers, especially breast cancer in girls.

Brain Tumors

The diagnosis and management of neurologic malignancies are discussed in Chapter 14.

I. Epidemiology. Brain tumors in children are associated with certain underlying diseases, including neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau angiomatosis. Family clusters of CNS tumors have occasionally been reported.

II. Pathology and natural history

A. **Pathology.** Most CNS neoplasms in children are primary tumors of the brain; the single exception is meningeal metastases, which are common with leukemia and lymphoma. Astrocytomas are the most frequent type (30% of all cases). Medulloblastomas account for 25% of cases; ependymomas, 9%; and glioblastomas, 9%.
B. **Sites of disease.** Brain tumors in children tend to occur along the central neural axis (i.e., near the third or fourth ventricle or along the brain stem). Most brain tumors that occur during the first year of life are supratentorial. In patients between 2 and 12 years of age, 85% are infratentorial. In patients older than 12 years of age, the relative incidence of supratentorial tumors increases.

III. Symptoms and signs

A. **Symptoms.** The most common symptoms include headaches, irritability, vomiting, and gait abnormalities. Morning headaches are most characteristic, but drowsiness and abnormal behavior are also common. Symptoms may be intermittent, particularly in very young children who have open fontanelles.
B. **Physical findings** include enlarged or bulging fontanelles in very young children and cerebellar abnormalities, papilledema, and sixth cranial nerve abnormalities in older children.

IV. Treatment and survival
Survival rates for patients with low-grade astrocytomas are high if the tumor can be surgically removed (more than 90% at 5 years) and low if the tumor is high grade (less than 10% at 5 years). Survival for medulloblastoma depends on both local recurrence (less than 25% with radiation therapy [RT] and surgery) and spinal metastases (about 35% incidence without prophylactic spinal irradiation); this tumor is invariably recurrent when treated with surgery alone.

Chemotherapy is now being used more frequently in children with brain tumors in an attempt to improve survival and to reduce the use of radiation, which has devastating effects in young children. RT is being deferred in children younger than 3 years of age.

Neuroblastoma

I. Epidemiology and etiology Neuroblastoma is the most common congenital tumor and the most common tumor to occur during the first year of life. It rarely occurs in patients more than 14 years of age. About 40% occur in the first year of life, 35% from 1 to 2 years age, and 25% after 2 years of age. Rarely, family clusters are reported.

II. Pathology and natural history Neuroblastoma has the highest incidence of spontaneous regression of any tumor in humans.

A. **Histology.** Neuroblastoma closely resembles embryonic sympathetic ganglia. The tumors partially differentiate into rosettes or pseudorosettes, mature ganglion cells, or immature chromaffin cells. Although histologically similar to ganglioneuromas and pheochromocytomas, neuroblastomas are clearly distinctive. Electron microscopy shows typical dendritic processes that contain granules with dense bodies, probably representing cytoplasmic catecholamines. The most primitive histologic type of neuroblastoma is composed of small round cells with scant cytoplasm. The ganglioneuroma is composed of larger, more mature ganglion cells with more abundant cytoplasm.

Homogeneously staining regions and double minutes chromosomes seen in poor-prognosis neuroblastomas represent amplified *N-myc* segments. Amplification of *N-myc* is an intrinsic property of poor-prognosis tumors and can be rapidly detected by fluorescent *in situ* hybridization (FISH) concordant with Southern blot analysis.

B. **Sites.** The most common primary site is the adrenal gland (40% of cases); a tumor of the adrenal gland produces an abdominal mass. Involvement of posterior sympathetic ganglion cells results in both intrathoracic and intraabdominal masses, the so-called "dumb-bell tumor" that causes compression of the spinal cord.
C. **Mode of spread.** Most cases of neuroblastoma present with widespread metastatic disease. The most common metastatic sites include bone, bone marrow, liver, skin, and lymph nodes.

III. Diagnosis

A. **Symptoms.** Abdominal pain and distention, bone pain, anorexia, malaise, fever, and diarrhea.
B. **Physical findings.** Hepatomegaly, hypertension, orbital mass and ecchymosis, subcutaneous nodules (particularly in infancy), intra-abdominal mass, and Horner's syndrome.
C. **Laboratory studies**
   1. Complete blood count (CBC), serum chemistry panel
   2. Urine for total catecholamines and metabolites, including vanillylmandelic acid (VMA) and homovanillic acid (HVA)
   3. Chest and abdominal radiographs
   4. Computed tomography (CT) scan of the abdomen or thorax (possibly preceded by abdominal and renal ultrasound)
   5. Bone scan
   6. Bone marrow aspiration and biopsy to look for tumor cells
   7. ^{131}I-MIBG, which is specific for neuroblastoma and pheochromocytoma. See Chapter 2, section II.G.
   8. Examination of tumor for amplification of the *N-myc* gene

IV. Staging system and prognostic factors

A. **Staging system**

StageExtent of disease

I   Localized disease surgically removed *in toto*
II Regional disease, unilateral
III Tumor crossing the midline
IV Metastatic disease
IVS Stage I or II primary tumor with metastases to liver, skin, and/or bone marrow without radiographic evidence of bony involvement usually in very young infants

B. **Survival and prognostic factors.** The prognosis for neuroblastoma is closely related to the age of the patient and stage of disease.
1. **Age.** Patients with congenital tumors have the most favorable prognosis, even with widespread disease, and they also have the highest rate of spontaneous regression without treatment. Patients who are between 1 and 5 years of age do worse than patients younger than 1 year or older than 5 years of age.
2. **Stage.** Patients with advanced disease, except for stage IVS, have a poor survival rate. The overall 2-year survival for neuroblastoma is greater than 80% for stages I and II and less than 30% for stage IV. Stage IVS has a 90% survival rate. Patients with stage III and IV disease who have amplification of the *N-myc* gene do worse.
3. **The urinary VMA-to-HVA ratio** is an indirect measure of dopamine hydroxylase. Absence of this enzyme may convey a poorer prognosis (i.e., if the VMA-to-HVA ratio is less than 1.5) and may cast doubt on the diagnosis of neuroblastoma.

V. Management

A. **Surgery.** Localized disease is managed primarily by surgical resection. For metastatic disease, biopsy or excision of the primary tumor is important for *N-myc* gene assessment. Complete resection is usually delayed until after chemotherapy is administered but may be done at the time of diagnosis.
B. **RT** is used for bulky tumor in combination with chemotherapy and as part of the conditioning regimen for BMT.
C. **Chemotherapy**
1. **Residual localized or advanced disease.** Aggressive multimodal chemotherapy with doxorubicin (Adriamycin), cyclophosphamide, etoposide, and cisplatin, combined with surgical resection and BMT, has improved survival in stage III and IV disease.
2. **Congenital disease.** In patients with congenital disease, specifically for stage IVS, chemotherapy is not used unless the tumor causes significant symptoms.
D. **BMT** (usually autologous) after intensive radiation and chemotherapy appears to improve the outlook for patients with advanced disease.

Wilms' Tumor (Nephroblastoma)

I. Epidemiology and etiology

A. **Incidence.** Wilms' tumor most frequently affects children between 1 and 5 years of age, and rarely those older than 8 years of age. The incidence is about 7 per 1 million in the childhood age group. Familial clusters have been described, particularly in patients with bilateral Wilms' tumors.
B. **Associated abnormalities.** Wilms' tumor has been associated with certain congenital anomalies, including genitourinary anomalies, aniridia (absence of an iris), and hemihypertrophy (Beckwith-Wiedemann syndrome). Deletion of the short arm of chromosome 11 has been associated with a syndrome of Wilms' tumor, mental retardation, microcephaly, bilateral aniridia, and ambiguous genitalia.

II. Pathology and natural history

A. **Histopathologic classification** most accurately predicts the prognosis.
1. **Wilms' tumor.** Tumors that display mature elements and few anaplastic cells have the most favorable prognosis and are termed *favorable histology.* *Unfavorable histology* concerns tumors that have focal or diffuse anaplasia, rhabdoid sarcoma, or clear cell sarcoma. Unfavorable histology accounts for 12% of Wilms' tumors but almost 90% of deaths.
2. **Congenital mesoblastic nephroma** is a rare benign tumor that is common in infancy (the most common renal neoplasm during the first month of life) and can be histologically confused with Wilms' tumor. This tumor consists of spindle-shaped, immature connective tissue cells that have a distinctive fibroblastic appearance with only minimal nuclear pleomorphism and mitoses.
B. **Sites.** About 7% of Wilms' tumors are bilateral at the time of diagnosis.
C. **Mode of spread.** The lungs are the principal sites of metastases; liver and lymph nodes are the next most common sites. Bone marrow metastases are extremely rare and tend to be associated with clear cell subtypes of sarcomatous Wilms' tumor. CNS metastases are extremely rare.
D. **Paraneoplastic syndromes.** Wilms' tumors have been associated with increased erythropoietin (erythrocytosis) and with increased renin (hypertension).

III. Diagnosis

A. **Symptoms.** The most common symptoms include enlarged abdomen, abdominal pain, and painless hematuria.
B. **Physical findings.** A palpable abdominal mass is the most common finding. Hypertension is sometimes present.
C. **Laboratory studies**
1. CBC, serum chemistries, urinalysis, chest radiograph
2. Plane radiographs of the abdomen
3. CT or, preferably, magnetic resonance imaging (MRI) scan of abdomen

IV. Staging and prognostic factors

A. **Staging system**
StageExtent of disease

I   Well-encapsulated tumor that is surgically removed in its entirety
II Extension of tumor beyond renal capsule by local infiltration with extension along the renal vein, involvement of paraaortic nodes, and no residual macroscopic disease
III Macroscopic residual disease or peritoneal metastases or contamination during nephrectomy
IV Distant metastases, particularly to lung
V   Bilateral disease

B. **Survival and prognostic factors.** The most important prognostic factors are the histopathologic classification and the clinical and surgical staging. Age at diagnosis is of minor importance, although younger patients appear to have a slightly better outcome. The overall 2-year survival rate is greater than 95% for stage I, II, and III disease, with favorable histology, and about 50% for stage IV disease.

V. Management

A. **Surgery.** All patients must have surgery for both staging and removal of as much tumor as possible. A transabdominal incision is mandatory to examine the vessels of the renal pedicle and the noninvolved kidney. The tumor bed and any residual tumor should be outlined with metallic clips at the time of surgery.
B. **RT** is useful for treating stage III disease and metastatic disease to bone, liver, or lung.
C. **Chemotherapy.** Multiple courses of combination chemotherapy are the preferred treatment. The major active chemotherapeutic agents are actinomycin D, vincristine, and doxorubicin. Cyclophosphamide is an effective second-line drug. Cisplatin is active against Wilms' tumor and is being used in investigational protocols. The National Wilms' Tumor Study is ongoing, and several chemotherapeutic regimens are under study. The youngest patients are particularly susceptible to serious toxic effects from chemotherapy, particularly hematologic, and drug dosages should be reduced 50% for patients younger than 15 months of age.
D. **Treatment according to stage of disease.** Surgery and chemotherapy are used for all stages of disease.
1. **Stage I.** RT is not necessary.
2. **Stages II and III.** RT is not needed for stage II favorable histology but is used for unfavorable histology and stage III.
3. **Stage IV or recurrent disease.** If possible, surgery can be used. Chemotherapeutic agents can be restarted if they were discontinued, or changed if relapse occurred during treatment. RT is useful for metastatic disease. Intensive chemotherapy with BMT is being evaluated.
4. **Stage V.** Bilateral Wilms' tumor necessitates a special effort to preserve as much renal tissue as possible. Initially, biopsy is done, and then chemotherapy

followed by judicious resection of remaining tumor. Bilateral nephrectomy followed by chemotherapy, and renal transplantation is a last resort. The 3-year survival rate is 75% for these patients.

Rhabdomyosarcoma

I. Epidemiology and etiology Rhabdomyosarcoma is the most common soft tissue sarcoma in children; there are about 8 cases per million population. Suggestive evidence of C-particle viruses in these tumors has been observed with electron microscopy, but the viruses have not been isolated.

II. Pathology and natural history

    A. **Histology.** Four major histologic categories of this striated muscle neoplasm have been described: embryonal (including sarcoma botryoid), alveolar, pleomorphic, and mixed. Z bands can be seen with electron microscopy. Rhabdomyoblasts have acidophilic cytoplasm, which is often periodic acid– Schiff stain (PAS) positive.

    B. **Sites.** The head and neck are involved in 35% of cases, the trunk and extremities in 35%, and the genitourinary tract in 30%.

    C. **Mode of spread.** These tumors have a great tendency to recur locally and to metastasize early through the venous and lymphatic systems. Any organ may be involved with metastases, but the lungs are most frequently affected.

III. Diagnosis

    A. **Symptoms.** The most common presenting symptom is a painless, enlarging mass. Hematuria and urinary tract obstruction is seen with primary tumors of the genitourinary tract. The painless swelling is often noticed after minor trauma that calls attention to the enlarging mass.

    B. **Physical findings** include mass lesions, urinary tract obstruction, and a "cluster of grapes" protruding through the vaginal canal (sarcoma botryoid). Exophthalmos or proptosis occurs with head and neck primaries.

    C. **Laboratory studies**
        1. CBC, liver function tests (LFTs)
        2. Plain radiographs and MRI or CT scans of involved areas
        3. Bone marrow aspiration and biopsy
        4. Gallium (and perhaps thallium) scans

IV. Staging system and prognostic factors

    A. **Intergroup Rhabdomyosarcoma Study Staging System**

Stage	Extent of disease
I	Localized disease, completely resected
II	Localized disease, microscopic residual tumor
IIA	Grossly resected disease with microscopic residual tumor and negative lymph nodes
IIB	Regional disease, completely resected, with no microscopic residual disease
IIC	Regional disease with positive lymph nodes, grossly resected
III	Incomplete resection or biopsy with residual gross disease
IV	Distant metastases

    B. **Survival and prognostic factors.** Survival is closely correlated with stage. The 5-year survival rate with the standard VAC chemotherapy regimen (vincristine, actinomycin D, and cyclophosphamide) is almost 100% for stage I and II disease, greater than 60% for stage III disease, and about 40% for stage IV disease. The overall survival rate is 70%.

V. Management. The treatment of rhabdomyosarcoma should be aggressive, even with localized disease. Surgery, RT, and chemotherapy should be used for all cases with any residual disease.

    A. **Surgery** should include total excision, if possible, but radical surgery is unnecessary and unwarranted. Lymph node dissection is useful for staging in extremity or genitourinary tract tumors.

    B. **RT** usually consists of 5000 to 6000 cGy given over 5 to 6 weeks to the primary tumor site with wide ports to include margins of all dissected tumors.

    C. **Chemotherapy.** The VAC regimen is most commonly given. Studies are comparing doxorubicin, etoposide, and ifosfamide to VAC for advanced disease. Chemotherapy is necessary for patients with the following indications:
        1. Adjuvantly with stage I disease
        2. With RT for stage II disease
        3. To shrink the primary tumor either before or after surgery for stage III and IV disease, and continued as adjunctive therapy

Ewing's Sarcoma and Primitive Neuroectodermal Tumor (Ewing's Family Tumors)

I. Epidemiology and etiology The incidence of Ewing's sarcoma and primitive neuroectodermal tumor (PNET) is about 1.5 cases per 1 million population. The disease is very rare among black children. Seventy percent of patients are younger than 20 years of age. The peak incidence is at 11 to 12 years of age for girls and 15 to 16 years of age for boys. The male-to-female incidence ratio is 2:1. The associated chromosomal abnormality is a balanced translocation of chromosome 22.

II. Pathology and natural history

    A. **Histology.** Ewing's sarcoma is a small cell tumor of bone characterized by islands of anaplastic small round cells. Undifferentiated tumors are Ewing Sarcoma; those with neural elements are PNETs.

    B. **Sites of disease.** These tumors occur predominantly in the midshaft of the humerus, femur, tibia, or fibula, but they also occur in the ribs, scapula, pelvis, or extraosseous sites. PNETs in the chest are called *Askin's tumors.*

    C. **Mode of spread.** At the time of diagnosis, 20% to 30% of these tumors have metastasized. Most metastases are to the lung. Metastases to other bones or lymph nodes can also occur. CNS metastases, particularly meningeal, have been reported but are rare.

III. Diagnosis

    A. **Symptoms.** Pain that is followed by localized swelling is the most frequent manifestation.

    B. **Physical findings** include tenderness and a palpable mass over the tumor site.

    C. **Preliminary laboratory studies** may show an elevated erythrocyte sedimentation rate and lytic bone lesions on radiograph (frequently, the lesions have an "onion-skin appearance"). A chest radiograph and CT should be obtained in all patients.

    D. **Special diagnostic studies**
        1. Bone scan
        2. MRI or CT scans of involved sites
        3. Gallium scan

IV. Staging and prognostic factors

    A. **Staging.** The two major stages for Ewing's sarcoma and PNET are simply:
        1. Localized disease

2. Metastatic disease
B. **Survival and prognostic factors.** Patients with a primary tumor in a central location have a higher incidence of local recurrence and a generally poorer prognosis than do patients with tumors in other primary sites. The prognosis for patients with metastatic disease at time of diagnosis remains grave; bone metastases have the worst prognosis. High white blood cell count and fever at diagnosis also are associated with a poor prognosis. The disease-free survival depends on the response to chemotherapy.

V. Management

A. **Treatment according to stage of disease**
1. **Localized disease.** All patients with localized disease should receive intensive chemotherapy followed by complete surgical resection if possible. If resection is not feasible or complete, RT is given. RT is not needed if the tumor can be removed with more than a 1-cm margin.
2. **Metastatic disease** is treated with intensive chemotherapy followed by surgical resection (if possible) or RT.
B. **Chemotherapy** involves multiple drugs given in multiple cycles. The most active agents include vincristine, actinomycin D, high-dose cyclophosphamide, doxorubicin, ifosfamide, and etoposide; combinations of these drugs are effective. Carmustine, methotrexate, and bleomycin also have activity against this disease and are useful in combination with the more active agents. The optimal combination of agents is controversial. High-dose chemotherapy with peripheral stem cell transplantation is being studied for metastatic disease.
C. **Surgery.** Control of the primary tumor site is essential. Surgery is used in selected patients with localized disease and in patients with bulky metastatic disease. The total removal of tumor is not necessary in instances in which severe disabilities could result. Concerted efforts at limb preservation should be made.
D. **RT** is aimed at eradicating all disease while preserving limb function. The optimal volume of bone to be irradiated has not been determined.
1. **Nonbulky lesions.** When combined with chemotherapy, delivering 4000 to 5000 cGy of RT to the entire bone with additional 1000 to 1500 cGy coned down to the involved site yields good results.
2. **Leg-length discrepancies.** In the past, when the probabilities for leg-length discrepancies were excessive (e.g., for younger children with lesions near the knee), patients underwent primary amputation plus chemotherapy. Expandable endoprosthetic reconstruction now makes surgical resection an option for younger children. This regimen usually results in better extremity function than limbs treated with orthovoltage irradiation. Limb-salvage procedures using chemotherapy are also frequently performed when appropriate.
3. **Pelvic primaries.** Moderate doses of RT (4000 cGy) with limited surgery are used for pelvic primary tumors because excessive morbidity is associated with large doses of radiation delivered to bowel and bladder. Chemotherapy must be used as well.

Retinoblastoma

I. Epidemiology and etiology

A. **Incidence.** Retinoblastoma occurs about in 3 per 1 million children annually. The average age of patients is 18 months, and more than 90% are younger than 5 years old. The incidence in Asians is four times that in whites. Patients have a high risk for other neoplasms, particularly radiation-induced osteosarcomas that arise in treatment portals.
B. **Familial retinoblastoma.** About 40% of cases are "hereditary." These have bilateral multifocal involvement, early age at diagnosis, secondary tumors, and a positive family history. Siblings have a 10% to 20% chance of developing retinoblastoma if the affected child has bilateral disease and about 1% if unilateral. The offspring of a patient who survived bilateral retinoblastoma have about a 50% chance of developing the disease.

II. Pathology and natural history

A. **Histology.** Retinoblastoma is a malignant neuroectodermal tumor. It appears histologically as undifferentiated small cells with deeply stained nuclei and scant cytoplasm. Large cells are sometimes seen forming pseudorosettes, particularly in bone marrow aspirates.
B. **Mode of spread.** Multiple foci of tumor in the retina are typical at the outset. Most patients die from CNS extension through the optic nerve or widespread hematogenous metastases.

III. Diagnosis

A. **Symptoms.** The disease typically presents with a "cat's eye" (white pupil or leukokoria). A squint or strabismus is occasionally noted. Orbital inflammation or proptosis rarely occurs.
B. **Physical findings** are usually limited to the eye, but patients must have a complete neurologic examination. Ophthalmologic examination under anesthesia is essential for infants and small children, for both those with symptoms and those at high risk for developing the disease. Two pathognomonic features are as follows:
1. The typical pattern of fluffy calcifications in the retinas
2. The presence of vitreous seeding by tumor cells
C. **Preliminary laboratory studies**
1. CBC, LFTs
2. MRI or CT scans of head and orbit (both scans performed with contrast)
D. **Special diagnostic studies**
1. Lumbar puncture with cerebrospinal fluid by cytocentrifuge
2. Bone marrow aspiration and biopsy
3. Serum levels of CEA and a-fetoprotein, which are frequently elevated in this disease
4. Urinary catecholamine levels, which are infrequently elevated

IV. Staging system and prognostic factors

A. **Staging system.** The Reese-Ellsworth classification is most frequently used

Group	Extent of disease
I	Solitary lesion or multiple tumors less than 4 disc diameters in size at or behind the midplane of the eye
II	Solitary lesions or multiple tumors 4–10 disc diameters at or behind the midplane of the eye
III	Any lesions anterior to the midplane, or solitary lesions larger than 10 disc diameters and behind the equator
IV	Multiple tumors, some larger than 10 disc diameters, or any esion extending anteriorly to the ora serrata (junction of the retina and ciliary body)
V	Massive tumor that involves more than half the retina, or presence of vitreous seeding or optic nerve involvement
VI	Residual orbital disease, optic nerve involvement and extrascleral extension

B. **Survival and prognostic factors.** The prognosis is related to both stage and the interval between discovery of clinical signs and the initiation of treatment. The survival rate is virtually 100% for groups I to IV and 83% to 87% for group V. After disease has invaded the orbit, the mortality rate is virtually 100% despite aggressive chemotherapy.

V. Management

A. **Surgery** is the primary modality of treatment. Prompt enucleation in unilateral disease and enucleation of the most extensively involved eye in bilateral disease are most commonly employed. Another approach has been to enucleate only those eyes with optic nerve involvement and to treat the remaining disease with RT. When enucleation is performed, as long a segment of the optic nerve as possible should be removed. Chemotherapy, photocoagulation, cryotherapy, and plaque radiotherapy may be used in selected cases.
B. **RT** is given, in most cases, to either the tumor bed or to the nonremoved involved eye. Usually, the dose given is about 3500 cGy in nine fractions over a 3-week period to the posterior retina. This technique, particularly when using megavoltage irradiation, is used to attempt to spare the anterior chamber and avoid cataract formation; it is unsuitable for tumors at or beyond the midpoint of the eye.
1. **Radiocobalt applicators** have been used for single lesions or discrete groups of small lesions.
2. **RT without surgery** is usually reserved for patients with advanced disease in both eyes, residual tumor after surgery, or tumors involving the optic nerve.

Most patients should not have RT without surgery.
3. **Light coagulation and cryotherapy** have been used for discrete lesions, particularly for small recurrences.
C. **Chemotherapy** is useful for metastatic disease. Adjuvant therapy for localized disease has not been shown to increase longevity. Many chemotherapeutic agents are active (vincristine, actinomycin D, cyclophosphamide, and doxorubicin).

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Chapter 19 Miscellaneous Neoplasms

Dennis A. Casciato and Barry B. Lowitz

I. Primary tumors of the mediastinum

A. **General features**
   1. **Anatomy.** The mediastinum is bounded by the sternum anteriorly, the thoracic vertebral bodies posteriorly, the diaphragm inferiorly, and the first thoracic vertebrae superiorly. Its lateral boundaries are the parietal and pleural surfaces of the lungs. The mediastinum is arbitrarily divided into anterior, middle, and posterior segments by the heart and great vessels.
   2. **Incidence.** The annual incidence of mediastinal tumors is 2 per 1 million population. Seventy-five percent of mediastinal tumors are benign. Many are detected serendipitously in chest radiographs obtained for other reasons.
      a. **The most common mediastinal masses** are thymoma, teratoma, goiter, and lymphoma. Most mediastinal malignancies represent lymphomas or metastatic cancers from other sites.
      b. **Lymphomas** can involve the anterior, middle, or posterior mediastinum. Hodgkin lymphoma is the most common cause of isolated mediastinal disease among the lymphomas; the nodular sclerosing subtype has a predilection for the anterior mediastinum. Other lymphomas are infrequently limited to the mediastinum at the time of diagnosis. Lymphomas are discussed in Chapter 21.
      c. **Mediastinal goiters** without a cervical component is rare. They usually descend into the left anterosuperior mediastinum. Infrequently, they descend behind the trachea into the middle and posterior mediastinum. Mediastinal goiters contain foci of malignancy rarely.
   3. **Age and sex.** Most of the tumors show no sexual predilection. Mediastinal teratomas usually arise after the age of 30 years. Benign thymomas may occur in any age group. Thymic carcinomas are more common in elderly men. Tumors of nerve tissue origin may occur at any age but are more common in children.
   4. **Symptoms and signs.** Presenting symptoms depend on the tumor location, type, and rate of growth. Symptoms are more likely to be present with rapidly growing, malignant tumors. Hypertrophic osteoarthropathy can occur with any primary mediastinal tumor, particularly sarcomas.
      a. **Anterior mediastinal tumors** can present with retrosternal pain, dyspnea, upper airway obstruction, and development of collateral venous circulation over the chest. Dullness to percussion may be observed over the upper sternum.
      b. **Posterior mediastinal tumors** can cause tracheal compression (cough and dyspnea), phrenic nerve compression (hiccoughs or diaphragm paralysis), involvement of left recurrent laryngeal nerve (hoarseness), esophageal compression (dysphagia), vena cava obstruction, Horner's syndrome or pain, or palsies in the brachial or intercostal nerve distribution.
B. **Tumors of the anterior and middle mediastinum**
   1. **Thymomas** represent 20% of all mediastinal tumors and are the most common cause of anterior mediastinal masses. They are composed of cells of both lymphocytic and epithelial origin. Thymomas are benign in 70% of cases and are locally invasive in 30%. Invasive thymomas involve the pericardium, myocardium, lung, sternum, and large mediastinal vessels. Disseminated metastases are uncommon. Histologic details have little bearing on prognosis or evaluation of malignant potential; invasiveness of a thymoma at surgery is the best index of its malignancy.
      a. **Paraneoplastic syndromes** associated with both benign and malignant thymomas do not affect prognosis. These syndromes include the following:
         1. **Myasthenia gravis** occurs in more than half of patients with thymoma; manifestations are improved in about 70% of patients who undergo thymectomy. About 20% of patients with myasthenia gravis have thymomas. Patients suspected to have thymoma should have an assay of serum anti–acetylcholine-receptor antibody.
         2. **Pure red-cell aplasia** (5% of thymomas); about half of patients with pure red-cell aplasia have a thymoma.
         3. **Acquired hypogammaglobulinemia** (10% of thymomas)
         4. **Rare paraneoplastic syndromes** associated with thymoma
            a. Ectopic Cushing's syndrome
            b. Polymyositis, dermatomyositis, granulomatous myocarditis
            c. Systemic lupus erythematosus
            d. Hypertrophic osteoarthropathy
      b. **Therapy**
         1. **Surgical extirpation** results in a cure rate that exceeds 95% for encapsulated, noninvasive thymomas. Less than 10% of resected encapsulated thymomas recur, sometimes years after excision. Surgery alone appears to be insufficient therapy for invasive thymomas.
         2. **Radiation therapy** (RT), 3000 to 5000 cGy given postoperatively for locally invasive or incompletely excised thymoma, reduces the local recurrence rate from about 30% to 5% in 10 years. The recurrence rate for locally invasive thymomas treated with RT alone is 20% to 30%.
         3. **Combination chemotherapy** regimens for locally advanced or metastatic disease usually involve cisplatin, doxorubicin, and cyclophosphamide. Corticosteroid therapy is also beneficial. All reports of chemotherapy efficacy are either anecdotal or small phase II studies. These combinations consistently result in response rates that are more than 50%, less than half of those are complete responses. The median duration of complete responses in widespread disease is about 12 months. The 5-year survival rate for these patients is about 30%. For patients with advanced disease (for whom there is no standard therapy), it is reasonable to use induction chemotherapy first, followed by resection and RT.
   2. **Thymic carcinomas** are obviously malignant histologically and are usually not associated with paraneoplastic syndromes. Neoplasms that are well circumscribed, are low grade, and have a lobular growth pattern have a relatively favorable prognosis for survival (90% 5-year survival rate). High-grade thymic carcinomas are locally invasive, are frequently associated with pleural or pericardial effusions, and frequently metastasize to regional lymph nodes and distant sites. Cisplatin-based chemotherapy plus RT for high-grade tumors is associated with a 5-year survival rate of 15%.
   3. **Thymic carcinoids** are rare. About half have endocrine abnormalities, especially ectopic production of adrenocorticotropic hormone and multiple endocrine neoplasia syndrome, but carcinoid syndrome rarely occurs. Regional lymph node metastases and osteoblastic bone metastases develop in most patients. Metastases are often refractory to therapy.
   4. **Germ cell tumors** (see Chapter 12). Teratomas (or dermoids) represent 10% of mediastinal neoplasms. About 10% of these are malignant, usually with a predominant epithelioid component, but occasionally with sarcomatous or endodermal elements. Malignant germ cell tumors of the mediastinum are usually large and solid.
      a. **Benign teratoma** accounts for about 70% of mediastinal germ cell tumors, especially in children and young adults. They appear as a round, dense mass (often with a calcified capsular shell and occasionally with teeth). They are usually small with multilocular cysts and asymptomatic, but they can attain a large size. The serum of a patient with benign teratoma contains no a-fetoprotein (a-FP) or b-human chorionic gonadotropin (b-HCG). These characteristics often differentiate benign teratoma from germ cell malignancy. The treatment is surgical excision.
      b. **Seminoma** is the most common malignant germ cell neoplasm of the mediastinum and occurs most frequently in 20- to 40-year-old men. The lesions are rarely calcified. Less than 10% of cases have an elevated b-HCG, and none has an elevated a-FP. Treatment of mediastinal seminoma is surgical excision if the tumor is small, followed by irradiation of the mediastinum and the supraclavicular nodes. For locally advanced disease, combination chemotherapy (see Chapter 12, section VI), followed by resection of residual disease, is preferred. The 5-year survival rate for these patients is more than 80%.
      c. **Mediastinal nonseminomatous germ cell tumors** are malignant, aggressive, and usually symptomatic. They are usually associated with elevations of serum levels of b-HCG, a-FP, or lactate dehydrogenase (LDH). Choriocarcinoma in the mediastinum presents with gynecomastia and testicular atrophy in half of patients. Embryonal or yolk sac tumors of the mediastinum are highly aggressive cancers that are large and bulky at the time of diagnosis. Surgery may be required initially to establish the histologic diagnosis. Definitive treatment consists of aggressive chemotherapy (as outlined for testicular cancer; see Chapter 12, section VI) followed by resection of residual masses. Mediastinal irradiation delays the initiation of chemotherapy, compromises bone

marrow reserve (thus limiting the chemotherapy doses), and probably should not be used.

    5. **Other anterior mediastinal masses**
      a. Goiter and thyroid cysts (10% of mediastinal masses)
      b. Lymphomas
      c. Parathyroid adenoma (10% are ectopic)
      d. Rare causes of anterior mediastinal masses
        1. Thymic cysts
        2. Thymolipoma
        3. Lymphangioma (cystic hygroma)
        4. Soft tissue sarcomas and their benign counterparts
        5. Plasmacytoma
    6. **Middle mediastinal masses**
      a. Lymphomas
      b. Goiter
      c. Aortic aneurysm (10% of mediastinal masses in surgical series)
      d. Congenital foregut cysts (20% of mediastinal masses). About 50% of foregut cysts are bronchogenic, 10% are enterogenous (including esophageal duplication), and 5% are neuroenteric.
      e. Pericardial cysts
  C. **Tumors of the posterior mediastinum**
    1. **Neurogenic tumors** are the most common cause of a posterior mediastinal mass and constitute 75% of neoplasms in the posterior mediastinum; about 15% are malignant, and half of these are symptomatic. Among mediastinal neoplasms, neurogenic tumors constitute 20% of cases in adults and 35% of cases in children.
      a. Neurofibromas and schwannomas are most common. *Malignant tumor of nerve sheath origin* is their malignant counterpart.
      b. Sympathetic ganglia tumors originate from nerve cells rather than nerve sheath. They are rare and range from benign ganglioneuroma to malignant ganglioneuroblastoma to highly malignant neuroblastoma. Some produce a syndrome identical to pheochromocytoma.
    2. **Mesenchymal tumors,** including lipomas, fibromas, myxomas, mesotheliomas, and their sarcomatous counterparts, are rare mediastinal tumors; more than half are malignant. Therapy necessitates surgical debulking. RT, chemotherapy, or both are used as a surgical adjuvant for treating sarcomas.
    3. **Other posterior mediastinal masses**
      a. Lymphomas
      b. Goiter
      c. Lateral thoracic meningocele

II. Retroperitoneal tumors

  A. **Etiology.** Excluding renal tumors, 85% of primary retroperitoneal neoplasm are malignant. About one sixth of cases are Hodgkin lymphoma, and one sixth are non-Hodgkin lymphoma. Sarcomas often appear in the retroperitoneum, particularly rhabdomyosarcoma (in children), leiomyosarcoma, and liposarcoma. Germ cell tumors, adenocarcinomas, and rare neuroblastomas account for most of the remainder of cases. Carcinomas of the breast, lung, and gastrointestinal tract can metastasize to retroperitoneal structures by way of the bloodstream or the spinal venous plexus.
  B. **Evaluation**
    1. **Symptoms.** Back pain, upper urinary tract obstruction, and leg edema due to lymphatic or vena cava obstruction frequently are manifestations of retroperitoneal malignancies; arterial insufficiency does not appear to occur. Some patients develop fever or hypoglycemia as paraneoplastic syndromes.
    2. **Laboratory studies.** History, physical examination, chest radiographs, and routine blood studies are performed. Uremia may result from entrapment of the ureters. Intravenous pyelography, barium contrast study of the colon, and abdominal computed tomography (CT) scanning are performed to evaluate the extent of tumor.
  C. **Management.** Exploratory surgery is necessary to establish the tissue diagnosis and to attempt resection of the tumor for potential cure, particularly for sarcomas. RT is used to treat residual disease. Chemotherapy is used for patients with lymphoreticular neoplasm or with tumors that are not responsive to RT. The specific chemotherapy selected depends on the tumor type.

III. Cardiovascular tumors. Primary cardiac tumors are exceedingly rare; cardiac metastases are more common (see Chapter 29, section V). Tumors of blood vessels are mostly sarcomas, which are discussed in Chapter 17. Some special types are discussed here.

  A. **Malignant heart tumors** include fibrosarcoma, angiosarcoma, rhabdomyosarcoma, and endothelial sarcoma. Tumors usually arise in the right auricle and extend into the heart substance and valves. Their aggressive course is characterized by heart failure, angina, life-threatening arrhythmias, or cardiac rupture. The prognosis is hopeless.
  B. **Benign heart tumors**
    1. Fibroma, myxoma, lipoma, and hemangioma typically arise in the atria. Presenting features include intermittent valvular obstruction with syncope or episodes of dyspnea and cyanosis.
    2. Atrial myxoma may cause a syndrome resembling microbial endocarditis with heart murmur, fever, joint pain, and systemic emboli. Patients with these findings and sterile blood cultures should have an echocardiogram, which is highly accurate for diagnosing myxoma of the heart. Occasionally, the diagnosis is established by the finding of myxomatous tissue in arterial embolectomy specimens.
  C. **Hemangiopericytomas** are tumors of the capillaries, which look like very cellular fibrosarcomas but are rarely malignant. Histologic appearance and grade do not closely correlate with the metastatic potential; metastases occur in cases with apparently benign tumors. These highly vascular tumors are treated by resection after embolic therapy. Postoperative RT may reduce local recurrence. Metastatic tumors respond to doxorubicin.
  D. **Primary intravascular sarcomas** are rare tumors that present with signs of focal vascular obstruction. Venous sarcomas, particularly leiomyosarcomas, are the most common intravenous sarcomas. Vena cava tumors may produce Budd-Chiari syndrome, renal failure, or pedal edema; patients may present with poorly defined back or abdominal pain. CT scan or venography suggests the diagnosis. Treatment is surgical resection, when technically feasible.

IV. Mastocytosis

  A. **Pathogenesis.** Cutaneous mastocytosis typically presents as urticaria pigmentosa or diffuse cutaneous mastocytosis, accounts for more than 85% of cases, and usually has a benign course. Malignant mastocytosis is an uncommon disease; it is most frequently reported in Israelis and light-skinned whites. The *c-kit* protooncogene plays an important role in hematopoiesis in general and in mast cell growth in particular. The histopathologic diagnosis may be difficult but is facilitated using basic dyes and immunostaining against tryptase.

  Mast cells infiltrate any organ that contains mesenchymal tissue (particularly the lymph nodes, liver, spleen, and bone marrow) and produce local destructive or fibrotic changes. Organ infiltration often indicates acceleration of the disease.

  B. **Clinical features**
    1. **Skin changes.** Urticaria pigmentosa is the most common early manifestation of systemic disease. Brownish skin nodules diffusely infiltrated with mast cells may be localized or diffuse, flat or raised, bullous or erythematous. Mild skin trauma may produce urticaria or dermographia.
    2. **Organ infiltration** may develop years after skin lesions have appeared and is manifested by hepatomegaly, lymphadenopathy, bone pain (osteosclerotic lesions on radiographs are common), bone marrow fibrosis, and occasionally mast cell leukemia. Hyperchlorhydria occasionally occurs and can result in peptic ulcer and malabsorption.
    3. **Hyperhistaminemia symptoms** may be precipitated by exposure to cold, alcohol, narcotics, fever, or hot baths, and include the following:
      a. Erythematous flushing, urticaria, edema, pruritus
      b. Abdominal pain, nausea, vomiting (occasionally diarrhea), flatulence, steatorrhea
      c. Sudden hypotension
  C. **Therapy.** Results of various treatments have been unsatisfactory. Histamine antagonism by H_1- and H_2-receptor blockade may help flushing, itching, and gastric distress. Cyclooxygenase inhibition may prevent prostaglandin D_2–induced hypotension when indicated. Oral chromalyn may prevent gastrointestinal symptoms and bone pain. Alkylating agents, cyclosporine, and corticosteroids occasionally help.

V. Carcinosarcomas. Carcinosarcomas are rare tumors, which have a histologic appearance of combined sarcomatous and epithelial elements. Typically, they arise in the myometrium, prostate, or lung. Surgical resection is the treatment of choice. The role of postoperative irradiation is not clear.

VI. Adenoid cystic carcinoma ("cylindroma"). Adenoid cystic carcinomas are rare tumors, which most often arise in salivary glands or the large airways but also can develop in the skin, breast, and other sites. Local recurrence after surgery is common. Pulmonary metastases are radiologically dramatic but often have an indolent course over several years. Primary tumors are treated surgically. Local recurrences may respond to RT. Symptom-free patients with lung metastases do not need specific treatment. Patients with symptomatic disease may respond to fluorouracil or doxorubicin.

VII. Dental tumors

A. **Ameloblastomas** appear to originate in dentigerous cysts. Eighty percent occur in the mandible (70% in the molar areas). The remaining 20% of histologically similar tumors arise in other bones and, occasionally, soft tissues. Ameloblastomas are locally invasive and have a high risk for local recurrence after surgery. Distant metastases do not occur. Therapy is by surgical resection. Some surgeons use intraoperative cauterization or cryotherapy for better local control. RT has no role in managing the tumor or recurrences.
B. **Cementoma** is probably an area or calcified fibrous dysplasia and not a neoplasm.
C. **Other dental tumors.** Ameloblastic adenomatoid tumors, calcifying epithelial odontoma, ameloblastic fibroma, dentinoma, ameloblastic odontoma, and complex odontoma are all benign tumors of the embryologic precursors of teeth. Surgical removal is the therapy of choice.

VIII. Olfactory neuroblastoma Olfactory neuroblastoma (or, esthesioneuroblastoma) is an uncommon tumor of the sensory epithelium of the nasal cavity close to the cribriform plate. This malignancy is considered in the differential diagnosis of poorly differentiated, round cell neuroectodermal neoplasms. Its aggressive biologic behavior, which is usually reflected in its histologic grade, is characterized by inapparent submucosal spread, local recurrence, atypical distant metastases, and poor long-term prognosis. Presenting features are unilateral nasal obstruction, epistaxis, rhinorrhea, sinus pain, or proptosis. Metastases to neck nodes develop in about 30% of patients.

Multimodality therapy has improved survival in these patients. Surgical resection is the treatment of choice, particularly for locally contained low-grade tumors. Neoadjuvant RT appears to be helpful. Chemotherapy with cisplatin-based regimens is helpful for high-grade malignancies, including in the neoadjuvant setting with RT.

IX. Urachal cancer. Urachal cancer arises in the primitive embryonic connection between the apex of the bladder and the umbilicus. Most of these tumors arise near the dome of the urinary bladder. The most common histologic type is adenocarcinoma. Adenocarcinomas evolve slowly and are asymptomatic until late in the course of disease. Presenting symptoms are painless hematuria, suprapubic mass, or passage of mucus in the urine. The presence of stippled calcification of a lower midline abdominal wall mass is almost pathognomonic for urachal carcinoma. Surgical resection is the therapy of choice.

X. Merkel cell carcinoma (MCC) is a rare cutaneous tumor that predominantly affects the skin in the head and neck region of older patients. These cells, first discovered by Merkel in the snout skin of voles in 1875, are thought to originate from the neural crest and to act as mechanoreceptors. MCC is a highly aggressive neoplasm with a marked propensity for local and distant metastases. Systemic disease is preceded by the appearance of nodal metastases and is uniformly fatal regardless of subsequent therapy. The 5-year survival is 65% and is best in the absence of lymphadenopathy at the time of presentation.

The treatment of choice for MCC is wide excision of the primary tumor and early or elective regional lymph node dissection. RT may be palliative but has no proven role as an adjuvant. Chemotherapy produces a high rate of short-lived responses. The response rate and duration of response are poorest in patients with visceral metastases.

XI. Paragangliomas (or chemodectomas) have also been called receptomas, glomus tumors, carotid body tumors, and tympanic body tumors. These neoplasms originate in the neural crest and develop from paraganglia tissues, which are themselves chemoreceptor organs that are distributed throughout the body in association with the sympathetic chain. Nearly half originate in the head and neck region (particularly at the carotid bifurcation and in the temporal bone), and the remainder develop in the mediastinum, retroperitoneum, abdomen, and pelvis.

A. **Occurrence.** These uncommon neoplasms are either familial (predominantly men) or nonfamilial (predominantly women). They are multiple at several locations in 25% to 50% of the familial type and in 10% of the nonfamilial type.
B. **Natural history.** Paragangliomas, which are usually considered to be benign, are characterized by slow and inexorable growth from the site of origin. Manifestations depend on the cellular characteristics and tumor location. About 5% of tumors are functional, manifest excessive secretion of neuropeptides and catecholamines, and produce a syndrome identical to pheochromocytoma. Metastases, which are the exception rather than the rule, develop in organs that do not contain paraganglia tissue (lungs, lymph nodes, liver, spleen, and bone marrow).
C. **Evaluation.** Paragangliomas must always be considered as potentially multiple, especially in patients with a family history of such tumors. Patients should be screened for evidence of excessive catecholamine secretion.

CT or MRI is useful in delineating the tumors. Arteriography may be useful for tumor embolization done just before surgery or for evaluating contralateral crossover blood supply. Radionuclide scintigraphy using MIBG may be helpful in localizing both paragangliomas and pheochromocytomas. These tumors have a rich blood supply; caution must be exerted not to cause hemorrhage during biopsy. Fine-needle aspiration cytology is often useful if performed carefully.

D. **Treatment.** Surgical extirpation is the treatment of choice, particularly for small head and neck lesions, but technical expertise in vascular surgery is mandatory. RT is effective in local control and is probably the treatment of choice for lesions that are large or erode bone, particularly in older patients. Chemotherapy is generally ineffective for metastatic disease. To do nothing is an acceptable option in some patients because these lesions are often well tolerated for long periods.

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Chapter 20 Metastases of Unknown Origin

Dennis A. Casciato

The definition of metastases of unknown origin (MUOs). MUOs are metastatic solid tumors (hematopoietic malignancies and lymphomas are excluded) for which the site of origin is not suggested by thorough history, physical examination, chest radiograph, routine blood and urine studies, and thorough histologic evaluation.

The predicament of MUO. The detection of MUO usually represents the discovery of a far-advanced malignancy that is rarely curable and that is usually refractory even to palliative chemotherapy. Tumors that are potentially responsive to systemic treatment are found in only about 20% of all patients with MUO. The diagnostic evaluations inflicted on these patients in pursuit of the primary site are typically excessive and futile. The primary site is found in less than 15% of cases, and that discovery rarely affects the prognosis or treatment. All efforts to manage patients who meet the criteria defined above should be guided by the understanding that there are two basic categories of MUOs: (1) those that are treatable and (2) those that are not.

I. Epidemiology and biology

A. **Mechanisms** that could explain the presence of occult primary neoplasms include the following:
   1. Excision or electrocautery may have removed unrecognized primary lesions years before the appearance of metastatic lesions.
   2. The primary cancer may have shed metastases and then undergone spontaneous regression.
   3. The primary tumor may be too small to be detected, even at autopsy.
   4. The site of origin may be obscured by the extensiveness of metastases or by the atypical pattern of dissemination.
B. **Incidence.** About 4% of patients with cancer present with MUO. MUO is the seventh most frequent malignancy, ranking below only cancers of the lung, prostate, breast, cervix, colon, and stomach.
C. **Age.** The average age at onset is 58 years. Patients who present with a midline distribution of poorly differentiated carcinoma (10% of all MUO patients) have a median age of 39 years.

II. Histopathology

A. **Performing a biopsy** should be the first order of business. Remarkably, physicians commonly engage in a vigorous diagnostic pursuit of the primary tumor before proving the type of cancer that exists. The pathologist should be informed before the biopsy that the primary site is not evident so that special studies can be planned.
   1. **Patients with metastases to neck lymph nodes only.** Suspicious cervical nodes should not undergo excisional biopsy until a complete diagnostic evaluation of the head and neck has been performed (see section VI.B). About 30% to 40% of these patients have potentially curable cancers of the upper aerodigestive tract. This is not the case for patients with supraclavicular lymph nodes, which may be directly excised for histologic examination.
   2. **Other patients who have suspected metastatic cancer.** Biopsy of *the most accessible site* should be performed *before* specialized blood or radiologic studies are done; the histologic findings provide an invaluable guide for a rational diagnostic workup. Biopsy proof of metastatic cancer is necessary *at only one site*. If several areas of tumor involvement are suggested by the findings from the screening evaluation, the preferred biopsy site is that associated with the least morbidity (e.g., peripheral lymph nodes when palpable, bone marrow when a leukoerythroblastic blood picture is present, cytology of sampled effusions, or suspect skin lesions). The biopsy specimen should be placed in a fixative that allows immunoperoxidase analysis and perhaps electron microscopy to be done well.
B. **Role of the pathologist.** Close communication between the clinician and the pathologist is especially important in cases of MUO. Morphologic clues may make certain anatomic sites more likely and direct the sequence of investigation.
   1. **Histologic problems**
      a. **Poorly differentiated tumors,** including adenocarcinomas, epidermoid carcinomas, and small cell neoplasms, may be indistinguishable by light microscopy.
      b. **Squamous metaplasia** overlying adenocarcinoma may be misread as squamous cell cancer.
      c. **Extensive fibrosis,** a common sequela of squamous cell carcinoma and breast adenocarcinoma, may mask the underlying tumor.
      d. **Limitations of pathology.** Pathologists are able to identify the primary site based on review of the biopsy alone in about 20% of cases of MUO. If they are given clinical information (especially the site of metastasis), the accuracy improves. However, the histologic appearance of these tumors usually defies categorization for the origin of the tumor.
   2. **Histologic and histochemical clues for origin** are shown in Appendix C1.
   3. **Poorly differentiated, undifferentiated, or anaplastic carcinomas** should be further evaluated with immunoperoxidase stains and, in special circumstances, electron microscopy (if possible). Immunohistochemistry is useful for poorly differentiated neoplasms to confirm the diagnosis of carcinoma, to identify patients with other neoplasms (e.g., lymphoma), and to identify a site of recognized cancer (e.g., prostate). The predominant tumors identified by specific antigens delineated by immunohistochemistry are shown in Appendix C2. Immunophenotypes expected to be found on biopsies for a wide range of malignancies are shown in Appendix C3.
      a. The most useful immunoperoxidase stains in the evaluation of patients with the MUO syndrome are leukocyte common antigen (for lymphoma), S100 protein or HMB45 (for melanoma), cytokeratins, vimentin, and prostate-specific antigen (PSA).
      b. Immunoperoxidase stains for neuron-specific enolase, synaptophysin, and chromogranin are helpful in patients who could have primitive neuroendocrine tumors (PNETs).
      c. Immunoperoxidase stains for b-human chorionic gonadotropin (b-HCG) and a-fetoprotein (a-FP) are frequently performed for the possibility of a germ cell neoplasm but have not been helpful in these patients.
      d. Electron microscopy for undifferentiated small cell and large cell neoplasms is used to evaluate for possible secretory granules, oat cell carcinoma, melanoma, and lymphoma (see Appendix C1).
C. **Histologic types of metastases**
   1. **Adenocarcinomas and undifferentiated carcinomas** account for more than 75% of cases of MUO. The natural history, prognosis, and poor responsiveness to therapy are similar for both these histopathologies.
      a. **The primary site** is determined antemortem in only 15% of cases, even with exhaustive diagnostic efforts. When a primary site is determined, the sites of origin and relative frequencies are as follows:
         1. Pancreas (25%)
         2. Lung (20%)
         3. Stomach, colorectum, hepatobiliary tract (8% to 12% each)
         4. Kidney (5%)
         5. Breast, ovary, prostate (2% to 3% each)
         6. Other sites (less than 1% each)
      b. **Undifferentiated and poorly differentiated large cell neoplasms** may represent carcinoma, extragonadal germ cell tumors, malignant melanoma, or large cell lymphoma. Lymphomas rarely are mistaken for adenocarcinomas, but the chance of confusion is increased if the tissue obtained is small or of poor quality. For example, gastric lymphoma and Ki-1 lymphoma (a T-cell malignancy characterized by long survival times and spontaneous remissions) are frequently misdiagnosed as carcinoma. These patients, in particular, require special study with immunoperoxidase or electron microscopy techniques. Many patients with MUO who have been reported to achieve good results with chemotherapy ultimately were proved to have lymphomas.
   2. **Squamous cell carcinomas** account for 10% to 15% of all MUO cases, and less than 5% if patients with metastases to cervical lymph nodes alone are excluded. Most squamous cancers that appear as MUO originate in the head and neck or lung. Other squamous cell cancer primary sites include the uterine cervix, penis, anus, rectum, esophagus, and occasionally, urinary bladder. Acanthocarcinomas (squamoid tumors) may develop in the gastrointestinal (GI)

tract, notably in the pancreas and stomach. Squamous skin cancer that arises in a chronic osteomyelitis fistula may not be apparent until regional draining lymph nodes become involved.

3. **Melanoma** constitutes 2% to 5% of all cases of MUO. About 4% of malignant melanoma cases present as MUO. It is important to distinguish melanoma from other histologies because metastases frequently involve lymph nodes alone, and these patients may be cured with appropriate therapy (see section VI.A).

   a. Amelanotic melanoma may be mistaken as undifferentiated carcinoma. Malignant melanoma may be distinguished from tumors having obscure histology by use of immunohistochemical reagents that are specific for melanocytic lineage (HMB45 or Epl-3) or for S100 protein (a cytoplasmic protein that is specific for nervous system tissue and is also present on human melanoma cell lines).

   b. Explanations of how melanoma can present as MUO
      1. The primary lesion may have been destroyed (e.g., by prior excision or cautery).
      2. The primary lesion may have regressed spontaneously.
      3. The tumor may have arisen *de novo* within a lymph node.

4. **Clear cell tumors.** Polygonal cells with clear cytoplasm can represent artifactual changes, benign neoplasms, or malignancies. Neoplastic proliferation of epithelial, mesenchymal, melanocytic, and hematopoietic lineage may manifest a virtually identical clear cell appearance, regardless of whether they are benign or malignant in nature. This pathologic dilemma of clear cell tumors is exceptionally important for patients with MUO because seminomas, nonseminomatous germ cell carcinomas, and lymphomas can be clear cell tumors. Differentiation of the various types of malignancies in these circumstances requires detailed analysis of clinical, histologic, immunohistochemical, and occasionally electron microscopic features.

5. **Undifferentiated small cell neoplasms,** including PNETs or "oat cell" carcinomas, develop in the entire alimentary canal, upper aerodigestive tract, thymus, breast, prostate, urinary bladder, skin, uterine cervix, and endometrium as well as the lung. About 2.5% of small cell carcinomas originate in extrapulmonary sites. Although this subtype comprises only a small percentage of the patients who present with MUO, it represents one of the treatable varieties. Immunohistochemical analysis of biopsies in patients with small cell malignancies is essential.

This histology may also represent a number of cancers that can be recalled with the mnemonic *MR. MOLSEN* (*m*yeloma, *r*habdomyoblastoma, *m*elanoma [amelanotic], *o*at cell carcinoma, *l*ymphoma, *s*eminoma [anaplastic], *E*wing's sarcoma, *n*euroblastoma).

III. Sites of metastases and natural history

A. **Manifestations.** Symptoms of metastasis, which are present in nearly all patients with the MUO syndrome, are multiple in 30% of patients. The most frequent presenting features are the following:
   1. Pain (60%)
   2. Liver mass or other abdominal manifestations (40%)
   3. Lymphadenopathy (20%)
   4. Bone pain or pathologic fracture (15%)
   5. Respiratory symptoms (15%)
   6. Central nervous system abnormalities (5%)
   7. Weight loss (5%)
   8. Skin nodules (2%)

B. **Sites of metastatic tumors**
   1. **Neck lymph nodes.** Neck masses in adults, other than thyroid nodules, are malignant in 80% of cases. After 50 years of age, 90% of neck masses are malignant. The histologic type of metastases to neck nodes varies in incidence according to anatomic location (Table 20.1); the probability for squamous carcinoma rises the higher the node is on the chain. Involved nodes are single in 75% of patients, multiple but ipsilateral in 15%, and bilateral in 10%. Multiplicity is often associated with adenocarcinoma.

Table 20.1 Histology of neck node metastases from unknown primary site

   a. **Cervical nodes** (70% of cases). The primary site of most squamous tumors that present as MUO in the upper half of the neck is the upper respiratory passages. With skillful endoscopic evaluation and computed tomography (CT) scanning, a primary site can be determined in at least 30% of cases. About 35% of these patients can potentially be cured.
      1. Carcinomas of the nasopharynx, hypopharynx, base of the tongue, and tonsil present with cervical node MUO as the first manifestation of disease in 30% to 50% of cases. Studies have shown that these sites or the larynx harbored the primary tumor 95% of the time when the primary site was found to be head and neck cancer that initially manifested as MUO.
      2. About two thirds of metastases to the low cervical nodes originate in sites below the clavicle, most commonly in the lung.
   b. **Supraclavicular nodes** (30% of cases). Involvement of this group of lymph nodes with malignancy nearly always indicates disease that is far advanced. The primary site is usually the lung or GI tract. The expected survival time is less than 6 months.
   2. **Axillary lymph nodes.** Axillary lymphadenopathy that is excised for diagnosis is found to have benign disease in 75% of cases, lymphoma in 15%, and solid tumors (particularly adenocarcinoma) in 10%.
      a. **The most likely sites of origin** of a solid tumor metastasizing to the axilla are the breast, lung, arm, and regional trunk. In patients with isolated malignant axillary lymphadenopathy, the primary site is detected in only half of cases.
      b. **Breast cancer.** Breast cancer accounts for 70% of cases of MUO involving axillary lymph nodes in women when the primary site is eventually diagnosed. About 0.5% of all breast cancer patients present with masses palpable in the axilla and not in the breast.
   3. **Groin lymph nodes.** The primary tumor is detectable in 99% of patients having malignant groin lymphadenopathy. Metastases are most likely to arise from the skin (especially the lower extremities and lower half of the trunk), genital and reproductive organs, rectum, anus, or urinary bladder. If a primary tumor is not evident, a lymphoproliferative disease is most frequently the cause.
   4. **Midline lymphadenopathy** (anterior mediastinal or retroperitoneal with or without peripheral lymphadenopathy) represents a highly treatable presentation of MUO when it is associated with "poorly differentiated carcinomas" (undifferentiated carcinoma, poorly differentiated carcinoma, or poorly differentiated adenocarcinoma). This presentation was classic for proven extragonadal germ cell tumors, but the cell lineage with this form of MUO is uncertain. Most patients are men, with a median age of 39 years and rapidly growing tumor masses. Many patients have achieved excellent responses to cisplatin-based combination chemotherapy (see section VI.E).
   5. **Other sites of metastases.** The most likely primary tumor sites according to the histology and site of metastases are shown in Table 20.2. These correlations may have limited usefulness in patients with MUO, however, because of the frequent occurrence of atypical metastatic patterns (see section III.C). Special considerations for each site are as follows:

Table 20.2 Probability of primary site according to site of presentation

   a. **Bone and bone marrow metastases**
      1. **Bone cortex.** When a primary site is found, carcinoma of the lung accounts for most patients with MUO who have bone metastases. When presenting as a MUO, pancreatic carcinoma frequently involves the skeleton. The median survival time of patients presenting with MUO and predominantly bone metastases is 3 months.
      2. **Bone marrow** is shown to be involved (by aspiration or biopsy techniques) in 10% to 15% of MUO cases during life, particularly in patients who prove to have lung, breast, or prostate cancer. Leukoerythroblastotic peripheral blood smears are the most accurate barometers of bone marrow involvement in patients with solid tumors (see Chapter 34, Cytopenia, section I.A). The median survival time of patients presenting with MUO and marrow metastases is less than 1 month.
   b. **Intrathoracic metastases**
      1. **Pulmonary metastases** may be solitary, and primary lung cancer lesions may be multiple. MUO presenting as a solitary pulmonary nodule is rare; when it does occur, it is most frequently associated with colorectal carcinoma or sarcoma. The median survival time of patients presenting with MUO and predominantly intrathoracic metastases is variable.
      2. **Effusions.** Pleural effusions, when caused by malignant disease, are associated with an unknown primary tumor in 20% of cases. Pericardial

effusions rarely occur as the predominant manifestation of MUO.

   c. **Intra-abdominal metastases** most frequently involve the liver and originate in the GI tract, but the primary site is determined during life in only about 30% of cases.
      1. **Liver metastases.** Differentiating between primary hepatocellular carcinoma and metastatic carcinoma of unknown origin in the liver may be difficult. Carcinomas of the prostate or ovary metastasize to the liver more frequently when they present as MUO than when they occur as known primaries. The median survival time of patients presenting with MUO and predominantly liver metastases is less than 4 months.
      2. **Ascites,** when caused by malignant disease, is associated with MUO in 10% of cases. The median survival time of patients presenting with MUO and predominantly malignant ascites is less than 1 month, except for women with peritoneal carcinomatosis that is considered to be a variant of ovarian carcinoma (see section VI.F).
   d. **Central nervous system metastases**
      1. **Brain metastases** are most frequently associated with bronchogenic carcinoma and second most frequently with the MUO syndrome. The primary site eventually becomes evident during life in 40% of cases, and 90% of these are lung carcinoma. Excision of single metastatic brain lesions does not improve survival beyond that experienced by other patients with the MUO syndrome. The median survival time of patients presenting with MUO and single brain metastasis that is resected is 3 to 6 months.
      2. **Spinal cord compression** is occasionally a manifestation of MUO syndrome. In these cases, laminectomy has been traditionally recommended as the first step to establish the histopathologic diagnosis. However, the median survival time of patients presenting with MUO and epidural metastasis is less than 2 months, and such an aggressive approach is often not justified.
   e. **Cutaneous metastases** are associated with carcinomas of the breast and lung in most cases. When skin metastases represent the initial manifestation of cancer, renal adenocarcinoma or bronchogenic carcinoma is the most likely possibility. The region of the skin near the primary tumor is most often involved.
   f. **Umbilical nodules** ("Sister Joseph's nodules") represent intra-abdominal carcinomatosis. The median survival time of patients presenting with MUO and predominantly skin metastases is 7 months if the primary site does not prove to be the lung.
C. **Aberrant natural history** of tumors in the MUO syndrome compromises the ability to predict the primary site of disease.
   1. **Origin.** Carcinomas that occur commonly in the general population (namely carcinoma of the breast, prostate, and bowel) make up only a small percentage of cases with MUO. About 75% of tumors in the MUO syndrome originate below the diaphragm.
   2. **Patterns of dissemination** by tumors do not follow typical pathways in the MUO syndrome. Examples are shown in Table 20.3.

Table 20.3 Patterns of dissemination by tumors

IV. Prognosis. *The prognosis in patients with the MUO syndrome is unaffected by whether the primary lesion is ever found.*

A. **Unfavorable prognostic features** in patients with MUO include the following:
   1. Multiple metastatic sites
   2. Supraclavicular lymph node involvement
   3. Well-differentiated or moderately differentiated adenocarcinoma histology
   4. Elevated serum alkaline phosphatase level
   5. Older age
   6. Lower performance status
B. **The 5-year survival rates** according to sites of involvement are as follows:
   1. Upper or middle cervical nodes alone (30% to 50%)
   2. Axillary nodes alone in women (25%)
   3. Groin nodes alone (50%, perhaps)
   4. Midline lymph node distribution with poorly differentiated adenocarcinoma, particularly in young men (30%)
   5. Melanoma to single peripheral lymph node region (30% to 45%)
   6. Any other metastatic site (less than 5%)
C. **Patients with metastases to sites other than peripheral lymph nodes alone.** The median survival time for all patients ranges between less than 1 month and 5 months. More than 75% of patients die within 1 year of diagnosis. Subcutaneous metastases have a more favorable prognosis if the primary site is not the lung; bone marrow and epidural metastases have the worst prognosis (median survival time of less than 1 month).

V. Searching for the primary tumor site. When the primary site of metastases is evident, the biopsy is performed 1 week earlier and the number of diagnostic tests ordered is significantly fewer than when patients present with MUO. Unfortunately, the usual behavior of physicians is to delay biopsy while in pursuit of a primary site through a prolonged investigative pathway with a bewildering scope of expensive, time-consuming, and potentially dangerous tests.

Even if all patients undergo exhaustive evaluation with barium enema (BE), upper GI series, intravenous pyelogram (IVP), skeletal survey, lung tomography, mammography (women), abdominal and pelvic CT scans, endoscopy, and a variety of radionuclide scans, *less than 15% of patients* with the MUO syndrome (excluding those who have disease only in cervical nodes) have the primary site established before death. Part of the 15% includes patients in whom the primary tumor becomes clinically evident on follow-up. The primary tumor site remains undiagnosed in 25% of patients even after postmortem examination.

Searching for the primary tumor site should be guided by the following questions:

A. **What are the clinical clues?**
   1. **Histology.** The finding of squamous carcinoma obviates the need to investigate organs in which adenocarcinomas develop. If the pathologist is not certain of the diagnosis because of the morphology or quality of the specimen, special studies or another biopsy may be in order.
   2. **Presentation.** The history, physical examination, and screening studies should be reviewed with awareness of the natural histories of the potentially causal malignancies. The atypical behavior patterns of certain malignancies when presenting as MUO should also be remembered (see section III.C).
B. **Which advanced malignancies are treatable?**
   1. **Metastases to unilateral lymph nodes alone**
      a. Melanoma to peripheral lymph nodes in a single region
      b. Squamous cell or undifferentiated carcinoma in the upper two thirds of the cervical chain
      c. Adenocarcinoma in the axillary chain in women
      d. Carcinoma in unilateral groin nodes
   2. **Metastases that are exquisitely sensitive to chemotherapy**
      a. Small cell carcinomas (PNETs)
      b. Peritoneal carcinomatosis in women
      c. Poorly differentiated carcinoma metastatic to retroperitoneum, mediastinum, or peripheral lymph nodes, particularly in men
      d. Adenocarcinomas that are treatable in advanced stages (breast, ovary, prostate, and thyroid) constitute less than 15% of cases of MUO. These tumors should be considered in patients with appropriate constellations of findings.
      e. Lymphomas should be considered in any patient with a poorly differentiated or undifferentiated neoplasm.
C. **What are the limitations of diagnostic studies?** Despite subjection to an alarming battery of tests, more than 85% of patients with MUO do not have the primary site determined while they are alive. Furthermore, most of the diagnostic tests are *just as frequently misleading as they are helpful.*
   1. **Pathology.** Review of the initial biopsy does not contribute to the origin of the malignant neoplasm in 80% of cases of MUO. Histopathologic classification of tumors can vary by more than 50% among different reviewers of the same specimen.
   2. **Chest radiographs.** No chest radiographic pattern, including the number of lesions, can distinguish a metastasis from a primary lung cancer.
   3. **Upper GI series, BE, and IVP.** Fewer than 5% of patients with MUO who undergo these studies have abnormal results in the absence of abdominal symptoms, occult blood in the stools, or hematuria. Abnormal results usually consist of findings that provide no useful information (e.g., organ displacement by tumor) in the presence of these manifestations. Upper GI series, BE, and IVP each suggests a primary malignant lesion in 5% to 10% of cases of MUO; the numbers of true-positive and false-positive results and the minimum number of false-negative results are about equal, however.
   4. **Mammography** is usually performed in women with MUO but has not been helpful in identifying the primary site, even in women with axillary lymph node metastases alone who eventually develop palpable masses in their breasts.

5. **CT scans** have not improved the frequency of detecting occult primary sites except in the head and neck.
6. **Radionuclide scans.** Staging disease in asymptomatic sites is a dubious practice for patients with disease that is already considered lethal.
   a. **Thyroid scans** are associated with equal frequencies of true-positive, false-positive, and false-negative results. Thus, these scans are virtually useless in MUO.
   b. **Positron emission tomography** (PET) with F^{18}-fluoro-2-deoxy-d-glucose has not been helpful in evaluating patients with MUO.
   c. **Bone scans** may be abnormal in the absence of symptoms related to the skeleton and may be useful for determining the extent of disease if that information is believed to be helpful.
   d. **Gallium scans** are useless in MUO.
7. **Ultrasonograms** have a high rate of false positivity in the evaluation of MUO, giving particularly erroneous results in retroperitoneal areas.
8. **Arteriography and screening endoscopy,** including bronchoscopy, upper GI endoscopy, sigmoidoscopy, and colonoscopy, are overly invasive and of no value in the MUO syndrome.
9. **Serum tumor markers,** including CEA, CA125, CA15-3, CA19-9, and b-HCG, are generally of little use in determining the primary site because of their lack of specificity. All five of these markers are commonly elevated in patients with MUO. Even PSA determinations are associated with false-positive and false-negative results.
10. **Estrogen receptor** determination has not been helpful in identifying the primary site or in prescribing therapy for patients with MUO.
11. **Postmortem examination,** the ultimate diagnostic test, fails to detect the primary site in 25% of MUO cases.

VI. Management. My recommendations for the treatment of patients with the MUO syndrome are diagrammed in Fig. 20.1.

Figure 20.1 An approach to the treatment of patients with metastases of unknown origin. AC, adenocarcinoma; PDC, poorly differentiated carcinoma; SC, squamous cell carcinoma; UC, undifferentiated carcinoma; MM, malignant melanoma; CNS, central nervous system.

A. **Malignant melanoma involving peripheral lymph nodes only**
   1. **Evaluation**
      a. Inquire about skin lesions that may have been removed previously.
      b. Search the skin carefully for a possible primary lesion; biopsy any suspect lesion.
      c. Exclude visceral disease with history and physical examination (especially ophthalmoscopy), chest radiographs, liver function tests, and CT scans of the liver and brain.
   2. **Recommended treatment** for malignant melanoma involving lymph nodes alone is radical lymphadenectomy of the affected nodal region. The procedure is repeated if the tumor recurs and the patient has no other evidence of disease.
   3. **Results of treatment.** Both the 5- and 10-year survival rates using radical lymphadenectomy are 30% to 45%. The prognosis with lymphatic metastasis is affected neither by knowing the primary site nor by having a history of a preexisting lesion. The prognosis is best if the metastasis involves only one node, and not the cervical chain, and if surgical intervention is prompt and aggressive.
B. **Metastatic disease in neck lymph nodes only,** particularly in the upper and middle cervical nodes, is potentially curable with node dissection (ND) under appropriate circumstances. Excisional biopsy of these nodes should not be performed because it distorts surgical planes and may result in poor outcomes if it proved to be a primary squamous cell carcinoma originating in an occult site in the head and neck. Fine-needle aspiration for cytology is preferable. Supraclavicular lymphadenopathy, on the other hand, rarely represents curable disease; these nodes may be excised directly for histologic examination.
   1. **Evaluation.** The recommended sequence of evaluation of cases of potentially cancerous cervical nodes is as follows:
      a. **Initial evaluation.** Carefully inspect and palpate all accessible areas of the mouth and nose. Then perform a complete evaluation of the upper airways, especially the nasopharynx, with mirrors or Hopkin's laryngoscope.
      b. **Imaging.** Obtain a CT or magnetic resonance imaging scan of the neck and paranasal sinuses to search for a primary tumor. PET may detect more metastatic sites and provide a higher rate of positive biopsy results during panendoscopy for cervical lymph node MUO, but the clinical relevance of this information is marginal.
      c. **Biopsy.** If these efforts fail to demonstrate any hint of a primary cancer, and if pathologic expertise is available, fine-needle aspiration is performed. The results of cytologic evaluation direct further evaluation, as follows:
         1. **Squamous cell or undifferentiated carcinoma.** Perform panendoscopy and manage the patient for a primary head and neck cancer.
         2. **Indeterminate or equivocal histology.** Excise the node, and perform special studies on the tissue, such as immunoperoxidase stains or electron microscopy, as necessary.
         3. **Adenocarcinoma.** Manage as for MUO to viscera. The outlook is hopeless.
         4. **Melanoma.** Manage as discussed previously (see section VI.A).
         5. **Lymphoma.** Manage accordingly (see Chapter 21).
      d. **Panendoscopy** (nasopharyngoscopy, laryngoscopy with tracheoscopy, bronchoscopy, and esophagoscopy) is performed under general anesthesia. All suspected lesions and random areas of apparently normal tissue of the base of tongue, tonsillar fossa, pyriform sinus, and nasopharynx are subjected to biopsy; these sites are statistically most likely to harbor a primary source. If a primary tumor is found, treatment is planned with consideration of the primary and presumed neck metastasis.
   2. **Treatment alternatives.** The treatment approach varies greatly among physicians and institutions. Both ND and comprehensive radiation therapy (RT; encompassing the nasopharynx, oropharynx, hypopharynx, and both sides of the neck), particularly when used in combination, achieve a high rate of local control in the involved neck. In theory, RT encompasses the undiscovered primary tumor. The complications associated with treatment are discussed in Chapter 7, General Principles, section VI.F.3. However, RT to encompass all potential nasopharyngeal drainage sites is considered to be unnecessary according to several authorities; less extensive RT has been shown to be associated with the same good results and less morbidity (namely, xerostomia and other complications).

   Depending on criteria of selection, 20% to 50% of patients treated with surgery alone develop contralateral neck disease or subsequently manifest a primary tumor site. The incidence of contralateral neck disease is much less after RT. The major factors influencing prognosis are the N stage (size and multiplicity of nodes) and the presence or absence of extracapsular extension into connective tissue.

   3. **Recommended treatment** (many centers use RT for all cases)
      a. **Stages N1 and N2a** (solitary, mobile, upper or middle neck node; N1 nodes are 3 cm or less and N2a nodes are 6 cm or less in diameter). Perform ND. If the specimen reveals other involved nodes (stage N2b) or if extracapsular invasion is demonstrated, administer postoperative RT. Alternatively, treat patients with RT alone.
      b. **Stage N2b** (multiple, larger [less than 6 cm] upper and middle neck nodes). Use RT followed by ND in 3 to 6 weeks (or vice versa). Adjuvant chemotherapy can be considered.
      c. **Stage N3** (massive or bilateral nodes). Use cisplatin-based chemotherapy with RT. Supplemental ND may be considered in selected cases.
      d. **Squamous cell carcinoma of low cervical or supraclavicular nodes or adenocarcinomas.** Administer RT alone (survival rates are poor no matter what is done; the goal of treatment is control of local disease).
   4. **Results of treatment**
      a. **Patients with upper neck nodes.** The 5-year survival rate for all patients is 30% if the primary tumor is eventually found and 60% if it is not found.
         1. Stage N1 or N2a. The 5- and 10-year survival rates are both 70% to 80%.
         2. Stage N2b. The reported survival rates are variable.
         3. Stage N3. The 5-year survival is about 20%.
      b. **Patients with low cervical or supraclavicular node metastases.** The 5-year survival rate is 5% (median survival time is 7 months).
C. **Metastatic disease in unilateral axillary lymph nodes only.** The major treatable malignancies presenting as MUO in axillary lymph nodes are occult breast carcinoma, amelanotic melanoma mistaken as undifferentiated carcinoma, and malignant lymphoma mistaken as carcinomas. Axillary metastases from breast cancer without an evident breast mass are most likely to emanate from the upper outer quadrant of the ipsilateral breast.
   1. **Evaluation**

a. Search for a primary site in the breasts, lungs, and regional skin.
b. If no primary lesion is found, perform an excisional biopsy.
c. In women with adenocarcinoma or poorly differentiated carcinoma, perform mammography (although the diagnostic yield is poor) and assess estrogen receptor activity.
2. **Occult breast cancer** (axillary nodal metastasis without a clinically detectable primary tumor in the breast) accounts for 0.5% of all breast cancer patients. Ultimately, 30% to 50% of female patients develop evidence for a primary breast cancer. The primary tumor becomes evident in less than 20% of these patients if the breast is treated with RT.
3. **Recommended treatment**
   a. **Lymphoma.** See Chapter 21.
   b. **Malignant melanoma.** See section VI.A.
   c. **Women with adenocarcinoma or poorly differentiated carcinoma.** Treat for stage II breast cancer. Mastectomy had been traditionally performed but is not justifiable in these patients.
   d. **Other patients.** Axillary node dissection is performed, attempting to achieve local control and long-term survival.
   e. **RT** to the axilla is frequently given, but there is no evidence to indicate that survival is improved over that achieved with resection of the involved nodes alone.
4. **Results of treatment.** Patients who have MUO and prove to have breast cancer can be expected to have the same survival as patients with stage II disease. The 5- and 10-year survival rates are identical with and without mastectomy and with and without the primary tumor ever becoming manifest. All other patients who are treated with excision of clinically involved nodes or axillary dissection have a 20% to 25% long-term survival rate (2 to 10 years).

D. **Metastatic disease in unilateral groin lymph nodes only**
1. **Evaluation**
   a. Search for a primary site on the skin, anus, rectum, pelvis, and lower urinary tract.
   b. If no primary lesion is found, perform an excisional biopsy.
2. **Recommended treatment**
   a. **Lymphoma.** See Chapter 21.
   b. **Melanoma.** See section VI.A.
   c. **Carcinoma.** Perform a superficial groin node dissection (affords local control with less morbidity than radical dissection). Simple excision of the involved node may be sufficient treatment, however.
   d. **RT** does not appear to be necessary.
3. **Results of treatment.** Half of patients treated with excisional biopsy or superficial groin dissection alone appear to survive more than 2 years. A significant proportion of these patients had unclassifiable carcinomas that may have been amelanotic melanoma.

E. **Poorly differentiated carcinoma with midline lymphadenopathy** (especially in men)
1. **Evaluation**
   a. Perform CT scans of the chest, abdomen, and pelvis.
   b. Measure serum levels of b-HCG and a-FP, but the results do not affect the probability of response to treatment.
2. **Recommended treatment.** Administer four cycles of cisplatin-based combination chemotherapy using regimens recommended for testicular cancer.
3. **Results of treatment.** The response rate with disease confined to the mediastinum, retroperitoneum, or peripheral lymph nodes is 75%, with complete remissions observed in 50% of patients. In some series, the median survival time for patients achieving a complete remission is more than 4 years; the 5-year survival rate is 35% for patients with disease confined to the retroperitoneum and peripheral lymph nodes and 15% for those with disease affecting predominantly the mediastinum. For patients with metastases to other sites, the response rate to cisplatin-based chemotherapy is 20%, and the 5-year survival rate is about 5%.

F. **Peritoneal carcinomatosis in women**
1. **Evaluation**
   a. Perform pelvic examination and paracentesis with cytologic and biochemical analysis of the ascitic fluid.
   b. Evaluate for other causes of malignant ascites clinically.
   c. Perform CT scans of the abdomen and pelvis.
2. **Recommended treatment.** If no extraovarian primary site is evident, perform exploratory laparotomy. If peritoneal carcinomatosis is confirmed without an extraovarian primary site, treat the patient as if she had ovarian carcinoma by performing total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and cytoreductive debulking of metastases. Thereafter, treat with a platin-based combination chemotherapy regimen for 6 to 8 months. Second-look laparotomy is not a consideration in these patients.
3. **Results of treatment.** The median survival rates are 1.5 to 2 years for all patients, 2.5 years for patients with limited residual disease after surgery, and 1 year for patients with extensive residual disease after surgery. About 10% to 25% of patients survive 3 years.

G. **Small cell carcinoma (PNET) MUO**
1. **Evaluation**
   a. Perform CT scans of the chest and abdomen.
   b. Perform bone marrow biopsy if the patient has a leukoerythroblastic anemia or increased serum alkaline phosphatase.
   c. Evaluate the biopsy with panneuroendocrine markers (e.g., chromogranin, synaptophysin, neuron-specific enolase).
2. **Recommended treatment.** Use cisplatin and etoposide combination chemotherapy. If a complete remission is obtained, consider administering RT to the known previous sites of disease. For patients with small cell carcinoma MUO to cervical lymph nodes alone, some authorities recommend treatment with ND or RT alone.
3. **Results of treatment.** The response rate to chemotherapy is about 70%. Long-term survival can be seen in patients who achieve a complete response after treatment for limited disease. Prolonged survival also occurs in patients presenting with cervical node metastases from occult primary small cell tumors in the minor salivary glands or paranasal sinuses after treatment with ND or RT alone.

H. **All other patients with the MUO syndrome**
1. **Evaluation.** Because of the low frequency of detecting the primary site in patients with MUO and the frequently misleading results of radiologic studies, radiologic or radionuclide studies are justified only in the presence of either specific abnormalities in the screening evaluation or possibilities suggested by review of histopathology. When the initial database does not suggest a primary organ site, further evaluation is usually fruitless and is not indicated. Even when the primary site can be determined, therapy is not likely to be affected. It is important to recognize that these patients have incurable cancer that is usually refractory to treatment. With the exception of treatable malignancies, documenting a site is more important to the patient (or physician) psychologically than therapeutically.

All patients should receive a complete history and physical examination (including the rectum and pelvis), chest radiograph, urinalysis, complete blood count, and serum liver and renal function tests. In patients with **adenocarcinoma or undifferentiated carcinoma**, perform the following:

   a. **Women.** Mammograms and careful pelvic examination
   b. **Men.** Careful examination of the testes and prostate gland, possibly in conjunction with random needle biopsies of the prostate (if there is an elevated serum PSA level, unexplained lower extremity edema, or pelvic bone metastases).
2. **Recommended treatment** for patients who may have specific neoplasms is as follows for findings consistent with the following:
   a. **Breast carcinoma** in women (e.g., bone or upper torso soft tissue metastases, even with negative mammography results)
      1. **Estrogen receptor–positive tumors,** even with negative mammography results: tamoxifen
      2. **Estrogen receptor–negative tumors:** CMF combination chemotherapy (see Appendix A)
   b. **Prostate carcinoma** (e.g., men with metastases only to pelvic bones, particularly if the PSA level is elevated: luteinizing hormone– releasing hormone agonists, such as leuprolide.
3. **Recommended treatment for other patients.** Nearly 80% of patients who have MUO have metastases from cancers of the pancreas, GI tract, lung, and other or never-to-be-known sites that are usually refractory to chemotherapy. When patients with malignancies that are poorly differentiated or metastases that are restricted lymph nodes are excluded, less than 20% of patients with adenocarcinomatous MUO experience partial tumor regression after treatment with cytotoxic agents (used singly or in combination). Partial responses are associated with only a minimal (if any) improvement in survival. Median survival is reported to be improved by 4 to 6 months in patients who respond to therapy compared with those who do not; this form of reporting data, however, is largely discredited.

For most patients with MUO, particularly those with low performance status, we do not recommend chemotherapy. Our recommendations are as follows for patients who request therapy and who have the following clinical features:

   a. **Good performance status.** Combination chemotherapy with fluorouracil and leucovorin, doxorubicin and mitomycin C, or carboplatin and paclitaxel

b. **Poor performance status.** Fluorouracil alone, nontoxic drugs, or nontoxic drug dosages

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Chapter 21 Hodgkin and Non-Hodgkin Lymphoma

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Evaluation of Suspected Lymphoma

I. Symptoms and signs

A. **History**
   1. **Painless lymphadenopathy** involving any of the superficial lymph nodes, is the most common chief complaint of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).
   2. **Systemic symptoms.** Fevers, night sweats, and weight loss are characteristic in advanced presentations of HL and aggressive NHL but may be encountered in all stages and pathologic types of lymphoma. Marked fatigue and general weakness may also be reported.
      a. **Pruritus,** often intense, may be the presenting symptom in HL, particularly the nodular sclerosis subtype, and may antedate diagnosis by months or years.
      b. **Pel-Ebstein fever** is periodic and uncommon, but characteristic of HL.
   3. **Pain**
      a. **Alcohol-induced pain** in areas of involvement is infrequent but is pathognomonic of HL.
      b. **Abdominal pain** or discomfort may be due to splenomegaly.
      c. **Bone pain** may reflect localized areas of bone destruction or diffuse marrow infiltration.
      d. **Neurogenic pain** is caused by spinal cord compression, plexopathies, nerve root infiltration, meningeal involvement, and complicating varicella zoster.
      e. **Back pain** suggests massive retroperitoneal nodal involvement.
B. **Physical examination** should evaluate for hepatosplenomegaly, the presence of effusions, evidence of neuropathy, and signs of obstruction (e.g., extremity edema, superior vena cava syndrome, spinal cord compression, hollow viscera dysfunction). Lymph node chains must be carefully examined, including the submental, supraclavicular, infraclavicular, epitrochlear, iliac, femoral, and popliteal nodes.
   1. **The lymph nodes** are examined for size, multiplicity, consistency, and tenderness. Lymphomatous involvement typically imparts a rubbery consistency, not the rock-hard quality of carcinoma.
   2. **The tonsils and oropharynx** are thoroughly examined. Waldeyer's ring involvement mandates complete evaluation of the nasopharynx, oropharynx, and hypopharynx by endoscopy.

II. Differential diagnosis (Table 21.1) compares clinical features of HL and NHL.

Table 21.1 Comparison of Hodgkin and non-Hodgkin lymphomas

A. **Lymphadenopathy**
   1. **Infections.** Patients, particularly young children with apparent viral or other infections, may develop striking lymphadenopathy. Such patients should be evaluated for infectious processes and observed for clear-cut resolution. Microorganisms associated with prominent lymphadenopathy include Epstein-Barr virus (EBV; infectious mononucleosis), cytomegalovirus, human immunodeficiency virus (HIV), secondary syphilis, mycobacteria, some fungi, and *Toxoplasma, Brucella,* and *Rochalimaea* species infection. In some cases biopsy is required for diagnosis of specific infectious diseases.
   2. **Systemic immune disorders,** such as rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus, are associated with both benign lymphadenopathy and lymphoma. Progressive or asymmetric lymphadenopathy mandate biopsy.
   3. **Patients at risk for HIV infection** present problems requiring individualization in management. Persistent generalized lymphadenopathy is a part of the acquired immunodeficiency syndrome (AIDS) spectrum (see Chapter 36), but lymphadenopathy can also be caused by opportunistic infections, Kaposi's sarcoma, or lymphoma.
   4. **Lymph nodes that are usually benign**
      a. **Occipital.** Consider scalp infection.
      b. **Posterior auricular.** Usually viral or scalp infection
      c. **Shotty inguinal nodes.** Suggest lower extremity infection.
   5. **Cervical nodes.** Patients with isolated enlargement of high or middle cervical lymph nodes often harbor occult primary carcinoma of the head and neck. The special approach required for these patients is discussed in Chapter 20, section VI.B.I.
B. **Midline masses**
   1. **Retroperitoneal masses** (see Chapter 19, section II)
   2. **Mediastinal masses** may occur in a variety of nonneoplastic and neoplastic (both primary and metastatic) conditions (see Chapter 19, section I).
   3. **Hilar masses.** Isolated symmetric bilateral hilar lymphadenopathy (without mediastinal mass) is strongly suggestive of sarcoidosis, and many experts believe that observation alone could suffice in this clinical setting. Unilateral hilar masses are frequently secondary to lung cancer; metastatic disease must also be considered. Coccidioidomycosis and histoplasmosis enter the differential diagnosis in the appropriate clinical and geographic milieu.
C. **Splenomegaly.** The diagnosis can usually be made with careful history taking and physical examination, laboratory evaluation, computed tomography (CT) scans of abdomen, bone marrow biopsy or aspiration, and occasionally liver biopsy. When a diagnosis cannot be established by these means, careful follow-up of the patient is warranted. Splenectomy should be considered for diagnosis in patients with massive or progressive isolated splenomegaly.
   1. **Normal.** A palpable spleen is occasionally seen in otherwise healthy young adults of thin body habitus.
   2. **Infections** include most pathogens listed in section II.A.1, bacterial endocarditis, and abscess.
   3. **Secondary to portal hypertension** (congestive splenomegaly). Patients with chronic liver disease or portal or splenic vein thrombosis may have no other

findings to direct the diagnostic search. Portal hypertension may be documented by ultrasound of the abdomen with Doppler or by liver-spleen scanning, which reveals redistribution of the radionuclide to the spleen and marrow.

4. **Storage diseases,** particularly Gaucher's disease, may produce prominent splenomegaly; characteristic cells are seen in the bone marrow in most cases.
5. **Tumors** are predominantly hematologic, including lymphomas and leukemias. Metastases, particularly from melanoma and breast cancer, and primary splenic sarcomas may also occur.
6. **Myeloproliferative disorders** such as polycythemia vera, myelofibrosis with myeloid metaplasia, essential thrombocythemia, and chronic myelogenous leukemia may cause marked splenomegaly.
7. **Autoimmune disorders.** Rheumatoid arthritis (Felty's syndrome), systemic lupus erythematosus, and autoimmune hemolytic anemia may produce splenomegaly (not isolated autoimmune thrombocytopenia) and can usually be diagnosed by history and associated laboratory findings.
8. **Miscellaneous.** Splenic cysts, thyrotoxicosis, sarcoidosis, and amyloidosis are unusual causes of splenomegaly.

III. Biopsy procedures

A. **Sites and methods of diagnostic biopsy.** Tissues or organs that are suspected of involvement are subjected to generous open biopsy for primary diagnosis wherever possible. Fine-needle aspiration cytology is mainly used for staging evaluation or for proving recurrence but may sometimes allow cytologic diagnosis *if expertise in interpretation is available.*
   1. **Peripheral node biopsy.** One of the largest accessible lymph nodes is excised whenever peripheral lymphadenopathy is present. Small lymph nodes may be more readily removed but may be uninvolved.
   2. **Inguinal lymph nodes** are frequently enlarged because of chronic inflammatory processes in the lower extremities. These nodes should only be excised when other sites are not suspect or when pathologic involvement is clearly anticipated.
   3. **Bone marrow biopsy** combined with aspiration is used for staging and may lead to diagnosis, particularly in the presence of abnormal circulating cells or cytopenias.
   4. **Mediastinoscopy or limited thoracotomy** (e.g., Chamberlain's procedure) for definitive diagnosis is required for a substantial proportion of patients with mediastinal masses.
   5. **Laparotomy** is used to diagnose some cases of lymphoma restricted to the abdomen and should include biopsies of the liver and random lymph nodes as well as the primary area in question. If HL is suspected, splenectomy may be performed as part of a staging procedure. Staging laparotomy is performed infrequently in NHL.
   6. **Laparoscopy** assesses the liver and peritoneum and allows extensive biopsy, obviating the need for staging laparotomy in some patients.
   7. **Endoscopic gastric biopsy** with staining for *Helicobacter pylori* may be helpful in the diagnosis of gastric maltoma. Repeated attempts with deeper biopsies and immunoperoxidase staining for leukocyte-common antigen (LCA) and keratin intermediate filaments may be helpful in the differential diagnosis between lymphoma and carcinoma. Small bowel involvement beyond the duodenum usually requires open biopsy, although capsule biopsies may be suggestive of lymphoma in some cases.
   8. **Retroperitoneal and mesenteric masses** may be evaluated by Trucut biopsy or fine-needle aspiration with immunologic analysis of the specimens, perhaps obviating the need for laparotomy. Such techniques are most useful for NHL and less so for HL.
B. **Handling the biopsy material.** The procured biopsy specimen is submitted to the pathologist directly and *not placed in a fixative* by the operating surgeon to ensure the best use of the available tissue. Prior communication with the pathologist is advantageous. Pathology tissue processing includes in the following procedures:
   1. **Touch preparations** (imprints), which provide cytologic detail and material for immunologic phenotyping
   2. **Immunologic phenotyping** with monoclonal antibodies, which can be crucial to diagnosis. Lymphoid cells are characterized immunologically using flow cytometry. Discriminatory immunophenotypes in lymphoma are shown in Appendix C4. A common NHL panel should include assessment of expression of CD2 or CD3, CD5, CD19 or CD20, and CD23 in blood, bone marrow, or biopsy specimens. Reed-Sternberg (RS) cells are usually CD15 and CD30 positive. More surface markers may need to be analyzed if this screening is inconclusive, or rare entities (such as natural killer [NK] cell or hairy cell leukemia) are considered.
   3. **Special handling of tissues** for procedures that may occasionally be used in difficult diagnostic problems or research such as cytogenetics, molecular genetic analysis, and electron microscopy
   4. **Microbial culture** of submitted material when the clinical picture or tissue suggests infection

IV. Clinical evaluation. The extent of the staging evaluation is determined by the individual case presentation, the histopathologic diagnosis, and the effect of the stage on treatment planning.

A. **Evaluation of blood tests**
   1. **Hematologic manifestations** are discussed in Chapter 34.
   2. **Diagnostically abnormal circulating lymphoid cells or lymphocytosis** are seen in some patients with either indolent or aggressive forms of NHL. Lymphoid cells are characterized immunologically using flow cytometry, and monoclonality may be established by k–l ratios (B cell) or gene rearrangement technology (T and B cell); these techniques are capable of detecting minute clones of circulating lymphoma cells not detectable by inspection of the blood smears.
   3. **Acute-phase reactants,** such as the erythrocyte sedimentation rate (ESR), fibrinogen, haptoglobin, and serum copper levels, may parallel disease activity, especially in HL.
   4. **Liver function tests** are unreliable in predicting lymphomatous involvement of the liver. Marked elevation of alkaline phosphatase and occasionally frank cholestatic jaundice may complicate HL as a paraneoplastic event without direct liver involvement. Extrahepatic biliary obstruction may also occur with lymphoma caused by enlarged nodes in the porta hepatis.
   5. **Renal function tests.** Elevated creatinine and blood urea nitrogen levels suggest ureteral obstruction and, less commonly, direct renal involvement. Uric acid nephropathy or hypercalcemia may contribute to renal insufficiency. Frank nephrotic syndrome as a paraneoplastic phenomenon may complicate HL and other lymphomas (see Chapter 31).
   6. **Serum uric acid.** Hyperuricemia is a common manifestation of high-turnover-rate (aggressive) NHL and may also be seen with extensive lower-grade lymphomas. Treatment of high-grade NHL may provoke brisk tumor lysis, leading to further elevation of uric acid and renal shutdown (see Chapter 27, section XIII). Hypouricemia may be seen in HL.
   7. **Hypercalcemia** has been noted in some cases of lymphoma and may be secondary to production of osteoclast-activating factors, such as lymphotoxin, or activation of vitamin D by lymphoma tissue.
   8. **Serum lactate dehydrogenase** (LDH) levels may reflect tumor bulk and turnover, particularly in the aggressive NHL.
   9. **Serum immunoglobulins.** Polyclonal hypergammaglobulinemia is commonly seen in HL and NHL. Hypogammaglobulinemia is particularly common in the small lymphocytic lymphomas and late in the disease. Monoclonal spikes are seen occasionally in NHL patients.
B. **Evaluation of the chest**
   1. **Chest radiographs** may demonstrate mediastinal and hilar lymphadenopathy, pleural effusions, and parenchymal lesions. A cavitating lesion is more typical of infection than lymphomas.
   2. **CT scans** can demonstrate parenchymal and mediastinal abnormalities.
   3. **Thoracentesis and pleural biopsy** may demonstrate direct lymphomatous involvement of the pleura. Obstruction of mediastinal lymphatic-venous drainage may result in cytologically negative or chylous effusions.
C. **Evaluation of the abdomen and retroperitoneum**
   1. **CT scans** are useful in delineating abnormal enlargement of nodes in retroperitoneal, mesenteric, portal, and other lymph node sites. The CT scan also detects splenomegaly and, with constant enhancement, may define space-occupying lesions in the liver, spleen, and kidneys.
   2. **Bipedal lymphangiography** (LAG) visualizes the periaortic and iliac lymph nodes, not the mesenteric, celiac, and portal nodes. Enlargement or a foamy appearance of the nodes is characteristic of lymphomatous involvement. Experienced evaluators can achieve false-negative and false-positive rates for lymphomas that are less than 15%. LAG tends to be abandoned, however, because both available expertise and the need for detailed staging of infradiaphragmatic disease are dwindling (see later). **Contraindications to LAG** include iodine allergy, respiratory disease, prior pulmonary irradiation, extensive mediastinal or retroperitoneal involvement, right-to-left cardiac shunts, and insufficient radiologic expertise.
   3. **Abdominal ultrasonography** is too insensitive to be useful in routinely assessing abdominal lymphadenopathy. It is occasionally helpful in distinguishing hepatic or splenic lesions (cystic versus solid) and in excluding an obstructive basis for renal insufficiency and jaundice.
D. **Evaluation of the gastrointestinal** (GI) **tract.** Direct involvement of the GI tract is uncommon in HL but is common in NHL. Patients with Waldeyer's ring lymphoma, suggestive GI symptoms, extensive abdominal nodal involvement, or GI bleeding are evaluated with upper GI series and complete small bowel follow-through. Barium enema may be necessary. Endoscopic examination and biopsy of accessible abnormalities are performed.
E. **Evaluation of the central nervous system** (CNS). Spinal fluid examination is routinely used to exclude occult lymphomatous involvement of the meninges in patients with Burkitt lymphoma or lymphoblastic lymphoma and is often performed in patients with intermediate-grade or high-grade lymphoma involving bone

marrow, testes, or paranasal sinuses. Patients with AIDS-related lymphoma require CT scans of the brain and spinal fluid analysis. Symptoms suggestive of intracranial, spinal cord, or peripheral nerve involvement require immediate diagnostic evaluation.

F. **Nuclear scans**

1. **^{67}Ga scans** are primarily used in assessing residual radiographic mediastinal and, less often, retroperitoneal abnormalities after therapy. Persistent ^{67}Ga uptake in these areas strongly suggests residual tumor instead of fibrosis or necrosis. To be useful in such follow-up, a ^{67}Ga body scan is recommended before therapy. ^{67}Ga scans can be unreliable below the diaphragm because of competing uptake in the GI tract, liver, and spleen (see Chapter 2, section II.D).

2. The **^{99m}Tc diphosphonate bone scan** is a sensitive technique in discovering early bone lesions and is performed whenever bone pain, alkaline phosphatase or calcium elevation, or equivocal radiographs are encountered. The ^{99m}Tc bone scan is often insensitive to purely osteolytic bone lesions. HL is associated with predominantly osteoblastic bone lesions, and hence the bone scan is reliable.

Hodgkin Lymphoma

I. Epidemiology and etiology

A. **Incidence.** HL accounts for about 1% of new cancer cases annually in the United States, or 7000 cases per year.

1. **Age.** HL demonstrates a bimodal age–incidence curve in the United States and some industrialized European nations. The first peak, constituting predominantly the nodular sclerosis subtype, occurs in the 20s and the second peak after 50 years of age. In third-world countries, the first peak is absent, but there is a significant incidence of mixed cellularity and lymphocyte-depleted HL in boys.

2. **Sex.** About 85% of children with HL are boys. In adults, the nodular sclerosing subtype of HL shows a slight female predominance, whereas the other histologic subtypes are more common in men.

B. **Risk factors.** In Western countries, the first peak of HL is associated with a higher social class, advanced education, and small family size; a delayed exposure to a common infectious or other environmental agent has been suggested. HL is associated with EBV infection, but the significance of this association is unclear. A slightly increased incidence of HL has been demonstrated with HIV infection; HIV-associated HL (see Chapter 37, section III) often presents with constitutional symptoms, advanced stage, and unusual sites of involvement (e.g., marrow, skin, leptomeninges).

II. Pathology and natural history

A. **Histology.** See Appendix C4. Discriminatory immunophenotypes for lymphocytic neoplasms

1. **Reed-Sternberg (RS) cells** are giant cells that have more than one nucleus and large, eosinophilic, inclusion-like nuclei. The lineage of these cells is probably B-cell lymphocytes. RS cells and the accompanying mononuclear *Hodgkin cells* are the neoplastic cells in HL, surrounded by a reactive cellular infiltrate. RS cells usually express CD15 (LeuM 1) and CD30 (Ki-1, an antigen that is also expressed in anaplastic large cell lymphoma). Infrequently, RS cells can coexpress CD20 or LCA (CD45).

   a. **Lymphocyte and histiocyte cells** (L&H cells) are RS-like and were identified in nodular lymphocyte-predominance HL (see section A.4.a). They manifest B-cell markers (CD20) and LCA (CD45). Although the L&H cells are believed to be of monoclonal origin, these B-cell infiltrates may be polyclonal.

   b. **The lacunar cell,** a variant of the RS cell, characterizes nodular sclerosing HL and is often far more plentiful than classic RS cells in that subtype.

   c. **RS-like cells** are found in a variety of infectious, inflammatory, and neoplastic disorders, including infectious mononucleosis, lymphoid hyperplasia associated with phenytoin therapy, and immunoblastic lymphomas.

2. **The pathologic diagnosis of HL** depends on the presence of RS cells and their variants in *an appropriate pathologic milieu*. The bulk of lymphatic tissue involved by HL is not composed of neoplastic cells but rather a variety of normal-appearing lymphocytes, plasma cells, eosinophils, neutrophils, and histiocytes existing in different proportions in the various histologic subtypes.

3. **The Rye classification** for HL relates the histopathologic subtypes to clinical behavior and prognosis, as shown in Table 21.2. This older classification system comprises lymphocyte-predominance (LP), nodular sclerosing (NS), mixed-cellularity (MC), and the uncommon lymphocyte-depleted (LD) varieties of HL. The LP subtype was further divided into nodular and diffuse subtypes (see section 4.a, section 4.b).

Table 21.2 Pathologic and clinical features of Hodgkin lymphoma subtypes (Rye classification)

4. **The World Health Organization (WHO) classification,** which has not yet been correlated with clinical behavior, divides HL into *nodular lymphocyte predominance HL* and *classic HL* (Table 21.3). Classic HL in this newer classification system comprises the lymphocyte-rich, NS, MC, and LD varieties.

Table 21.3 Hodgkin lymphoma: recommended treatment according to clinical presentation

   a. **Nodular LP HL** is now clearly recognized to be an indolent B-cell NHL and not true HL. This variety has L&H cells that are positive for CD20 and other B-cell markers, but no typical RS cells. For that reason, nodular LP HL is distinguished from classic HL in the new WHO classification.

   b. **Diffuse LP HL in the Rye classification** has disappeared as an entity. In the new WHO classification of lymphocytic neoplasms, what was thought to be diffuse LP HL is now classified as lymphocyte-rich classic HL (with true RS cells that are CD30 positive), Laennert's lymphoma (lymphoepithelioid peripheral T-cell lymphoma), T-cell–rich B-cell lymphoma, and other entities.

B. **Mode of spread.** HL almost always originates in a lymph node (Table 21.1). Whenever a primary diagnosis of HL is made in an extranodal site without contiguous nodal involvement, the diagnosis should be highly suspect. For much of its natural history, HL appears to spread in an orderly fashion through the lymphatic system by contiguity. Histologic types other than NS, however, often skip the mediastinum, and disease appears in the neck and upper abdomen. Hematogenous dissemination occurs late in the course of disease and is characteristic of the LD subtype.

C. **Sites of involvement.** The axial lymphatic system is almost always affected in HL, whereas distal sites (e.g., epitrochlear and popliteal) are rarely involved.

1. **Peripheral lymph nodes.** Cervical or supraclavicular lymphadenopathy occurs in more than 70% of cases. Axillary and inguinal lymph nodes are less frequently involved. Generalized lymphadenopathy is atypical of HL. Left supraclavicular lymphadenopathy is more strongly associated with abdominal involvement than is right-sided disease.

2. **Thorax**

   a. The anterior mediastinum is a prime location for NS HL.

   b. Mediastinal precedes hilar lymph node involvement. Lung involvement may occur by direct contiguity with hilar involvement in HL as well as by hematogenous dissemination.

   c. Pulmonary involvement by HL may produce discrete nodules and irregular, interstitial, or even lobar infiltrates.

   d. Pleural effusion may occur secondary to mediastinal compression of vascular-lymphatic drainage and by direct pleural involvement. Chylous effusions occasionally occur.

   e. Pericardial involvement may be found on CT scans, but overt cardiac tamponade is uncommon.

   f. Superior vena cava syndrome may occur in HL but is more frequent in NHL.

3. **Spleen, liver, and upper abdomen**

   a. The spleen, splenic hilar nodes, and celiac nodes are the earliest abdominal sites of involvement in infradiaphragmatic HL. Mes-enteric lymph nodes are rarely involved by HL.

   b. At least 25% of spleens not clinically enlarged harbor occult HL at laparotomy, and as many as half of spleens believed to be enlarged on physical examination or radiologic assessment are histologically normal.

   c. Liver involvement is uncommon at diagnosis and is almost always associated with infiltration of the spleen.

4. **Retroperitoneal lymph node** involvement tends to occur relatively late in the course of supradiaphragmatic HL and after spleen, splenic hilar, and celiac nodal involvement. Periaortic involvement without splenic involvement is uncommon. The retroperitoneal nodes are, however, affected early in the course of inguinal presentations of HL.

5. **The bone marrow** is rarely involved at the time of diagnosis of HL. Patients with advanced-stage disease, systemic symptoms, and MC or LD histologies have a higher risk for bone marrow involvement. Biopsy is mandatory to evaluate the bone marrow because HL is difficult to diagnose on marrow aspirates.
6. **Bone.** Osseous involvement of HL usually produces an osteoblastic reaction mimicking prostatic carcinoma. Extradural masses may result in spinal cord compression. Sternal erosion by mediastinal NS HL may occur.
7. **Other extranodal sites** are rarely involved in HL. Skin involvement is rare and usually a late manifestation of disease. CNS involvement is uncommon with the exception of spinal cord compression. Clinical involvement of meninges, brain, Waldeyer's ring, GI tract, kidney, and other extranodal sites is rare and suggests an alternative diagnosis.
D. **Immune abnormalities and infections.** Progressive loss of cell-mediated immunity with the development of cutaneous anergy, lymphocytopenia, and increased susceptibility to a variety of organisms is associated with advancing HL, even in the absence of therapy. Treatment with chemotherapy, corticosteroids, and radiation therapy (RT) accentuates these abnormalities. Late in the course of HL, hypogammaglobulinemia may also develop.
   1. **Infections associated with depressed cell-mediated immunity and therapy** (particularly corticosteroids) include *Listeria, Toxoplasma*, and *Mycobacterium* species, fungi, and slow viruses (such as progressive multifocal leukoencephalopathy). Patients treated with corticosteroids are at particularly increased risk for infections with *Pneumocystis carini* and cytomegalovirus.
   2. **Herpes zoster** appears in more than 25% of patients, particularly in patients with irradiated dermatomes and in those undergoing splenectomy. Generalized cutaneous involvement is not uncommon, but visceral involvement is rare.
   3. **Splenectomy-related infections** involve encapsulated microorganisms, particularly pneumococci, and less commonly *Haemophilus influenzae* and *Salmonella* species, especially in children. Pneumococcal infection in an asplenic host can be rapidly fatal. Vaccination with polyvalent pneumococcal vaccine is recommended before splenectomy, although its effectiveness in this population is not certain. Early aggressive treatment with antibotics of all febrile patients after splenectomy is mandatory.

III. Staging system and prognostic factors

A. **Staging** is the most crucial determinant of prognosis and treatment in HL. The *Ann Arbor staging system* had previously been universally used but has been modified to take into account important prognostic factors, particularly mediastinal bulk. The modified system is called the *Cotswolds Staging Classification.*
   1. **Cotswolds staging classification of HL**

   Stage **Description**
   I   Involvement of a single lymph node region or lymphoid structure
   II   Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is considered as a single site, whereas hilar lymph nodes are lateralized). The number of anatomical sites should be indicated by a subscript (e.g., II_3)
   III Involvement of lymph node regions or structures on both sides of the diaphragm
   III_1 With involvement of splenic hilar, celiac, or portal nodes
   III_2 With involvement of paraaoartic, iliac, and mesenteric nodes
   IV   Involvement of one or more extranodal sites in addition to a site for which the designation "E" has been used

   2. **Designations** applicable to any disease stage
   A   No symptoms
   B   Fever (temperature higher than 38°C), drenching night sweats, unexplained loss of more than 10% of body weight within the preceding 6 months
   X   Bulky disease (a mediastinal mass exceeding one third the maximum transverse diameter of the chest or the presence of a nodal mass with a maximal dimension greater than 10 cm)
   E   Involvement of a single extranodal site that is contiguous or proximal to a known nodal site
   CS Clinical stage
   PS Pathologic state (as determined by laparotomy or biopsy)
B. **Prognostic factors**
   1. **Stage** is clearly the single most important prognostic factor in HL. Within each stage, the presence of B symptoms confers a poorer prognosis. About 60% of patients with HL in the United States have stage I or II disease at the time of diagnosis. The percentage of patients with stage III or IV disease is generally higher in third-world countries or in lower socioeconomic enclaves.
   2. **Histopathology** was formerly closely related to prognosis. With advances in therapy, the value of histopathologic subtype as an independent prognostic variable (apart from stage) is less clearly defined.
   3. Age greater than 60 years, anemia, elevated ESR, bone marrow involvement, bulk of disease, and poor Karnofsky's scale performance status are so closely correlated with stage, systemic symptoms, and histopathology that it is difficult to prove independent prognostic importance.
   4. **Adverse prognostic factors** were evaluated by an international group in a multivariate retrospective analysis of 4,695 patients, mostly with extensive disease (see Hasenclever et al. in Suggested Reading). Patients with no adverse factors had an 84% freedom from progression, whereas the presence of *each factor* depressed the freedom from progression curve plateau by about 8%. Interestingly, neither tumor bulk nor histology emerged as independent factors. The seven independent prognostic factors identified were as follows:

Adverse factor	Relative risk of relapse
Male sex	1.35
Age $\geq$ 45 years	1.39
Stage IV disease	1.26
Hemoglobin <10.5 g/dL	1.35
White cell count (WBC) > 15,000/μL	1.41
Lymphocytes: Count < 600/μL or < 8% of WBC	1.38
Serum albumin < 4 g/dL	1.49

IV. Diagnosis

A. **Clinical evaluation.** See Evaluation of Suspected Lymphoma, section I, section II, section III, section IV.
B. **Staging evaluation**
   1. Adequate surgical biopsy reviewed by experienced hematopathologist.
   2. Thorough history and physical examination
   3. Laboratory tests: CBC, serum chemistries, protein electrophoresis, ESR, urinalysis
   4. CT scan of chest (include neck), abdomen, and pelvis with contrast
   5. Bone marrow aspiration and biopsy (bilateral iliac crest) unless clinical stage IA to IIA with no anemia or other blood count depression
   6. Bone scan in presence of bone pain, or elevated serum alkaline phosphatase or calcium level
   7. ^{67}Ga scans, particularly with high-dose single photon emission computed tomography scans (SPECT), and positron emission tomography (PET) scans are optional but are useful in follow-up of residual masses on chest radiograph or CT scan after therapy.
   8. Bone radiographs to corroborate findings on bone scan or in presence of bone pain
C. **Staging laparotomy**
   1. **Background.** Systematic evaluation by staging laparotomy revealed that at least 25% of patients with supradiaphragmatic presentations and negative clinical subdiaphragmatic evaluations had occult HL discovered at laparotomy (predominantly in the spleen, splenic hilar nodes, or celiac lymph nodes). Liver involvement was extremely uncommon in the absence of extensive splenic involvement.
      a. The main purpose of staging laparotomy and splenectomy was to save patients with truly supradiaphragmatic or stage III$_1$A disease from the long-term complications of alkylator-based chemotherapy (MOPP regimen in Appendix A1 and equivalent). Patients with a negative laparotomy or limited upper abdominal disease would be treated with radiation alone.
      b. The advent of less toxic curative chemotherapy (ABVD regimen in Appendix A1 and equivalent) and the success of combined-modality approaches have eliminated the need for aggressive staging.
   2. **Possible indications for staging laparotomy** include patients with limited supradiaphragmatic disease (CS IA, IB, and IIA) or equivocal stage IIIA disease, particularly if it is desired to avoid the use of chemotherapy.
   3. **Patients who should never have staging laparotomy** include those with the following clinical features:
      a. A requirement for a full course of chemotherapy: stage III or IV disease, bulky mediastinal disease, most patients with B symptoms
      b. Stage I or II disease for which the planned treatment is a combined-modality regimen

c. A low likelihood (less than 5%) of abdominal disease, that is, CS IA disease with unilateral high cervical HL, or with cervical, epitrochlear, or axillary LP HL, or with nonbulky mediastinal MC HL in girls and young women

4. **Possible benefits of staging laparotomy,** which alone do not justify "routine" staging laparotomy, include the following:
   a. Elimination of the need to radiate the spleen, a portion of the left lower lobe of the lung, and the left upper pole of the kidney
   b. Enhanced hematologic tolerance to therapy after splenectomy (never proved)
5. **Definition of an adequate staging laparotomy**
   a. Wedge and needle biopsies of both lobes of the liver
   b. Splenectomy with removal of splenic hilar lymph nodes
   c. Biopsies of random celiac, iliac, portal, and mesenteric nodes; any node that is enlarged or feels abnormal; and equivocal or abnormal nodes on LAG. Radiopaque clips are used to delineate sites of biopsies and large masses for treatment planning.
   d. Open iliac crest bone marrow biopsy
   e. Oophoropexy for young women, but the declining use of pelvic radiation has virtually eliminated this indication.
6. **Potential complications of staging laparotomy.** The operative mortality rate should be less than 0.5% and the significant morbidity rate less than 5% to justify this procedure. The most common anticipated complications include pneumonitis, pulmonary embolism, pancreatitis, and subdiaphragmatic abscess. Overwhelming pneumococcal sepsis is also a potential complication; patients who have undergone splenectomy should carry penicillin and must report any incident of fever or chills to a physician immediately.

V. Management: primary therapy

A. **Treatment philosophy.** More than one treatment approach may be used in the management of cases of HL. The challenge is to determine a course of therapy that preserves cure while minimizing long-term neoplastic and nonneoplastic complications.
B. **Surgery** is limited to diagnosis, possibly laparotomy, splenectomy for the rare patient with hypersplenism, and laminectomy for spinal cord compression.
C. **RT alone** is used in the United States to treat many patients with stage IA or IIA disease. A few institutions also use RT alone to treat stage IIB and IIIA disease, but this application has been largely replaced by combined chemoradiotherapy.
   1. **Radiation dose.** HL may be locally sterilized in almost all cases with 3500 to 4500 cGy given at a rate of about 1000 cGy per week.
   2. **Radiation fields** (Fig. 21.1)

Figure 21.1 Radiation fields used in Hodgkin lymphoma. Stippled area is the area irradiated. See text for descriptions.

   a. **Mantle field** encompasses the cervical, supraclavicular, infraclavicular, axillary, hilar, and mediastinal lymph nodes to the level of the diaphragm. Preauricular fields are added for patients with high cervical lymphadenopathy. The lungs and much of the heart are shielded by lead blocks, although many radiotherapists administer some radiation (1500 cGy or less) to the lung on the involved side, if hilar lymph nodes are enlarged. The whole heart may be treated if the pericardium is involved. A small gap must be left between the inferior border of the mantle field and the superior border of the periaortic field to obviate potential severe spinal cord injury caused by overlap.
   b. **Inverted-Y field** includes the spleen or splenic pedicle and the celiac, periaortic, iliac, inguinal, and femoral lymph nodes. The kidneys, much of the pelvic marrow, and the testes are shielded.
   c. **Spade and pelvic fields.** The inverted-Y field may be divided into a *spade field* encompassing the splenic pedicle (or spleen) and periaortic nodes, and a *pelvic field,* including the iliac, inguinal, and femoral lymph nodes.
   d. **Subtotal nodal or subtotal lymphoid irradiation** consists of mantle and spade fields.
   e. **Total nodal or total lymphoid irradiation** is uncommonly used and consists of mantle and inverted-Y fields.
   f. **Involved-field radiation therapy** (IFRT) consists of sites of known disease only and is used with curative intent only in combination with chemotherapy. It has become the most common use of RT in HL.
D. **Combination chemotherapy** is used for stage III, stage IV, and bulky disease. Chemotherapy is preferable for patients with early-stage disease and B symptoms, usually in combination with RT. The selection among the available regimens is often guided by the desire to avoid long-term toxicities associated with specific treatments. The advent of the nonleukemogenic, gonadal-sparing ABVD chemotherapy regimen expanded the use of chemotherapy to patients with earlier stages and obviated the need for laparotomy.
   1. **Useful chemotherapy regimens for HL** are shown in Appendix A1. These regimens must be strictly followed because delays in therapy or reduction in dosages not indicated by the protocol can clearly compromise results. The total dose and dose rate (dose intensity) are important in achieving cure. Regimens used as salvage therapy in HL are shown in Appendix A3.
   2. **MOPP regimen** (Appendix A1). The National Cancer Institute (NCI) recommends that vincristine should not be limited to a 2-mg maximum dosage in this regimen, but most clinicians sustain the 2-mg limit.
      a. MOPP therapy is administered in 28-day cycles for two additional cycles beyond the attainment of a restaged complete response (CR) and a minimum of six cycles (months).
      b. The CR rate using the MOPP regimen is between 70% and 80% for stages III and IV HL. About 60% to 70% of CR cases are durable, with relapses rare after 42 months. Half of patients are cured, with some deaths caused by treatment-related or unrelated disease. More than 80% of patients with stage IIIA or IVA disease survive 10 years without disease. Histologic subtype appears to have little effect on results with MOPP.
      c. Maintenance therapy beyond the initial complete course is unnecessary and not recommended.
      d. The MOPP regimen is associated with significant toxicities, including hematosuppression, nausea, neuropathy, leukemogenesis, and infertility.
   3. **ABVD regimen** (Appendix A1) is at least as effective as and probably superior to the MOPP regimen but has much less reported leukemogenesis and infertility. Potential cardiac toxicity caused by doxorubicin and potential pulmonary toxicity caused by bleomycin have been infrequent problems using this schedule but are of concern, especially when combined with RT. ABVD-based treatment has replaced MOPP as the standard regimen for HL.
      a. Generally, the same therapeutic rules as with the MOPP regimen apply: six to eight monthly cycles are usually administered, and at least two cycles beyond maximum response.
      b. Pulmonary function should be monitored. If dyspnea, pneumonitis, or significant reduction of more than 40% of lung diffusion capacity is noted, bleomycin should be discontinued. Bleomycin pneumonitis usually responds to corticosteroids.
      c. Cardiac function should be monitored in patients with preexisting heart disease and in those receiving high cumulative doses of doxorubicin.
   4. **MOPP and ABVD in alternating cycles** for 12 months have been found by Italian investigators to be superior to MOPP alone with respect to CR rate and relapse-free survival for patients with stage IV disease. The duration of treatment is longer than most investigators have reported in the United States, where patients are generally treated for 6 to 8 months.
   5. **MOPP–ABV hybrid regimen** (Appendix A1). Canadian investigators have combined the two effective combinations (minus dacarbazine) into a single hybridized regimen administered for a minimum of 8 months with excellent results.
   6. **Dose-intense regimens** have been developed hoping to improve outcome, especially in patients with high-risk HL. The value of these regimens remains unclear.
      a. **BEACOPP** (Appendix A1). This 3-week cycle regimen has been compared favorably to ABVD in studies with short follow-up. Higher response rates are reported with dose escalation and mandatory use of growth factors, possibly with a higher risk for secondary leukemia.
      b. **Stanford-V** (Appendix A1). Excellent results achieved with this weekly regimen in phase II studies need to be confirmed in randomized studies.
      c. **High-dose chemotherapy** followed by autologous stem cell transplantation for patients in first remission has been proposed but not satisfactorily tested.
   7. **Compared effectiveness.**
      a. A large, randomized trial conducted by a cooperative group showed that ABVD alone may be as effective as MOPP plus ABVD and more effective than MOPP alone in the management of most patients with advanced HL. ABVD is also increasingly being considered the treatment of choice for two reasons: (1) MOPP produces infertility in almost all male patients and in most female patients older than 26 years of age, and (2) MOPP has been associated with the development of acute myeloid leukemia.
      b. A three-arm randomized clinical study compared COPP plus ABVD with standard-dose BEACOPP and escalated-dose BEACOPP. The CR rate for COPP plus ABVD (83%) was inferior to the combined BEACOPP arms (92%). The 2-year survival rate was 89% for the COPP plus ABVD arm, 94% for the standard-dose BEACOPP arm, and 96% for the escalated-dose BEACOPP arm. Patients with adverse prognostic factors appear to derive benefit from dose escalation. Longer follow-up is required before definitive conclusions can be made.
      c. It is possible that certain subsets, such as patients with stage IVB disease and older patients, may benefit from MOPP-containing combinations (e.g., MOPP/ABV), but this is still uncertain.
   8. **Combined-modality treatment** is becoming popular in the management of early-stage disease. The advantage of this approach is the limitation of radiation to the involved area only (and thus the reduction of the total dose), reducing long-term radiation-related complications.

a. IFRT should be prescribed after a full course of chemotherapy to consolidate previously bulky areas of disease, which are at risk for relapse.
b. IFRT can complement an abbreviated course of chemotherapy in patients with CS I or II and nonbulky disease.
c. The practice of adding RT after a full course of chemotherapy for patients with stage III or IV disease but without large masses has been largely abandoned.

E. **Treatment controversies and recommendations** ([Table 21.3](#))
1. **Stages IA and IIA**
   a. **Supradiaphragmatic disease.** Traditionally, most patients underwent staging laparotomy and, if found to have pathologic stage I or II disease, would receive subtotal nodal irradiation. This approach resulted in an 80% probability of disease-free survival. Overall survival, on the other hand, may not be affected because most patients who relapse after RT can be salvaged by chemotherapy.

   Superior disease-free survival, however, has been documented after treatment with an abbreviated course of chemotherapy (two to four cycles) followed by IFRT. The VBM or ABVD regimen ([Appendix A1](#)) is often used. "First-line regimens," such as ABVD, are preferred for patients with features that are suggestive of more aggressive disease. These suggestive "inflammatory" features have been identified in some studies to be adverse for prognosis and include anemia, elevated ESR, hypoalbuminemia, leukocytosis, and other worrisome findings that are insufficient to classify the patient as having substage B disease. In a randomized study using four cycles of ABVD, there was no difference in outcome between groups irradiated with 2000 or 4000 cGy, suggesting that the dose of radiation can also be reduced.

   b. **Infradiaphragmatic disease.** Generally, similar principles apply for early disease. Most patients could be treated with a combined-modality approach. The rare patient with a unilateral inguinal presentation could receive inverted-Y radiation monotherapy.
   c. **Current studies** intend to assess the minimum number of cycles of a first-line regimen, such as ABVD, that can be given without compromising outcome. Less aggressive chemotherapy may suffice for patients with no risk factors, such as anemia, elevation of ESR, bulky disease, and so forth. Patients with very favorable presentation may receive extended-field RT without a preceding laparotomy, if desired.
2. **Stages IB and IIB** management is somewhat controversial. Early stage B disease has a nearly 50% relapse rate when treated with radiation monotherapy. It is preferable to treat such patients with a full course of chemotherapy, although a combined-modality approach may be considered.
3. **Bulky mediastinal presentations.** About 60% of patients with large (more than one third of the transverse diameter of the chest) mediastinal masses (stage IA to IIB disease) fail treatment with RT alone; relapses occur predominantly in the mediastinum and lungs. Full-course combination chemotherapy and IFRT, mantle-field irradiation, or subtotal nodal lymphoid irradiation are recommended for these patients. Patients with bulky mediastinal and more advanced stages (IIIA to IVB) disease should also receive mediastinal RT at the end of chemotherapy. Using both modalities, results approaching the cure rate for patients without large mediastinal masses may be attained. An alternating regimen, such as MOPP plus ABVD for 6 months, may be preferable over ABVD alone because it may reduce the cardiac and pulmonary complications of the combined treatment.
4. **Stage IIIA.** The 10-year disease-free survival rate using chemotherapy alone is 80%. Such results are superior to RT alone and probably cannot be improved by combined-modality therapy.
5. **Stage IIIB or IV.** The ABVD regimen is probably adequate management for most patients, although some patients with especially adverse features may benefit from MOPP plus ABVD, an MOPP–ABV hybrid, or a dose-intense regimen.
6. **E presentations.** Patients with contiguous limited extranodal disease (such as a single bone involved adjacent to an involved lymph node) can sometimes be managed by radiation alone or in combination with chemotherapy. Multiple E lesions and extensive E disease (such as a large pulmonary lesion) are best managed with chemotherapy or a combined approach.
7. **Pediatric HL.** Because of the retarding effects that radiation has on growing bone, chemotherapy is frequently and effectively used in children.
8. **HIV and HL.** Patients with HIV usually present with stage IV disease involving the bone marrow. The desired intensity of the treatment should be weighed against the patient's tolerance. Full-course chemotherapy should be tried with curative intent in patients with good performance status. The goal of treatment, however, should be palliation in many cases.

VI. Management after primary therapy

A. **Restaging**
1. All CRs resulting from either irradiation or chemotherapy must be verified by a restaging evaluation that consists of the repetition of all examinations that were initially abnormal.
2. The initial restaging occurs 1 to 2 months after completion of radiation and traditionally after three or four cycles of chemotherapy, provided that all palpable and radiographic disease has disappeared.
3. Restaging mandates rebiopsy of previously involved and accessible stage IV sites, such as liver or bone marrow.
4. Contrast dye remaining from previous LAG may remain for many months and is useful in determining nodal size changes (architectural abnormalities may remain indefinitely).
5. Persistent and stable abnormalities on chest radiograph or CT scan in the mediastinum are not uncommon (particularly in patients treated for NS). Occasionally, persistent stable abdominal masses or palpable nodal masses may also occur. These abnormalities demand close follow-up. In most cases, however, these findings represent only fibrosis and do not require biopsy. ^{67}Ga uptake may become negative in instances in which there is no longer viable disease. Positron emission tomography scanning may also be useful in distinguishing viable HL from fibrosis.

B. **Follow-up**
1. Most relapses after therapy occur within the first 3 to 4 years, although later recurrences have been observed.
2. Follow-up should occur every 2 months the first 2 years, every 3 months for the next 2 years, and then every 6 to 12 months.
3. Follow-up examinations
   a. History and physical examination
   b. CBC with ESR and chemistry panel
   c. Chest radiograph; abdominal radiograph (if dye remains); CT scans every 3 to 6 months for the first 3 years
   d. Thyroxine and thyroid-stimulating hormone (TSH) levels: at least annually (see [section VII.A.1](#))
   e. Health maintenance counseling and cancer screening is imperative for long-term survivors of HL. Smoking cessation and avoidance of practices associated with increased risk for cancer should be encouraged. Women should be encouraged to start annual mammograms 8 to 10 years after treatment, or earlier if older than 40 years of age.

C. **Salvage therapies**
1. **RT failures** are generally treated with combination chemotherapy with results at least as successful as with *de novo* chemotherapy.
2. **Chemotherapy failures**
   a. **Failure to achieve a CR** with effective combination chemotherapy is a poor sign. Although alternate combinations may be temporarily useful, long-term disease control is unlikely. Such patients should be referred for autologous stem cell or allogeneic bone marrow transplantation (BMT). The decision depends on the age of the patient, the availability of a donor, and responsiveness to a salvage chemotherapy regimen.
   b. **Relapses after chemotherapy-achieved CR.** The initial combination can be used again if the unmaintained CR lasts more than 1 year, but it should not be used again if the CR lasts less than 1 year. No known available regimen is capable of producing long-term disease-free survival in more than 10% to 20% of chemotherapy relapsed cases. Patients younger than 65 years of age who respond to salvage chemotherapy should be referred for autologous stem cell transplantation.
   c. **Patients who are resistant to MOPP and ABVD** may experience brief (although occasionally long) responses to alternate chemotherapy (single-agent therapy with a nitrosourea, or etoposide or combinations of these and other agents). Chemotherapy failures with predominantly nodal relapses may benefit from extended-field irradiation, which results in some long-term disease-free survival. Second-line and third-line chemotherapy regimens are shown in [Appendix A3](#). Allogeneic BMT can be considered for young patients.
3. **Intensive chemoradiotherapy with autologous stem cell rescue** has undergone extensive study. High doses of chemotherapy (potentially myeloablative), often combined with total-body irradiation, are administered ("conditioning regimen"), and either autologous bone marrow or peripheral stem cells (mobilized by growth factors) are used to rescue the patient from prolonged myelosuppression. This procedure is performed in most centers with a mortality rate of less than 5%; the hospital stay averages 3 weeks. Candidates include patients who have either relapsed after a CR or who have never achieved a CR with adequate combination chemotherapy. Perhaps 40% of chemosensitive candidates and 20% of patients failing induction chemotherapy may achieve prolonged disease-free survival.
4. **Other therapies.** Immunoconjugates, such as anti-CD25 or anti-CD30 immunotoxins, and radiommunotherapy have been tested in patients with HL in phase I studies, with inconclusive results so far. The use of interferon (IFN) and interleukin-2 (IL-2) has been disappointing.

VII. Special clinical problems in HL

A. **Sequelae and complications of therapy**
   1. **Hypothyroidism.** Overt hypothyroidism can be expected in 10% to 20% of patients and elevation of serum TSH in up to 50% of patients treated with mantle-field RT. Replacement therapy corrects the problem.
   2. **Sterility.** RT poses problems for female patients who receive pelvic irradiation. The testes are shielded during irradiation. MOPP and similar therapies produce near-universal sterility in male patients and can be anticipated to produce sterility in women in their late 20s or older. ABVD is not associated with sterility. Sperm banking is encouraged in male patients about to receive MOPP or similar therapies, or autologous stem cell transplantation.
   3. **Lung damage**
      a. **Radiation pneumonitis.** Mantle-field irradiation routinely produces a paramediastinal fibrosis that is usually not clinically significant. When large ports are necessitated by large mediastinal-hilar masses, the potential for more severe reaction exists. In addition, patients given MOPP who have a prior history of mantle-field irradiation may experience an abrupt episode of pneumonitis, presumably secondary to steroid withdrawal. Therefore, prednisone is omitted from MOPP after mantle-field irradiation, even if the radiation was administered years earlier.
      b. **Bleomycin pulmonary toxicity.** Almost all patients treated with bleomycin (in ABVD and the like) experience a reduction in their lung diffusion capacity. This reduction is usually asymptomatic and slowly improves after treatment. Severe idiopathic pulmonary toxicity is occasionally seen at bleomycin doses of more than 50 mg, although it usually does not occur until cumulative doses exceed 200 mg/m^2.

      More severe pulmonary toxicity (pulmonary infiltrates, restrictive defects, exertional dyspnea) is reported when bleomycin is given in combination with mediastinal RT. These adverse effects depend partly on the total dose of bleomycin and the radiation field. Because the pulmonary toxicity of the combination of ABVD and RT can be fatal rarely, some recommend the use of ABVD alternating with MOPP if a full course of chemotherapy and mediastinal irradiation is planned.

   4. **Cardiac damage**
      a. **Radiation.** The risk for radiation pericarditis is relatively small when modern anteroposterior weighted radiation ports are used and when large portions of the heart are not radiated. Radiation pericarditis with or without pericardial effusion or tamponade can develop, however. Constrictive pericarditis is a rare complication of RT.
      b. **Chemotherapy.** Doxorubicin, which is a component of ABVD and related regimens, is a well-known cardiotoxic agent. The incidence of cardiotoxicity is related to the cumulative dose and probably to peak serum levels. The cumulative dose of doxorubicin in ABVD is usually 300 mg/m^2, below the clinically significant cardiotoxic level when given without radiation. Administration of mediastinal RT, however, increases the chance of cardiomyopathy, pericarditis, or coronary artery disease as well as the potential for delayed cardiomyopathy.
   5. **Aseptic necrosis of the femoral heads** has been reported and is probably secondary to prednisone therapy in MOPP.
   6. **Depressed cellular immunity** was discussed previously (see section II.D).
   7. **Secondary neoplasms**
      a. **Acute myelogenous leukemia,** often preceded by a prodrome of myelodysplastic syndrome, develops in 2% to 10% of patients treated with MOPP or similar combined-modality therapy. The problem appears to be greatest in patients older than 40 years of age and may be increased in patients undergoing splenectomy. The leukemia generally occurs between 3 and 10 years after treatment, is often associated with total or partial deletion of chromosomes 5 and 7, and has an extremely poor prognosis. Acute leukemia is extremely uncommon in patients treated with RT alone and appears to be rare in patients treated with ABVD.
      b. **NHL** may occur during the course of HL and may represent an evolution of the natural history of disease rather than a treatment complication. Most reported cases are high-grade B-cell tumors, with a particularly high incidence in cases of LP HL (especially the nodular variant). As previously noted, LP HL may be a B-cell lymphoma (see section II.A.4). High-grade peripheral T-cell lymphomas have also complicated HL, particularly the NS type.
      c. **Epithelial tumors and sarcomas** are being increasingly reported as complications of RT and possibly of combined-modality therapy, and actuarial statistics suggest a rate of second neoplasms exceeding 20% with prolonged follow-up. Tumors may include breast cancer, sarcoma, melanoma, lung cancer, and other solid tumors. The relative risk for cancer appears to be higher for younger patients and synergistic to other predisposing factors. This significant risk applies to a patient population treated in the 1960s and 1970s; modern strategies limiting radiation exposure may reduce this risk.
   8. **Neurologic complications**
      a. **Lhermitte's sign,** which follows thoracic irradiation for HL, is an innocuous but worrisome finding for the patient. It consists of shocklike sensations down the back and legs, often precipitated by flexing the neck, and it gradually disappears.
      b. **Transverse myelopathy** is a rare but serious complication of RT that is usually caused by failure to leave an appropriate gap between the mantle and abdominal ports.
   9. **Retroperitoneal fibrosis** has been described as a complication of HL treatment.
B. **Synchronous neoplasms.** HL is said to be associated with an increased risk for simultaneous Kaposi's sarcoma, leukemia, NHL, and myeloma.
C. **Nephrotic syndrome,** as a remote effect of malignancy, occurs most often in patients with HL. Lipoid nephrosis is typical (see Chapter 31, section IV).
D. **Pregnancy in HL.** See Chapter 26.
E. **Ichthyosis.** Adult-onset ichthyosis is associated with HL in 75% of cases (see Chapter 28, section II.H).

Non-Hodgkin Lymphoma

I. Epidemiology and etiology

A. **Incidence.** NHL occurs roughly eight times as frequently as HL, with about 57,000 new cases annually in the United States. The incidence is rising dramatically, and this increased incidence cannot be totally explained by the AIDS epidemic.
B. **Age and sex.** Small lymphocytic lymphomas occur in the elderly. Lymphoblastic lymphoma has a predilection for male adolescents and young adults. Follicular lymphomas occur mainly in middle-adult life. Burkitt lymphoma occurs in children and young adults.
C. **Etiology.** Viral etiology and abnormal immune regulation have been implicated in the development of lymphomas. The two mechanisms may be interrelated. An etiologic agent, however, can be identified in only a minority of cases.
   1. **Pathogens**
      a. **RNA viruses.** The human T-cell lymphotrophic virus type 1 (HTLV-1) is associated with adult T-cell leukemia-lymphoma (ATLL). HIV produces AIDS, and the resultant immune deficiency is associated with high-grade B-cell lymphomas. Chronic hepatitis C virus infection has been associated with indolent B-cell lymphoma.
      b. **DNA viruses.** EBV has been found in the genome of African Burkitt lymphoma cells. This virus has also been associated with lymphomas in situations characterized by reduced immune surveillance, such as in patients with the X-linked lymphoproliferative syndrome, organ transplantation, and, in many instances, HIV-associated lymphoma.
      c. **Chronic *H. pylori* infection** of the gastric mucosa is clearly associated gastric lymphoma. Eradication of the infection produces remission in more than two thirds of patients.
   2. **Immunodeficiency or immune dysregulation** states associated with development of lymphomas include the following:
      a. AIDS
      b. Organ transplant recipients
      c. Congenital immunodeficiency syndromes (e.g., agammaglobulinemia, ataxia-telangiectasia, Wiskott-Aldrich syndrome)
      d. Autoimmune disorders (e.g., Sjögren's syndrome, rheumatoid disease, lupus erythematosus, Hashimoto's thyroiditis). Diphenylhydantoin may cause a spectrum from benign lymphoproliferation to frank lymphoma.
   3. **Treatment related.** The potential role of chemotherapy or RT in the development of NHL after HL and myeloproliferative disorders remains uncertain.

II. Pathology and natural history

A. **Classification systems for NHL.** Both the Working Formulation (WF) and the Revised European American Lymphoma (REAL) classification, as modified by the WHO, are used. These systems are complementary. The WF satisfactorily captures and describes the most common lymphomas. The REAL/WHO classifications intend to correlate lymphoma entities with the normal lymphocyte counterpart and are more applicable to the uncommon lymphomas. Because of their dependence on immunophenotypic and cell lineage analysis, the REAL/WHO system is more reproducible.
B. **The Working Formulation** is the most commonly used system for the classification of NHL. This scheme was developed in 1982 as the result of a consensus panel made up of distinguished hematopathologists, each espousing his or her own classification. The WF attempts to associate clinical behavior with descriptive histopathologic features of NHL. However, it does not incorporate accepted information regarding B-cell or T-cell origin of lymphomas and does not

recognize a large variety of newly described clinicopathologic entities. Table 21.4 shows the WF with the frequencies, some clinical correlates, and survival rates for the various types of NHL.

Table 21.4 Classification of non-Hodgkin lymphomas: The Working Formulation [a]

1. **Grades.** The WF divides NHLs into low, intermediate, and high grades that reflect their biologic aggressiveness. The dividing line between these categories is arbitrary.
   a. In general, small cell size, round or cleaved nuclei, and a low mitotic rate characterize low-grade NHLs. The intermediate/high-grade NHLs usually manifest larger cell size, prominent nucleoli, and a higher mitotic rate.
   b. Clinically, it is useful to consider low-grade NHLs as being indolent or nonaggressive, whereas the intermediate-grade and high-grade NHLs are aggressive diseases with a short untreated natural history. Many clinicians approach immunoblastic lymphomas in a similar fashion to the intermediate-grade NHLs and consider lymphoblastic lymphomas and the small noncleaved NHLs, particularly the Burkitt variant, as high-grade NHLs requiring special management.
2. **Survival curves** based on the WF are shown in Fig. 21.2.

Figure 21.2 Actuarial survival curves for the National Cancer Institute formulation subtypes of lymphomas. The *upper panel* shows the curves for individual subtypes (A through J with the numbers of patients in parentheses). The *lower panel* shows the curves for the three major prognostic categories (grades); each curve is significantly different from the other (p < 0.0001). Table 21.4 defines the subtypes A through J and the grades. (From Rosenberg SA, et al. *Cancer* 49:2112, 1982, with permission.)

C. **The REAL classification** was established after a consensus of hematopathologists in 1993. It incorporates immunophenotypic characteristics to determine cell lineage and to define subtypes by a more scientific method. It recognizes several less common entities unclassifiable by the WF. The WHO accepted the REAL proposal and, with some additions, should be the current classification standard. REAL with the WHO modifications serves as a common language among hematologists and is shown in Table 21.5.

Table 21.5 World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues

1. REAL entities may include lymphomas of various clinical behaviors, provided that they originate from the same cell type. For example:
   a. Leukemias are considered to be an extreme of the spectrum of certain lymphoproliferative disorders.
   b. Acute lymphocytic leukemias and lymphoblastic lymphomas are grouped together.
   c. All follicular lymphomas constitute one group.
   d. Chronic lymphocytic leukemia (CLL) is classified together with small lymphocytic lymphoma because they both consist of small round B lymphocytes that are positive for CD5 and CD23.
2. Mantle cell lymphoma (MCL) is recognized as a separate entity with its distinct features and clinical aggressiveness. MCL was often described as small lymphocytic lymphoma, diffuse small cleaved cell lymphoma, or at times follicular lymphoma in the WF.
3. Immunoblastic lymphoma is classified as diffuse large cell lymphoma and is no longer recognized as a separate entity.
4. Detailed classification of T-cell and NK-cell malignancies is attempted in this system. T-cell lymphomas were not recognized by the WF.
5. Because about two thirds of the NHL histologies are follicular or diffuse large cell, clinical decisions often rely on WF principles.
D. **Natural history.** NHL exhibits a remarkable range of natural histories, with doubling times varying between days (e.g., Burkitt lymphoma) and years (some low-grade NHLs). Treatment tends to have a much more dramatic effect on intermediate/high-grade NHLs than on low-grade NHLs. Early bone marrow involvement and hematogenous and noncontiguous dissemination characterizes NHL, particularly the low-grade types, in sharp contrast to the distribution in HL. Extraaxial nodes, including epitrochlear and mesenteric nodes, are often involved, again in contradistinction to HL (Table 21.1). Intermediate- and high-grade NHLs often present in extranodal sites, including Waldeyer's ring, GI tract, skin, bone, and CNS.
E. **Peripheral B-cell lymphomas: low-grade**
   1. **Small lymphocytic lymphoma** is the tissue or nodal counterpart of CLL and classically presents with diffuse lymphadenopathy and marrow involvement. Cells are CD5, CD20, and CD23 positive. CLL and chronic B-cell prolymphocytic leukemia are discussed in Chapter 23, Chronic Lymphocytic Leukemia.
   2. **Lymphoplasmacytic lymphomas** include Waldenström's macroglobulinemia and other B-cell lymphomas that may manifest monoclonal serum protein spikes. The cellular composition of plasmacytoid lymphocytic lymphoma is made up of lymphocytes, plasma cells, and hybridized forms with features of both. Cells are usually CD20 positive, in contrast to frank plasma cells. Hyperviscosity syndrome caused by the IgM protein that forms asymmetric pentamers may dominate the clinical picture in Waldenström's macroglobulinemia.
   3. **Follicular lymphoma.** The follicular lymphomas include the follicular small cleaved, mixed, and large cell types (grades I, II, III, respectively, according to REAL). Cells are positive for CD10 and CD20 and negative for CD5. Follicular small cleaved and mixed lymphomas are generally considered to be low-grade NHL, whereas the rarer follicular large cell type is considered to be intermediate grade by some authorities. Larger transformed cells constitute 25% to 50% of the cellular composition in mixed lymphomas, whereas follicular small cleaved lymphomas are composed of predominantly small cells.
      a. The follicular lymphomas tend to present as nodal disease. About 85% of cases are stage III or IV at presentation, with frequent bone marrow involvement (more than 50% of cases). The liver, spleen, and mesenteric nodes are often involved.
      b. Follicular lymphomas often progress slowly and may not require immediate therapy. Temporary spontaneous regressions are observed in up to 30% of cases. Follicular lymphomas are highly responsive to therapy, but the effect of treatment on survival is modest, and few patients are cured. Average survival times vary between 6 and 10 years.
      c. Cytologic transformation to intermediate-grade or high-grade NHL may occur at any point in the disease. A similar transformation may take place in some of the other forms of low-grade NHL.
      d. Follicular lymphomas bear the t(14:18) translocation that results in upregulation of *bcl-2* expression. The *bcl-2* gene product is considered a potent inhibitor of apoptosis. Transformation to large cell histology is often characterized by *p53* mutation.
   4. **Marginal-zone lymphoma** is believed to be derived from parafollicular or marginal-zone cells that surround the mantle zone. Cells are negative for CD10 and CD5 and positive for CD20.
      a. **MALTomas** (MALT: mucosa-associated lymphoid tissue) are a group of extranodal lymphomas that frequently present as localized tumors in the stomach, lung, breast, thyroid, and other extranodal sites. In some cases, a preexisting organ-associated autoimmune disease is noted (e.g., Sjögren's syndrome or Hashimoto's thyroiditis). Many of these were designated *pseudolymphomas* in the past. The natural history includes prolonged survival without widespread dissemination and suggests a role for RT or surgery in management. Gastric MALToma is clearly associated with *H. pylori* infection and typically regresses after its eradication. Often, a remission occurs up to 1 year after antibiotic treatment.
      b. **Splenic lymphomas** are an uncommon form of marginal-zone lymphomas. These are characterized by pronounced splenic enlargement, often without systemic disease. Cells often have villi (splenic lymphoma with villous lymphocytes).
      c. **Nodal marginal zone lymphomas** are also called **monocytoid lymphomas** because of their appearance.
   5. **Hairy cell leukemia** is characterized by an indolent course, hypersplenism, and neutropenia. Characteristic lymphocytes may be seen with the tartrate-resistant acid phosphatase (TRAP) stain. Cells are characteristically positive for CD103, CD22, CD11c, and often CD25. This disease is discussed in Chapter 23, Hairy Cell Leukemia.
F. **Peripheral B-cell lymphomas: intermediate-grade and high-grade**
   1. **Mantle cell lymphoma (MCL)** is a unique B-cell lymphoma with an adverse prognosis. It is derived from CD5 [+], CD20^{+}, CD23^{–} lymphocytes surrounding the germinal center. It is associated with the t(11:14) translocation, which results in upregulation of cyclin D1, a promoter of cell cycling.
      a. MCL may present with a variety of histologic variations ranging from a pseudofollicular pattern to a blastic form. The most common appearance is a diffuse small cell, slightly irregular infiltrate. It was recognized as centrocytic lymphoma in Kiel's classification.
      b. MCL usually presents at advanced stage with B symptoms and involvement of the GI tract and bone marrow. It responds poorly to chemotherapy, with short remissions to aggressive treatments. MCL is probably incurable and has a median survival time of about 2.5 years.

    c. **Mantle-zone lymphoma** is an uncommon indolent variety of MCL without invasion of the follicular center of the involved lymph nodes.

  2. **Diffuse large cell lymphomas.** About 30% of cases originate in extranodal sites, particularly the GI tract and Waldeyer's ring, but also in sinuses, bone, CNS, and other sites. In contrast to most low-grade NHLs, localized presentations (stage I and II disease) are common, and bone marrow involvement is less frequent (less than 25% of cases). Localized presentations (stage I and II disease) may be curable in up to 80% of cases, whereas disseminated disease (stage III and IV disease) is curable 30% to 40% of the time.

    a. **AIDS-related NHLs** are almost universally intermediate-grade or high-grade B-cell lymphomas (see Chapter 37, section II). Most patients present with extranodal disease, often including the GI tract, bone, jaw, and CNS (as parenchymal involvement), but almost any organ can be involved. Dissemination to bone marrow and meninges is characteristic.

    b. **Posttransplantation lymphoproliferative disorders** describe a continuum from oligoclonal lymphoproliferation to frank lymphomas that are similar to AIDS-related lymphoma. These lymphomas are associated with profound (iatrogenic) immunosuppression and share similar histology, potential EBV pathogenesis, and a proclivity for primary parenchymal brain involvement with AIDS lymphomas. Reduction in immunosuppression may lead to regression of lymphoma in some patients.

    c. **Primary effusion lymphoma** is an aggressive lymphoma originating in serosa and presenting with effusions. Dissemination of disease is the rule. It has been strongly associated with presence of the human herpes virus type 8 (HHV-8).

  3. **Small noncleaved lymphomas** are rapidly proliferating lesions with an extremely high mitotic rate and doubling times as brief as 24 hours. Many lymphomas associated with AIDS or organ transplantation are this type.

    a. **Burkitt lymphoma** has a distinctive morphology, natural history, and behavior and is divided into African (endemic) and sporadic types. The cells are nearly equal in size and contain prominent small nucleoli and cytoplasmic lipid vacuoles. In the non-Burkitt type of small noncleaved lymphoma, the cells have a less homogeneous cellular size and composition. The treatment strategy for Burkitt lymphoma has become specialized. Clinicians prefer to treat the non-Burkitt type as Burkitt lymphoma.

    b. **B-cell lymphoblastic lymphoma** is classified with B-lineage acute lymphoblastic leukemia (ALL) and is treated similarly.

G. **T-cell NHLs** constitute about 20% of NHLs in Western societies. They have been poorly characterized in the WF and comprise a number of clinicopathologic entities. T-cell lymphomas have been analyzed in detail by the REAL and WHO classifications, despite the difficulty arising from the rarity of certain categories.

  1. **Precursor T-cell lymphoblastic leukemia/lymphomas** (including T-ALL) are malignancies of immature T cells that occur predominantly in male adolescents and young adults. The nuclei are often "convoluted" in appearance, and the mitotic rate is high.

    a. **Terminal deoxynucleotidyl transferase** (TdT) activity is characteristically positive in these patients. TdT positivity is generally restricted to lymphoblastic lymphoma, ALL (pre-B, T, and null subtypes), and the lymphoid blast crisis of chronic myelogenous leukemia; it is not seen in other NHLs.

    b. Patients usually present with anterior mediastinal masses and often manifest pleural effusion, pericardial effusion, or superior vena cava syndrome. Bone marrow and peripheral blood involvement are frequent, and the syndrome then merges with T-cell ALL. Meningeal involvement is anticipated unless CNS prophylaxis is employed. Therapy that is similar to that used for ALL may cure 40% of cases of lymphoblastic lymphoma.

  2. **Peripheral T-cell and NK-cell neoplasms** refer to all NHLs of T-cell or NK-cell origin except lymphoblastic lymphoma. The spectrum includes low-grade disorders, such as the cutaneous T-cell lymphomas (CTCLs), and a variety of special clinicopathologic syndromes. With the exception of the CTCLs, peripheral T-cell lymphomas (PTCLs) tend to be clinically aggressive even if the morphology suggests a low-grade behavior. Although they have not been directly compared, it appears that the higher-grade PTCLs have a poorer prognosis than intermediate/ high-grade B-cell NHLs, particularly with stage IV disease. Occasionally, a hemophagocytic syndrome can occur.

    a. **The pathologic manifestations of PTCL** often include infiltration of T lymph node regions (paracortical) and increased atypical epithelioid venules. The pleomorphic tumor cells often exhibit clear cytoplasm and occasionally resemble RS cells. These tumors frequently contain an admixture of interdigitating cells, epithelioid cells, eosinophils, and plasma cells. Many peripheral T-cell lymphomas would be placed in the "diffuse mixed" category of the WF.

    b. **Clinical aspects.** PTCLs often develop in middle-aged to elderly patients, who present with constitutional symptoms (B symptoms). Most patients have nodal-based stage III or IV disease with frequent hepatosplenomegaly. Pulmonary and skin involvement are not uncommon. Eosinophilia and polyclonal hypergammaglobulinemia develop in some cases.

H. **Peripheral T-cell clinicopathologic syndromes**

  1. **Adult T-cell leukemia-lymphoma (ATLL)** was initially described in southwestern Japan but has been subsequently seen throughout the world, including the United States. The HTLV-1 virus apparently causes the disease. Cutaneous involvement, lymphadenopathy, organomegaly, a leukemic blood picture, hypercalcemia with osteolytic bone lesions, and CNS involvement characterize ATLL. The cells frequently show a remarkable "knobby" configuration. Immunologically, the cells are CD4 positive. The response to treatment has been poor; combinations of zidovudine and IFN may be useful. A prodromal, less aggressive smoldering phase is also recognized.

  2. **Aggressive NK-cell leukemia-lymphoma** is a rare and rapidly fatal NK-cell malignancy.

  3. **T-cell prolymphocytic leukemia** is discussed in Chapter 23, Chronic Lymphocytic Leukemia, section VI.B.

  4. **T-cell, NK-cell large granular lymphocytic leukemia** is an indolent disease with subtle lymphocytosis of the blood or bone marrow and paraneoplastic neutropenia. It does not usually require treatment. Responses to cyclosporine have been reported. This is also discussed in Chapter 23, Chronic Lymphocytic Leukemia, section III.D.6.

  5. **Lennert's lymphoma** (or lymphoepithelioid lymphoma) refers to an uncommon subtype of PTCL that was originally considered a variant of HL. In this disorder, small lymphocytes with an irregular "corkscrew" nucleus are associated with a marked infiltration by reactive epithelioid cells (activated histiocytes). The reactive cells are probably stimulated by lymphokines elaborated by the neoplastic T cells. Patients often have B symptoms and manifest diffuse disease with splenic involvement. Prognosis is poor.

  6. **Anaplastic large cell lymphoma (ALCL)** is usually of T-cell origin. Occasional cases appear to be of undefined lineage (null cell). The large anaplastic cells are positive for Ki-1 (CD30), an antigen initially described in HL but later found to be present in some neoplastic cells in a variety of aggressive NHLs. It is often associated with t(2;5), which results in fusion of the nucleophosmin gene *NPM* to a tyrosine kinase, ALK (anaplastic lymphoma kinase).

Pathologically, the cases are frequently confused with epithelial tumors (carcinomas) or melanoma. The confusion is sometimes compounded by positive staining for epithelial membrane antigen and by a sinusoidal distribution, which is characteristic of carcinomas or melanomas. Clinically and pathologically, it can be confused with HL, with cutaneous lymphomatoid papulosis (a benign condition with similar histology and spontaneous regressions), or with cutaneous anaplastic lymphoma, which has an excellent prognosis with local treatment. Treatment of ALCL is similar to that of large cell B-cell lymphoma and is believed to have slightly better outcome.

  7. **Angioimmunoblastic T-cell lymphoma.** Immunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) were originally described as abnormal immune reactions clinically characterized by fever, skin rash, autoimmune hemolytic anemia, polyclonal hypergammaglobulinemia, and generalized lymphadenopathy. Pathology revealed diffuse effacement of lymph node architecture, involvement by immunoblasts and plasma cells, and often an abnormal vascular network. Immunohistochemistry and gene rearrangement studies have indicated that many of these patients have underlying T-cell lymphomas from the onset. The course may vary in aggressiveness, with occasional spontaneous remissions. Satisfactory and prolonged responses to corticosteroids can be seen.

  8. **Nasal and nasal-type NK/T-cell lymphomas** include the former angiocentric lymphoma, lethal midline granuloma (malignant midline reticulosis) and lymphomatoid granulomatosis. The neoplastic cells in these disorders involve vessels and lead to an angiodestructive necrotizing process. Nasal NK/T-cell lymphoma involves the palate and sinuses, but metastasis can occur. The course may be indolent or aggressive. It is uncommon in the United States and more common in Asia. In contrast to aggressive diffuse large cell B-cell lymphoma of the nasal cavity, nasal NK/T-cell lymphoma does not usually extend to the CNS. Cells usually are positive for T-cell markers and CD56.

  9. **Hepatosplenic g–d lymphoma** is characterized by sinusoidal infiltration of the liver by T cells expressing the g–d rather than the most common a–b T-cell receptor complex. It is often associated with a hemophagocytic syndrome. Despite the bland appearance of the cells, the clinical course is usually relentless.

  10. **Enteropathy-type intestinal T-cell lymphoma** presents with ulcerative intestinal lesions in patients with gluten-sensitive or other enteropathy. It is uncommon in the United States.

  11. **Subcutaneous panniculitis-like T-cell lymphoma** is another rare form of T-cell lymphoma characterized by infiltration of the subcutaneous tissue.

  12. **CTCLs.** Mycosis fungoides and the Sézary syndrome are described separately (see section VI.A).

I. **Immunologic abnormalities**

  1. Hypogammaglobulinemia is typically seen in small lymphocytic lymphoma but may develop in other lymphomas, particularly after treatment.

  2. Paraprotein spikes, often IgM, are seen particularly in lymphoplasmacytic lymphomas, but are also noted in other B-cell malignancies and in AILD.

  3. Warm or cold antibody immune hemolytic anemias may be seen, particularly in the small lymphocytic type.

  4. Additional autoimmune phenomena, such as circulating anticoagulants (e.g., acquired von Willebrand's disease) may occur, especially in the small lymphocytic lymphomas.

  5. Polyclonal hypergammaglobulinemia is commonly observed in patients with AIDS or PTCL.

  6. Defects in T-cell function are prominent in ATLL and in other lymphomas after treatment.

J. **Pathogenesis**

  1. **Monoclonal antibodies** can identify epitopes on lymphoid cells characteristic of developmental stages of B-cell and T-cell ontogeny. The antibodies are

used with flow cytometry in cell suspensions and with indirect immunoperoxidase labeling in frozen sections. Some of the most useful antibodies are shown in Appendix C4, and leukocyte differentiation antigens are presented in Appendix C5. Monoclonality of B-cell lymphomas is usually established by showing marked dominance of a single light-chain (k or l) type.

2. **Gene rearrangements.** B cells and T cells must rearrange DNA to assemble antigen-specific receptors. Each clone rearranges its genes in a unique way that can be differentiated from the germ line pattern by Southern blot techniques. Identification of gene rearrangements for immunoglobulin and T-cell receptor loci can establish cellular lineage, monoclonality, and sometimes stage of differentiation for lymphoid neoplasms. The application of the polymerase chain reaction methodology may enable detection of down to one clonal cell in 1 million using amplification of breakpoint regions by specific primers.

3. **Specific chromosomal translocations** (Table 21.6) have been associated with histologically distinct lymphoma types. The genetic material found at or near the breakpoint of each translocated chromosome is frequently highly informative and provides clues regarding pathogenesis. For example, in Burkitt lymphoma, the transforming *c-myc* cellular oncogene found on chromosome 8 is involved in a translocation within or adjacent to the heavy-chain gene on chromosome 14 or to one of the light-chain genes (k on chromosome 2 or l on chromosome 22).

Table 21.6 Chromosomal translocations and immunophenotypic markers in lymphoma*a*

In the follicular lymphomas, the translocation also involves the heavy-chain gene on chromosome 14, which is this time juxtaposed with the so-called *BCL-2* gene on chromosome 18. The *BCL-2* gene appears to be significantly involved in the abrogation of *apoptosis* (programmed cell death). Thus, the activation of the *BCL-2* gene by translocation in follicular lymphomas may result in the excessive longevity or accumulation of lymphoma cells, implying a defect in cell death rather than a pure problem of proliferation in that disease. In MCL, the heavy-chain gene on chromosome 14 and the *BCL-1* gene on chromosome 11 are brought into proximity. The *BCL-1* gene encodes cyclin-D1, which is involved in the cell cycle.

4. **Production of lymphokines** by tumor cells may be related to the symptoms or manifestations of specific lymphomas. For example, production of IL-4 by T cells in Lennert's lymphoma may explain the exuberant proliferation of histiocytes in that disease, whereas in angioimmunoblastic lymphomas, IL-6 production may result in plasmacytosis and hypergammaglobulinemia.

5. **The pattern of surface antigens** (Appendix C4) found on lymphoma cells when flow cytometry is used may help identify or corroborate certain lymphoma types. For example, the CD5 antigen, a pan T-cell antigen expressed by a small minority of B lymphocytes, is found on the neoplastic cells of patients with small cell lymphocytic lymphoma and MCL but is absent from the cells of follicular lymphomas and monocytoid B-cell lymphoma.

III. Staging system and prognostic factors

A. **The Ann Arbor system** is used for both HL and NHL, but histopathologic subtype is the prime determinant of survival in NHL.
B. **Survival** (Fig. 21.2; Table 21.4)
   1. **Low-grade lymphomas** are rarely curable and appear to cause a steady percentage of deaths annually. It is possible that the rare, early stages of low-grade NHL (stage I or II) may be curable in some cases, but even this is uncertain. Survival time averages between 6 and 10 years for follicular lymphomas.
   2. **Intermediate-grade and high-grade lymphoma** survival curves generally display two components: a rapid fall off in the first 1 to 2 years followed by an eventual plateau representing a presumptively cured population. About 80% to 90% of patients with stage I or early stage II disease and 30% to 40% with stage III or IV intermediate/high-grade lymphomas may be curable.
   3. **MCL** survival curve shows a rapid and steady decline, with no survival plateau, and a median survival time of 2 to 2.5 years.
C. **Prognostic factors.** Extent of disease at presentation and survival rates are shown in Table 21.4.
   1. **Low-grade lymphomas**
      a. **Sensitivity to therapy** is a prognostic sign in that the attainment of a CR or an excellent partial response (PR) identifies patients who are likely to do well.
      b. **Early stage.** Stage I and II cases constitute less than 15% of all patients with low-grade lymphoma. In one small series, 80% of stage I and II patients younger than 40 years of age who were treated with RT were disease free 10 years after diagnosis.
      c. **Follicular mixed (small cleaved and large cell) lymphomas.** Although these lymphomas are probably rarely curable, extremely long-term remissions have been reported by some institutions using regimens both with and without doxorubicin. Other authorities believe that there is little difference, if any, in responsiveness to treatment or duration of remission between follicular small cleaved and mixed NHL.
      d. **The international prognostic index** described below is also useful in stratifying patients with indolent lymphoma.
   2. **Intermediate/high-grade lymphoma.** Stage I or II presentations, constituting 30% to 40% of these lymphomas, are highly curable (about 80%), although tumor bulk (more than 10 cm in largest diameter) adversely affects outcome. The International Non-Hodgkin's Lymphoma Prognostic Factors Project has identified a predictive model for outcome that has established **five independently important prognostic factors**. The 5-year survival rate was 73% for patients manifesting none or one of the adverse risk factors and 26% for patients with four or five risk factors. These important risk factors are as follows:
      a. Age (older than 60 years of age, adverse)
      b. Stage I or II versus III or IV (III and IV, adverse)
      c. Number of extranodal sites (more than 1 site, adverse)
      d. Performance status (low status, adverse)
      e. Serum LDH (elevated level, adverse)

IV. Staging

A. **Clinical evaluation.** See Evaluation of Suspected Lymphoma, section I, section II, section III, section IV.
B. **Initial staging evaluation**
   1. The staging evaluation as outlined in Hodgkin Lymphoma, section IV.B, is generally applicable in NHL, but patients may undergo two bone marrow biopsies.
   2. Flow cytometry on the peripheral blood and bone marrow in low-grade lymphomas may define a clonal excess and suggest hematogenous involvement, even when circulating lymphoma cells are not seen.
   3. Diagnostic spinal tap is indicated in lymphoblastic lymphoma, lymphomas occurring in AIDS, Burkitt lymphoma, and probably in intermediate/high-grade lymphomas with marrow, sinus, or testicular involvement.
   4. Upper GI and small bowel series should be performed in patients with GI symptoms and signs or involvement of mesenteric nodes or Waldeyer's ring because of the high association of these findings with GI involvement. Endoscopic evaluation is performed as indicated.
C. **Restaging evaluation** is performed to verify CR, particularly with potentially curable histologies. All abnormal studies are repeated, including biopsies of accessible previously involved sites. Patients with intermediate-grade or high-grade lymphomas and residual masses on CT scans or radiographs should be followed closely with repeat studies; stable residual masses usually do not contain lymphoma.

V. Management

A. **Surgery** is limited to the following indications:
   1. Biopsy for diagnosis. Staging laparotomy is rarely conducted.
   2. Splenectomy for large spleens and significant hypersplenism.
   3. Resection may be indicated in primary GI lymphoma (see section VI.C).
B. **Therapy for indolent lymphomas**
   1. **True stage I and II disease** (15% cases): RT to a dose of 3500 to 4000 cGy may be administered to all known sites of disease (including draining lymph nodes in E presentation). Large RT fields do not increase the cure rate and may decrease tolerance to chemotherapy later. Prolonged disease-free survival has been reported in some patients.
   2. **Stage III and IV disease**
      a. **No treatment.** Most patients with advanced indolent disease may be observed with no therapy and without adverse influence on survival. Therapy is instituted in the presence of any systemic symptoms, rapid nodal growth, or imminent complications of the disease, such as obstructive phenomena or effusions. The median times to "requiring therapy" vary from 16 months for the follicular, mixed group, to 48 months for the follicular, small cleaved group, to 72 months for the small lymphocytic group. Spontaneous remissions may occur during the period of no therapy.
      b. **Single-agent therapy** with chlorambucil or cyclophosphamide gives good responses that may develop slowly in indolent NHL. Cyclophosphamide has the disadvantages of alopecia and hemorrhagic cystitis. Data suggest that the purine analogues, fludarabine and cladribine, may exhibit activity rivaling

the alkylating agents, but relatively few previously untreated patients have been reported. Up to 40% to 50% of patients with previously treated low-grade lymphomas respond to these purine analogues. Dosages are as follows:

1. Chlorambucil, 4 to 6 mg/m^2 PO daily
2. Fludarabine, 25 mg/m^2 IV daily for 5 days every 4 weeks
3. Cladribine, 0.14 mg/kg per day IV over 2 hours for 5 days every 4 weeks, or 0.1 mg/kg/day by continuous IV infusion for 7 days every 4 weeks

  c. **Combination chemotherapy.** Multiagent therapy may be used if a rapid response is required. Chlorambucil or cyclophosphamide plus corticosteroids in pulse doses, and fludarabine plus mitoxantrone combinations are commonly used regimens (see Chl & P, CVP, and FMD in Appendix A2 for regimens and dosages).

Single-agent or combination chemotherapy produces CRs or excellent PRs 60% to 80% of patients. Doxorubicin-containing regimens have no clear advantages for low-grade NHL and are often reserved for later stages of the disease or adverse presentations. Treatment is generally continued until a maximum response is achieved. Maintenance chemotherapy does not appear to prolong survival, may compromise further treatment, and is potentially leukemogenic.

  d. **IFN-**a has demonstrable activity in the follicular lymphomas. No clear-cut dose schedule is superior, and doses as low as 2 to 3 million U three times weekly may produce responses in up to 40 to 60% of patients. The place of IFN- a in the routine management of follicular lymphoma is not clear. It has been used in several randomized studies as part of either induction or maintenance therapy for previously untreated patients. Results of some of these series suggest a potentiation of response rates, a prolongation of remission duration, and possibly an effect of IFN- a on survival.

  e. **RT**
    1. **Palliative RT** is used for sites of bulky disease and to relieve obstruction or pain. RT alone may be used when most of the disease sites do not require treatment but one or two areas are troublesome. However, multiple courses of RT exhaust the marrow and are discouraged when chemotherapy is an effective alternative.
    2. **"Limited" stage III.** Although some series have observed long-term disease-free survival with total lymphoid radiation for highly selected stage III presentations (e.g., no bulky disease, asymptomatic, fewer than five involved sites), this approach is not generally accepted for most patients.

  f. **Rituximab** (Rituxan, Mabthera) is a chimeric humanized anti-CD20 monoclonal antibody approved for the treatment of refractory or relapsed indolent B-cell lymphoma. It is believed to mediate cytotoxicity through activation of complement, through activation of antibody-dependent cytotoxic cells, and possibly directly by mediating an as yet undefined intracellular signaling.
    1. The established dose of rituximab is 375 mg/m^2 IV weekly for 4 weeks. The maximum tolerated dose has not been defined, but it is doubtful that higher doses or more prolonged administration improves outcome.
    2. An overall 50% response is expected in indolent B-cell lymphomas, with a median duration of about 1 year. It is believed that small lymphocytic lymphoma may be less responsive than follicular NHL because of lower expression of CD20 antigen. Responses of about 30% have been reported in large cell lymphoma. Combinations of rituximab with chemotherapy (CHOP and other regimens) are being studied.
    3. Mild infusion-related fever or rigors are common. Cytopenias develop occasionally. Reactions resulting in death (anaphylaxis, tumor lysis syndrome, adult respiratory distress syndrome) have also been seen, mainly in patients with circulating lymphoma or CLL cells; slow escalation of the dose as tolerated is recommended for such patients. Autoimmune phenomena have also been reported.

  g. **Histologic conversion.** Indolent lymphomas that transform to an aggressive cell type usually have a poor prognosis. Limited, relatively asymptomatic presentations, however, may respond well to treatment used for intermediate/high-grade NHL. The CNS is frequently involved (particularly the meninges) in transformed NHL and is rarely affected in low-grade NHL. High-dose chemotherapy and stem cell support for cases of transformed chemosensitive low-grade NHL should be considered.

3. **Experimental therapies**
  a. **Monoclonal antibodies** of several types, in addition to rituximab, have been employed in the treatment of low-grade (and some aggressive) NHL.
    1. **Monoclonal antibodies** to other lymphoma antigens are also under study. Targets include B-cell antigens (e.g., CD19, CD20, CD22) or more generalized common antigens (CD5, CD25). Campath-1H, a humanized antibody against CD52 (present in B cells, T cells, and monocytes) is believed to have satisfactory activity in CLL, prolymphocytic leukemia, and certain T-cell lymphomas.
    2. **Radioactive monoclonal antibodies** offer the advantage of targeted radioimmunotherapy. Responses in the range of 50% to 80% have been reported in previously treated patients. ^{131}I-labeled anti-CD20 (Bexxar) and ^{90}Y-labeled anti-CD20 (ibritumomab tiuxetan, Zevalin) are more advanced in clinical testing and are expected to be available soon. ^{131}I-Lym1 is being tested in aggressive NHL.
    3. **Immunotoxins** have been under investigation but remain of unclear benefit.
  b. **Idiotype vaccines** have been used in a limited fashion to stimulate cellular and humoral immune response against the idiotype of the lymphoma cells. Generation of idiotype vaccines is labor intensive. Infusion of autologous dendritic cells pulsed with idiotype have been used for the same purpose. Although an immune response is produced in most patients with minimal disease, the magnitude of clinical benefit is unclear.
  c. **Antisense oligonucleotide** treatment against *BCL-2* is being tested in phase I and II trials.
  d. **High-dose chemoradiotherapy** with bone marrow or peripheral stem cell support is undergoing extensive study in patients with relapsed or newly diagnosed low-grade NHL. Some centers are purging marrow with monoclonal antibodies. Researchers at the Dana Farber Cancer Center have observed a striking correlation between disease-free survival and the ability to purge marrow of cells expressing the t(14;18) rearrangement (using the sensitive polymerase chain reaction technique). Although no convincing data support high-dose therapy in the routine management of low-grade NHL, it is employed in relatively young patients with adverse presentations in an effort to prolong remissions.
  e. **Allogeneic BMT or stem cell transplantation** is proposed by certain centers for the treatment of refractory young patients with related donors and should probably be reserved as a last resort. Nonmyeloablative, less toxic preparative regimens are being tested and may render the procedure safer.

C. **Therapy for intermediate/high-grade NHL.** (Therapy for special lymphoma subtypes are discussed in section V.D, section V.E, section V.F, and in section VI).
  1. **Localized presentations.** Nonbulky (less than 10 cm) stages IA and IIA cases, including extranodal (E) presentations, can be successfully managed by three cycles of a doxorubicin-containing regimen (CHOP) followed by IFRT (equivalent to 3000 cGy in 10 fractions). Virtually all patients achieve CR, and the actuarial relapse-free survival exceeds 80%. Another approach is full-course chemotherapy with or without subsequent RT.
  2. **Stage I-II (bulky), III, and IV disease** is treated with CHOP chemotherapy (Appendix A2). For areas of bulky disease, IFRT may benefit the patient if all bulky disease that was present before giving chemotherapy can be safely encompassed by the radiation ports.

Despite claims to the contrary, there is no proof that any of the newer, more complex and more toxic regimens are superior to CHOP. The results of an intergroup trial comparing CHOP with three of the purportedly more effective newer combinations showed CHOP to be equally active and less toxic. One can expect long-term disease control ("cure") in roughly 30% to 40% of patients with advanced-stage, intermediate/high-grade NHL treated with CHOP and similar programs. The claims for improved outcome reported in single-institution trials using other regimens are likely the result of incomplete follow-up and selection bias. Some of these alternative regimens (m-BACOD, M-BACOD, MACOP-B, ProMACE/CytaBOM) are shown in Appendix A2.

  a. **Complete restaging** to assess completeness of response is mandatory. Restaging is usually done after three to four cycles of CHOP and again after six cycles. Patients are generally given at least two additional cycles of therapy after attainment of CR (usually a total of six to eight cycles).
  b. **CNS prophylaxis** using intrathecal chemotherapy, sometimes complemented by cranial irradiation, appears to be indicated in situations associated with a high risk for meningeal relapse. This strategy is particularly advised in cases of involvement of the paranasal sinuses, when there is contiguous spread to the CNS, and in the small noncleaved lymphomas (especially the Burkitt type). Other indications may include primary testicular lymphoma and intermediate/high-grade lymphomas involving the bone marrow extensively, although the latter indication is more controversial.
  c. **Maintenance therapy** does not enhance survival and thus is not advised.
  d. **Refractory patients** failing to achieve a CR may be salvaged with consolidation RT if the involved area is not extensive. Salvage chemotherapy (see later), followed by autologous stem cell transplantation, is the preferred approach, if feasible. Patients achieving a PR may have a 10% to 30% chance of cure, but the long-term survival rate of truly refractory patients is reported in the 10% range, so that high-dose chemotherapy is not generally recommended. Allogeneic BMT can be considered for these patients.

3. **Relapsed intermediate-grade and high-grade lymphomas**
  a. **Salvage chemotherapy regimens** often employ high-dose cytosine arabinoside, corticosteroids, and cisplatin with or without etoposide (see DHAP and ESHAP in Appendix A3). MINE (ifosfamide, mitoxantrone, and etoposide) and other potentially helpful regimens (CEP, CEPP-B, EVA, miniBEAM, and VAPEC-B) are also shown in Appendix A3. These programs generally produce significant but short-lasting remissions in 30% to 50% of patients. A small proportion of patients, probably fewer than 10%, have prolonged responses.
  b. **High-dose chemotherapy plus RT with autologous bone marrow or stem cell support.** A similar strategy to that employed in HL has been adopted for intermediate-grade NHL after relapse from standard CHOP-like chemotherapy. A conditioning regimen based on high-dose chemotherapy, sometimes combined with total-body irradiation, is used and followed by reinfusion of cryopreserved marrow or peripheral blood progenitor cells (stem cells) mobilized by growth factors and sometimes by chemotherapy. The results of this strategy are best in chemosensitive recurrences, in which about 40% of patients may derive long-term, disease-free survival. The results are far less optimistic in patients whose disease is chemoresistant or in patients who

have never achieved remission. The relative merits of salvage chemotherapy followed by autologous BMT have been convincingly proved in a multicenter randomized European study (the PARMA study).

      c. **Allogeneic BMT** differs from autologous BMT in that a potential graft-versus-lymphoma immune reaction may complement the effects of the conditioning regimen. The degree to which this effect exists in lymphoma is subject to debate. Allogeneic transplantation may be most reasonable in young patients who have a suitable donor match and who do not fall into the favorable categories for benefit from autologous transplantation.

    4. **Experimental therapies.** Monoclonal antibody approaches similar to those employed in low-grade NHL are under investigation. Other programs attempt to reverse multiple drug resistance as mediated by the *MDR-1* gene (using agents such as calcium-channel blockers, quinine, and cyclosporine) or to intensify the dose of chemotherapeutic agents (using growth factors with repeated infusions of autologous, mobilized stem cells). Autologous stem cell transplantation has been proposed as consolidation during first remission for high-risk patients.

D. **Therapy for aggressive MCL** with standard chemotherapy regimens has generally been ineffective at achieving long-term remissions. The HyperCVAD and high-dose methotrexate plus cytarabine regimen followed by transplantation has been proposed for treatment of mantle cell NHL by the M. D. Anderson Cancer Center. Long-term results appear to be better than those in historical controls. The courses in this regimen are repeated every 21 days, if possible, as follows:

Induction course 1 (HyperCVAD)

Cyclophosphamide, 300 mg/m^2 IV, every 12 hours on days 1 to 3

Vincristine, 2 mg IV, on days 4 and 11

Doxorubicin, 25 mg/m^2, infused over 24 hours on days 4 and 5

Dexamethasone, 40 mg IV or PO, on days 1 through 4 and 11 through 14

Granulocyte colony-stimulating factor (G-CSF), 5 µg/kg IV or SC daily, beginning on day 6, until the granulocyte count is > 4500/µL

Induction course 2 (to be started immediately after recovery from course 1)

Methotrexate, 200 mg/m^2 IV bolus on day 1, followed by 800 mg/m^2 infused IV over 24 hours; alkaline IV fluids are administered

Leucovorin, 50 mg PO given 24 hours after the end of methotrexate infusion, followed by 15 mg PO every 6 hours for eight doses (dosage adjusted according to the serum methotrexate level)

Cytarabine, 3000 mg/m^2 IV over 1 hour every 12 hours for total of four doses beginning on day 2 (dosage is reduced to 1000 mg/m^2 per dose for patients older than 60 years of age or with serum creatinine levels higher than 1.5 mg/dL)

Allogeneic or autologous transplantation after two or four rounds of chemotherapy is considered for patients younger than 65 years of age.

E. **Therapy for lymphoblastic lymphoma** is patterned after therapy for the closely related ALL. Overall results of therapy indicate a 40% long-term, disease-free survival, with the best prognosis seen in patients who have minimal or no marrow involvement, no CNS involvement, and normal serum LDH levels. Patients with poor prognostic presentations of lymphoblastic lymphoma are being considered for early autologous or allogeneic transplantation or more intensive primary chemotherapy programs.

Stanford University researchers reported a 94% freedom-from-relapse rate at 5 years for patients without the above adverse prognostic factors with a regimen that involves 1 month of induction therapy, 1 month of CNS prophylaxis, 3 months of consolidation, and finally 7 months of maintenance therapy, as follows:

Cyclophosphamide, 400 mg/m^2 PO for 3 days, on weeks 1, 4, 9, 12, 15, and 18

Doxorubicin, 50 mg/m^2 IV, on weeks 1, 4, 9, 12, 15, and 18

Vincristine, 2 mg IV, on weeks 1, 2, 3, 4, 5, 6, 9, 12, 15, and 18

Prednisone, 40 mg/m^2 daily for 6 weeks (tapered off); then for 5 days on weeks 9, 12, 15, and 18

CNS prophylaxis consists of whole-brain RT (2400 cGy in 12 fractions) and intrathecal methotrexate (12 mg for each of six doses) given between weeks 4 and 9

l-Asparaginase, 6000 U/m^2 IM (maximum, 10,000 U) for five doses at the beginning of CNS prophylaxis

Maintenance therapy consists of methotrexate (30 mg/m^2 PO weekly) and 6-mercaptopurine (75 mg/m^2 PO daily) during weeks 23 to 52.

F. **Therapy for specific types of intermediate/high-grade lymphomas**
    1. **Therapy for AIDS-associated lymphoma.** See Chapter 37, .
    2. **Therapy for ATLL** is ineffective. A combination of zidovudine (AZT) and IFN- a has been stated to show promise. Occasional patients may benefit briefly from combination chemotherapy programs used in intermediate/high-grade NHL or from 2-deoxycoformycin, a purine analogue.
    3. **Posttransplantation lymphoproliferative disorder** includes a spectrum of lymphoproliferation after intense iatrogenic immunosuppression in organ transplant recipients. It is believed that polyclonal or oligoclonal B-cell proliferation is initially driven by EBV infection escaping immune surveillance. Ongoing proliferation results in true malignant transformation and development of monoclonal aggressive NHL. The disease typically manifests with hectic fever, malaise, and cytopenias. Nodal involvement may or may not be present at presentation. Bone marrow and CNS involvement are common. This disorder may respond to withdrawal of immunosuppression in early stages, but systemic chemotherapy is usually required. The prognosis depends largely on comorbid conditions.
    4. **Therapy of peripheral T-cell lymphomas**
        a. **Angioimmunoblastic lymphoma** (AILD) has been managed with generally poor results by conventional chemotherapy or corticosteroids, although occasional long-term responses or spontaneous regressions have occurred. More recently, responses to IFN- a, cyclosporine, or high-dose chemotherapy with stem cell support have been described in small series or case reports.
        b. **Angiocentric lymphoma** with localized involvement of the palate and sinuses (lethal midline granuloma) may benefit from RT alone or three courses of CHOP followed by RT.
        c. **Primary cutaneous CD30-positive T-cell disorders**
          1. **Lymphomatoid papulosis** is usually a self-limited disease.
          2. **Cutaneous anaplastic lymphoma** can sometimes be treated with single-agent chemotherapy (cyclophosphamide or methotrexate) with or without corticosteroids or RT. It can often be confused with ALCL that is treated as a common aggressive lymphoma.
    5. **Histiocytic and dendritic cell neoplasms** represent a rather confusing category of ill-defined rare diseases.
        a. **Malignant histiocytosis-hemophagocytic syndrome** (fever, jaundice, hepatosplenomegaly, coagulopathy, and hemophagocytosis) has been described and most likely represents a variant of T-cell lymphoma. Etoposide has been reported to control this syndrome.
        b. **Langerhans' cell histiocytosis** is a condition caused by clonal proliferation of Langerhans' cells. It may be localized or generalized with variable aggressiveness. Combination chemotherapy may often be necessary.

VI. Special lymphoma syndromes

A. **Mycosis fungoides** (MF) **and Sézary syndrome** (SS) are CTCLs. Both are malignant cutaneous lymphoproliferative disorders of helper T cells (CD4).
    1. **Dermatologic presentation** is localized plaques evolving into tumor nodules in MF and diffuse exfoliative erythroderma associated with abnormal circulating cells in SS.
    2. **Histopathology** shows atypical T cells with irregular cerebriform nuclei (MF cells) infiltrating the epidermis and a zone beneath it, forming characteristic Pautrier's microabscesses. Enlarged lymph nodes may not always show overt lymphomatous infiltration, but techniques such as T-cell–receptor gene arrangement may reveal early involvement.
    3. **Natural history.** A long history of undiagnosed skin disease often precedes the specific diagnosis.
        a. **Cutaneous stages of MF**
          1. Premycotic stage: nonspecific eczematoid or erythematous lesions may last many years.
          2. Plaque stage
          3. Tumor stage
        b. **Lymph node involvement** occurs with increasing skin involvement. Histologically confirmed lymph node involvement indicates a poor prognosis.

c. **Visceral involvement.** Almost any organ can be involved late in the disease, particularly the liver, spleen, lung, and GI tract, but the marrow is relatively spared. A peculiar epitheliotropic pattern of dissemination may be observed.

4. **Staging system.** A variety of systems have been proposed, including a TNM system. One example is the following:

Stage I (without lymphadenopathy)
  Stage IA Limited plaques
  Stage IB Generalized plaques
Stage II (without histologic involvement of nodes)
  Stage IIA   Limited or generalized plaques with adenopathy
  Stage IIB   Cutaneous tumors with or without adenopathy
  Stage III   Generalized erythroderma with or without adenopathy but without histologic involvement of lymph nodes or viscera
  Stage IV   Histologic involvement of lymph nodes or viscera at any cutaneous stage

5. **Prognosis.** The overall median survival time is 8 to 9 years from time of diagnosis. Survival time is 2 to 4 years from onset of tumor stage or lymph node involvement and less than 18 months from visceral involvement.

6. **Treatment for skin involvement**
   a. **Topical chemotherapy with nitrogen mustard** is useful in the plaque stage. Cutaneous allergic reactions may develop.
   b. **Electron-beam RT** is technically demanding but has produced durable remissions, particularly in early stages of disease.
   c. **Psoralen with ultraviolet light** (PUVA) repeated three times a week is effective for the plaque phase. Long-term benefits and side effects are poorly defined.
   d. **Retinoids.** Bexarotene (Targretin) and other retinoids (such as *cis*-retinoic acid**)** has demonstrated activity, particularly in the plaque stage. Only Targretin has been approved for this indication.

7. **Systemic chemotherapy and investigational approaches**
   a. **Systemic therapy** is recommended only for patients with extracutaneous disease. A variety of single agents (e.g., doxorubicin, cyclophosphamide, methotrexate, bleomycin, steroids) and combinations have provided temporary responses. Combinations produced more CRs than did single agents.
   b. **The purine analogues** 2-deoxycoformycin (pentostatin), cladribines, and fludarabine have all shown activity; fludarabine may be less active than the others.
   c. **IFN-**a has a response rate of 45% in CTCL.
   d. **Denilukin diftitox** (DAB389-IL-2, Ontak) is a fusion protein between IL-2 and diphtheria toxin that was recently approved for the treatment of CTCLs failing other treatments. Immunosuppression is a common side effect.
   e. **Antibody therapy.** Transient responses to monoclonal T-cell antibodies have been observed in CTCL, and radiolabeled monoclonal antibodies have demonstrated activity.

B. **Primary CNS lymphoma** is essentially always of high histologic grade (large cell, immunoblastic) and of B-cell origin. Lesions are primarily parenchymal and involve deep periventricular structures. Multiple lesions occur in 20% to 40% of cases. The leptomeninges are involved in 30% of cases at diagnosis and in most cases at autopsy.

1. **Etiology and epidemiology**
   a. Primary CNS lymphoma accounts for about 1% of brain tumors and 1% of extranodal lymphomas. The disease is associated with advanced age (older than 60 years of age), AIDS, drug-induced immunosuppression (e.g., for transplantation), and congenital immunodeficiency syndromes.
   b. Primary CNS lymphoma accounts for roughly 50% of all lymphomas seen in transplant recipients and occurs at a somewhat lower frequency in AIDS.
   c. Relationship to EBV infection is suggested by discovery of the EBV genome in some cases of CNS lymphomas arising in transplant recipients and AIDS patients.
   d. In AIDS cases, primary CNS lymphoma appears in a setting of severe CD4 depression, with counts frequently less than 50/mm^3.

2. **Clinical presentations** include headache, personality changes, and hemiparesis. Symptoms of meningeal infiltration or spinal cord compression are less common. Associated systemic lymphoma is rare. Ocular lymphoma (uveitis) may precede or follow the diagnosis of CNS lymphoma.

3. **Evaluation.** The diagnosis can usually be made with stereotactic biopsy and without formal surgical exploration.
   a. **CT scan.** Deep periventricular lesions often involve the corpus callosum, basal ganglia, or thalamus and often appear hyperdense before contrast dye injection. Contrast often produces generalized intense enhancement, unlike the picture of gliomas and metastases. In AIDS patients, the precontrast scan may be hypodense.
   b. **Magnetic resonance imaging scan** may reveal additional lesions not seen by CT scan.
   c. **Lumbar puncture.** Nonspecific elevation of CSF protein is common. Abnormal cells may be found in 25% to 35% of patients undergoing lumbar puncture at diagnosis. Identification of malignant cells may be enhanced by immunofluorescent techniques with monoclonal antibodies.
   d. **Ophthalmologic examination,** including slit-lamp examination
   e. HIV antibody; HIV titer if positive
   f. Enumeration of the CD4 count
   g. Abdominal CT scan, chest radiograph
   h. Bone marrow biopsy

4. **Therapy**
   a. **Corticosteroids** are extremely effective in primary CNS lymphomas. Lesions may disappear on steroids alone and preclude histologic diagnosis after steroids are given.
   b. **Cranial RT.** Doses of 4000 to 5000 cGy appear necessary, with 1000 to 1500 cGy focal boost to the tumor bed. RT is the preferred treatment in patients who are not suitable candidates for chemotherapy.
   c. **Chemotherapy** with high doses of CNS-penetrating drugs (methotrexate, cytarabine) followed by intrathecal chemotherapy and RT has become the preferred treatment, especially for younger patients, because it appears to improve disease-free survival significantly. Because combined-modality treatment is associated with a high incidence of dementia, several investigators are trying chemotherapy alone and reserving RT for relapses.

   The following popular regimen achieves a median time to progression of 3 years but a high incidence of dementia that is often debilitating:

   Methotrexate, 1 g/m^2 IV, on days 1 and 8

   Methotrexate, 12 mg/dose, given into Omaya reservoir on days 1, 4, 8, 11, 15, and 18

   Dexamethasone, 16 mg/day, tapered by day 18

   Followed by whole-brain RT (4000 cGy with 1440 cGy boost)

   After 3 weeks of rest: cytarabine (3 g/m^2 IV daily for 2 days); repeated in 3 weeks

5. **Clinical course.** Initial response is generally followed by relapse in the CNS, meninges, or intraocular contents. Systemic relapse is uncommon. Survival time is usually less than 2 years, although longer survivals are occasionally observed. Primary CNS lymphoma complicating AIDS is associated with a median survival time of less than 3 months.

C. **Primary gastrointestinal lymphoma** (PGL) is the most common form of solitary extranodal disease and may occur in the stomach, small bowel, and large bowel.

1. **Associated diseases.** The incidence of enteropathy-type T-cell lymphoma is increased in patients with ulcerative colitis, regional enteritis, or celiac disease. a-Heavy-chain disease is present in some patients with the Mediterranean type of PGL. MALToma of the stomach is associated with *H. pylori* infection.

2. **Histopathology.** *H. pylori*–associated MALToma of the stomach usually has low-grade histology. Occasionally, transformation to a large cell lymphoma may occur. Significant mucosal thickening may be present before spread to regional or distant nodes. *H. pylori* can usually be found in endoscopic biopsies. MALToma, follicular lymphoma, MCL, or other aggressive lymphomas may be found elsewhere along the GI tract.

3. **Symptoms and physical findings.** Anorexia, nausea, vomiting, weight loss, GI bleeding, or abdominal pain is present in most patients. An abdominal mass may be present, but peripheral lymphadenopathy is not common.

4. **Complications.** Obstruction may complicate the course of PGL. Perforation or hemorrhage may be either a presenting sign or, more often, a complication of treatment for PGL. Therapy can cause perforation by the lysis of the lymphoma's involvement of the full thickness of the wall of the organ involved.

5. **Diagnosis.** Endoscopy or barium contrast radiographs usually show large mucosal folds, ulceration, masses, lumen narrowing, or annular strictures. Gastric lymphomas may be indistinguishable from peptic ulcer by both radiologic and endoscopic criteria. Undifferentiated carcinoma of the GI tract may be confused with intermediate-grade and high-grade lymphoma even after expert histologic evaluation; immunohistochemical verification of diagnosis is often necessary. Multiple sites of involvement should be excluded by barium follow-through or endoscopy in patients with MALToma or MCL.

6. **Management of PGL**
    a. **Surgical management.** Laparotomy may be needed to establish the diagnosis or treat complications. Readily resectable solitary lesions of the small or large bowel should be considered for surgical removal. Gastrectomy for gastric lymphoma is largely abandoned.
    b. **Medical management** should be based on histologic subtype and extent of disease. Intermediate/high-grade lesions are treated primarily with combination chemotherapy.
    c. **Gastric MALToma** usually regresses after eradication of *H. pylori.* One of the following 2-week regimens can be used:

    Clarithromycin, 250 mg twice daily; metronidazole, 500 mg twice daily; and omeprazole

    Tetracycline, 500 mg four times daily; metronidazole, 250 mg four times daily; and Pepto-Bismol, 2 tablespoons four times daily

    Amoxicillin may be used instead of metronidazole or tetracycline in case of intolerance. At least a 70% CR is expected. Patients with a large cell component or with metastatic disease are not expected to respond to antimicrobial therapy. CHOP, IFRT, or a combination of these can be considered. Gastrectomy is probably not superior to RT for local control.

D. **Burkitt lymphoma** (BL) is a specific subtype of the small noncleaved cell high-grade NHL. The cells in BL are very uniform with round or oval nuclei, two to five prominent nucleoli, and cytoplasm rich in RNA. The cells are of B lineage, expressing monoclonal surface IgM. A consistent series of cytogenetic translocations (see Table 21.6) and explosive growth characterizes BL.
    1. **Epidemiology and etiology**
        a. BL is endemic in certain regions of equatorial Africa and other tropical locations. A sporadic form of BL occurs in the United States and throughout the world. The disease occurs predominantly in childhood but can be seen in young adults, particularly in the sporadic form.
        b. EBV has been found in the genome of endemic BL but rarely in the sporadic form. Very high EBV antibody titers are seen in the endemic form.
    2. **Clinical features** (Table 21.7)

Table 21.7 Clinical features of Burkitt lymphoma

    3. **Staging system.** A variety of systems have been proposed. The NCI system is as follows:
    StageDisease distribution
    A   Single solitary extra-abdominal site
    B   Multiple extra-abdominal sites
    C   Intra-abdominal tumor
    D   Intra-abdominal plus one or more extra-abdominal sites
    AR   Intra-abdominal: more than 90% of tumor resected
    4. **Prognosis.** Before effective treatment, only 30% of sporadic cases survived. Using combination chemotherapy and CNS prophylaxis, the survival rate is at least 60%. Children and young adults with limited (A, B, AR) disease have an excellent prognosis with a 90% survival rate. Bone marrow and CNS involvement carry a poor prognosis. Adult cases of BL, particularly those of advanced stage, do more poorly than childhood cases.
    5. **Treatment**
        a. Cyclophosphamide therapy alone has been curative for many localized presentations in Africa.
        b. Multiagent, aggressive regimens are necessary for the sporadic form as well as for Burkitt-like NHL. One such program combines cyclophosphamide, vincristine (Oncovin), methotrexate, and prednisone (COMP) with CNS prophylaxis. Similarly, the NCI protocol 89-C-41 alternates two cycles of CODOX-M with two cycles of IVAC (see Appendix A2) in patients with Burkitt-like NHL, with excellent results.
        c. Because of the extremely rapid growth rate, massive acute destruction of tumor with initial chemotherapy usually results in tumor lysis syndrome (see Chapter 27, section XIII).
E. **Systemic Castleman's disease.** Initially, Castleman's disease referred to *localized giant lymph node hyperplasia* usually involving the mediastinum or abdomen. The disease is associated with infection with HHV-8 and probably promoted by viral IL-6 production. A disorder exhibiting the histopathologic features of the plasma cell type of Castleman's disease but with a generalized presentation has been described.
    1. **Clinical features**
        a. Fever, malaise, and weakness
        b. Lymphadenopathy, usually generalized
        c. Organomegaly
        d. Edema, anasarca, and effusions
        e. Pulmonary and CNS involvement
        f. Anemia, thrombocytopenia, polyclonal hypergammaglobulinemia, and elevated ESR
    2. **Histopathology** shows preservation of lymph node architecture, but with prominent germinal centers, either hyperplastic or hyalinized, and diffuse marked plasma cell infiltration.
    3. **Clinical course** is either persistent or episodic with remissions and exacerbations. Lymphoma or Kaposi's sarcoma occasionally develops. The median survival time is 30 months.
    4. **Treatment.** Corticosteroids and antitumor agents used in NHL have met with occasional responses. IL-6 has been implicated in the pathogenesis of this disorder, with a reported clinical response to treatment with an anti–IL-6 antibody.

Suggested Reading

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Chapter 22 Plasma Cell Disorders

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Immunoglobulins are produced by B lymphocytes and plasma cells. A clone of cells producing immunoglobulins may proliferate to sufficient mass that a monoclonal protein (M protein) is detectable as a peak or "spike" on serum protein electrophoresis. Clonal growth may be progressive or stable for many years. Properties of normal serum immunoglobulins are shown in Table 22.1.

Table 22.1 Normal human serum immunoglobulins

I. Epidemiology and etiology

A. **Classification** of diseases associated with monoclonal paraproteinemia
   1. **Plasma cell neoplasms**
      a. Plasma cell myeloma (PCM)
      b. Waldenström's macroglobulinemia (WM)
      c. Heavy-chain disease
      d. Amyloidosis
      e. Papular mucinosis
   2. **Other neoplastic diseases**
      a. B-lymphocyte neoplasms (malignant lymphoma, chronic lymphocytic leukemia [CLL])
      b. Neoplasms of cell types not known to synthesize immunoglobulins (solid tumors, monocytic leukemia)
   3. **Non-neoplastic disorders**
      a. Monoclonal gammopathy of undetermined significance (MGUS)
      b. Autoimmune diseases (e.g., systemic lupus erythematosus)
      c. Hepatobiliary disease
      d. Chronic inflammatory diseases
      e. Immunodeficiency syndromes
      f. Miscellaneous diseases (e.g., Gaucher's disease)
      g. Pseudoparaproteinemia
B. **Incidence.** MGUS, PCM, and WM are the most common disorders associated with M proteins. The average age at the time of diagnosis is 60 years, and the incidence increases with age.
   1. **MGUS** (formerly *benign monoclonal gammopathy*). The approximate incidence of MGUS is 0.2% for patients 25 to 49 years of age, 2% for those 50 to 79 years of age, and 10% for those 80 to 90 years of age.
   2. **PCM** develops in 3 per 100,000 population. Sixty percent of patients are men. More than 98% of patients are older than 40 years of age. PCM is the most common lymphohematopoietic malignancy in African Americans.
   3. **WM** has an incidence that is about 5% to 10% of that of PCM. Two thirds of cases occur in men.
   4. **Lymphomas.** Excluding MGUS, PCM, and WM, about half of patients with monoclonal gammopathies have lymphocytic lymphoma or CLL. The paraprotein is nearly always either immunoglobulin M (IgM) or IgG, and patients are usually asymptomatic from the paraprotein. Patients with other types of lymphoma do not have an increased incidence of monoclonal proteins.
C. **Etiology.** No specific etiologic agent for the plasma cell dyscrasias has been found. Predisposing factors in humans appear to be the following:
   1. **Radiation exposure,** which slightly increases the risk for PCM
   2. **Chronic antigen stimulation.** Many M proteins have been shown to be antibodies directed against specific antigens, such as microbial antigens, red blood cell antigens, lipoproteins, rheumatoid factors, neural antigens, and coagulation factors. Chronic antigenic stimulation (e.g., chronic osteomyelitis or cholecystitis) may predispose to the development of PCM or MGUS.
   3. **Environmental exposure.** Exposure to benzene in the workplace and the use of hair dye are associated with an increased incidence of PCM.
   4. **Human herpesvirus 8** (HHV-8), a new human herpesvirus, has been found in the nonmalignant bone marrow dendritic cells of patients with myeloma. It remains to be determined if HHV-8 contributes to the growth of the malignant plasma cells in these patients.
D. **Genetics**
   1. **PCM.** Multiple, complex karyotypic changes are observed in the malignant plasma cells of most patients.
      a. Fluorescent *in situ* hybridization (FISH) analysis has shown that most PCM patients have malignant cells with translocations involving chromosome 14 at the site of the immunoglobulin heavy-chain gene locus and a limited number of nonimmunoglobulin partner chromosomes. Unlike the site of translocation in other B-cell malignancies that involves the joining region JH, the location of the breakpoint in myeloma usually occurs in the switch regions that are involved in heavy-chain class switching from Cμ to another heavy-chain class.
      b. The most common sites of the nonimmunoglobulin breakpoints include chromosomes 11 at the site of cyclin D, chromosome 16 at the site of the *c-MAF* proto-oncogene, and chromosome 4 at the site of the fibroblastic growth factor receptor 3. Loss of material on the long arm of chromosome 13 occurs in nearly 20% of patients and portends a poor outcome.
      c. Mutations of *ras* genes occur in about 20% of myelomas and are associated with a poor prognosis. Similarly, mutations of *p53* are found in 15% to 20% of cases and are associated with more advanced and clinically aggressive disease. Abnormalities in *c-MYC* proto-oncogene may occur much more commonly than was previously suggested.
   2. **MGUS.** Studies have shown that patients with MGUS have similar karyotypic abnormalities to patients with PCM.
   3. **WM.** Complex karyotypes are also commonly observed in WM. Occasional patients have translocations involving the immunoglobulin heavy-chain locus on chromosome 14 and either *c-MYC* on chromosome 8 or *BCL-2* on chromosome 18.

II. Pathology and natural history

A. **Bone marrow pathology** is usually distinctive in PCM and WM. Plasma cells that constitute more than 20% of the nucleated marrow cells (*excluding erythroblasts*) are characteristic but not diagnostic of PCM.
   1. **MGUS.** Normal plasma cells rarely exceed 10% of bone marrow cells.
   2. **PCM.** Plasma cells usually constitute 20% to 95% of the marrow cells, have abundant basophilic cytoplasm, and have eccentric nuclei with paranuclear clear zones. Immaturity of the plasma cells is evident with the presence of prominent nucleoli ("myeloma cells"). Bone marrow biopsy showing monotonous infiltration with plasma cells is the only diagnostic criterion for PCM accepted by many authorities. The presence of large, homogeneous infiltrates or nodules of plasma cells is highly suggestive of PCM. Early in its course, however, marrow involvement is patchy, and normal marrow particles may be obtained.
   3. **WM** may closely resemble CLL. Bone marrow in WM contains 10% to 90% plasmacytoid lymphocytes or small mature lymphocytes; mast cells are often

prominent.

4. **Reactive plasmacytosis.** Peripheral blood plasmacytosis occurs in many viral illnesses (including human immunodeficiency virus infection) serum sickness, and plasma cell leukemia (which is rare). Bone marrow plasmacytosis, when not caused by myeloma, is characterized by a diffuse distribution (not infiltrative), and alignment of mature plasma cells along blood vessels or near marrow reticulum cells. Reactive bone marrow plasmacytosis is commonly seen in many disorders, including the following:
   a. Viral infections
   b. Serum sickness
   c. Collagen vascular disease
   d. Granulomatous disease
   e. Liver cirrhosis
   f. Neoplastic disease
   g. Marrow hypoplasia

B. **Natural history of MGUS.** Although patients with MGUS are symptom free at diagnosis, nearly 25% of cases progress to a malignant disorder (usually PCM) over 8 to 10 years. Importantly, the risk for malignancy remains constant over time (about 1% to 2% per year). Karyotypic abnormalities in these patients are similar to those seen with PCM. The presence of depressed normal immunoglobulin levels occurs in many patients with MGUS but is not associated with a higher risk for infection and does not predict a higher risk for malignancy. **Peripheral neuropathy** is not uncommon and may be associated with a monoclonal antibody with reactivity to a myelin-associated glycoprotein (see section VIII.B).

C. **Natural history of WM.** The natural history of WM resembles lymphocytic lymphoma much more than PCM. Indeed, separating WM from MGUS, CLL, or lymphocytic lymphoma with IgM spikes may be more arbitrary than real. WM originates from clones of lymphocytes or plasma cells that synthesize μ chains. Lymphadenopathy, splenomegaly, and hyperviscosity are hallmarks of WM; skeletal lesions and impaired renal function are unusual. Concomitant macroglobulinemia and osteolytic lesions usually signify malignant lymphoma or solid tumor rather than primary WM. Glomerular lesions are frequent in WM, but renal failure is uncommon. Low levels of light chains in the urine occur in about 25% of patients.

D. **Natural history of PCM.** Three to 20 years of clonal growth may pass before PCM becomes clinically evident. The disease may be localized (7% of cases), indolent (3%), or disseminated and progressive (90%). Manifestations of disease progression arise from bone marrow and skeletal involvement, plasma protein abnormalities, and the development of renal disease.

   1. **Plasmacytomas** (plasma cell tumors) may develop anywhere in the skeleton or, rarely, in extraskeletal sites, such as the nasopharynx or paranasal sinuses. Localized plasmacytomas produce a monoclonal spike in the serum or urine protein electrophoresis in only half of cases. The median survival is more than 8 years. Most plasmacytomas that appear to be solitary become generalized in about 3 years, particularly those involving the skeleton. Extraskeletal plasmacytomas have a better prognosis than those of skeletal origin and less frequently progress to multiple myeloma.

   2. **Hematopoiesis** is often impaired. At the time of diagnosis, 60% of patients have anemia; 15%, leukopenia; and 15%, thrombocytopenia. Nucleated red blood cells and immature granulocytes may be present in the peripheral blood (leukoerythroblastic reaction).

   3. **Skeletal disease.** Pain develops in about 70% of patients.
      a. **Bone lesions.** Multiple osteolytic lesions are present in about 70% of patients, single osteolytic lesions or diffuse osteoporosis in 15%, and normal skeletal radiographs in 15%. Lesions are most commonly seen in the skull, vertebrae, ribs, pelvis, and proximal long bones. The use of magnetic resonance imaging (MRI) indicates that skeletal abnormalities exist in nearly all patients with myeloma.

      It used to be thought that the demineralization and lytic lesions occurred as a result of osteoclastic-activating factors produced by neoplastic plasma cells and activated by inflammatory cytokines. The loss of bone in these patients, however, now appears to be a complex interplay involving the tumor cells, stromal cells in the bone marrow, and both the osteoblasts and osteoclasts. Moreover, the factors responsible likely involve other important molecules, including macrophage colony-stimulating factor, vascular endothelial growth factor, specific matrix metalloproteinases, and the recently described osteoprotegrin.

      b. **Osteoblastic lesions** occur in less than 2% of patients, often in association with neuropathy and the POEMS syndrome. Because of their rarity, the diagnosis of PCM should be doubted in the presence of osteoblastic lesions.
      c. **POEMS syndrome** is a multisystem disorder usually associated with osteosclerotic myeloma. It is characterized by the combination of **p**olyneuropathy (chronic inflammatory demyelinating neuropathy), **o**rganomegaly, **e**ndocrinopathy, **M** protein (mainly IgG-g or IgA-g), **s**kin changes (hyperpigmentation, thickening, hypertrichosis), and various other signs, such as cachexia, fever, edema, clubbing, and telangiectasia. Auto-antibodies to peripheral nerve components are absent. The syndrome appears to be the result of marked activation of the proinflammatory cytokines.
      d. **Hypercalcemia.** About 10% of patients present with hypercalcemia, and 10% develop it during the course of their disease. This complication results from enhanced bone resorption, resulting in the release of calcium into the circulation. Hypercalcemia is a major cause of renal failure among PCM patients, and normalization of the serum calcium often reverses the renal dysfunction. It is important to avoid bed rest and immobilization because these factors can contribute to both the development and worsening of hypercalcemia. Serum alkaline phosphatase levels are usually normal but may be increased with recalcification of fractures.

   4. **Protein abnormalities**
      a. **Frequency.** The incidence of monoclonal immunoglobulins in PCM and in comparison to MGUS are as follows:

Paraprotein	PCM	MGUS
IgG	52%	65%
IgA	22%	25%
IgM	Very rare	10%
Light chains only	25%	Nil
Nonsecretory	<1%	—

      b. **Increased excretion** of k or l light chains in the urine depends on the rate of unbalanced synthesis of excess light chains, plasma volume, degradation rate, renal catabolism, and urine volume. Monoclonal light chains in the urine are present in two thirds of all patients with PCM and present without an M protein in the serum in 25%.
      c. **Normal immunoglobulins** are usually decreased in the serum of patients with PCM and are occasionally decreased in patients with MGUS. The mechanism of inhibition of their synthesis is unknown. Older series showed a high rate of infection with encapsulated organisms that was thought related to patients' marked decrease in normal serum immunoglobulins. The risk for infection, however, largely occurs during chemotherapy-induced neutropenia or at the terminal stages of the disease.
      d. **Other plasma alterations** (see section VIII.A). Hyperviscosity is unusual in PCM (less than 5% of patients).

   5. **Renal dysfunction,** both acute and chronic, occurs at diagnosis in 15% to 20% of cases and develops during their course in about 50% of patients with PCM. Patients with light-chain myeloma commonly present with renal failure. The most important causes of renal dysfunction in PCM patients are hypercalcemia and myeloma kidney.
      a. **Myeloma kidney** is generally attributed to the deposition of k and l chains in the distal and collecting tubules, which is where the light chains are catabolized. The tubules dilate, apparently obstructed by casts surrounded by multinucleated giant cells, and undergo cellular atrophy. Glomerular basement membrane disease also occurs in most patients with myeloma kidney. In most instances, proteinuria contains monoclonal light chains only. These abnormalities occur slightly more commonly in PCM associated with g chain production.

      PCM is the most common cause of the **adult Fanconi's syndrome** (aminoaciduria, glycosuria, phosphaturia, and electrolyte loss in the urine). Fanconi's syndrome may precede the recognition of PCM by many years.

      b. **Amyloidosis** is also common in PCM; it affects the glomeruli and results in nonselective proteinuria.
      c. **Inconstant findings** that may aggravate renal function include pyelonephritis, metabolic abnormalities in addition to hypercalcemia (nephrocalcinosis and hyperuricemia), glomerulosclerosis, and focal myeloma cell infiltration. Renal tubular acidosis occasionally occurs. Nephrotic syndrome is rare in PCM unless amyloidosis supervenes.
      d. **Intravenous contrast dye studies** should be done with caution because patients with PCM are more susceptible to renal dysfunction after such studies, particularly if they are dehydrated.

   6. **Neurologic dysfunction** often develops in PCM and is the result of several pathogenetic mechanisms.
      a. **CNS.** Spinal cord and nerve root compression develops in about 15% of patients and is usually caused by epidural plasmacytoma. Amyloidosis is a rare cause of epidural masses. Collapse of vertebral bodies may also cause spinal cord compression but, more likely, produces radicular symptoms secondary to nerve root compression. Cranial nerve palsies may develop from tumor occlusion of calvarial foramina. Intracerebral and meningeal plasmacytomas are rare.
      b. **Peripheral neuropathy.** The carpal tunnel syndrome, which is usually the result of amyloid infiltration of the flexor retinaculum of the wrist (causing entrapment of the median nerve), is a common peripheral neuropathy in PCM. Infiltration of nerve fibers and vaso nervorum with amyloid may also

produce peripheral neuropathy. Additionally, peripheral neuropathy may be associated with monoclonal immunoglobulins to myelin-associated glycoproteins (see section VIII.B). Rarely, patients with PCM and POEMS syndrome develop a characteristic peripheral neuropathy (see section II.D.3.c).
    c. **Neurologic paraneoplastic syndromes** (see Chapter 32, section V).

III. Diagnosis

A. **Symptoms.** Fatigue, weakness, and weight loss are common in both PCM and WM. Skeletal pain occurs in 70% of patients with PCM at the time of diagnosis but is rare in patients with WM.
    1. **Symptoms of hypercalcemia** (see Chapter 27, section I) are present in about 10% of patients with PCM at the time of diagnosis and develop in another 10% later in the course of the disease.
    2. **Hyperviscosity syndrome symptoms** (bleeding, neurologic dysfunction, visual disturbances, or congestive heart failure) are present in about 50% of patients with WM and in less than 5% of patients with PCM (see section VIII.A.1).
    3. **Cold sensitivity** may occur in patients with cryoglobulins, especially in WM (see section VIII.A.2).

B. **Physical findings**
    1. **Hepatosplenomegaly** is present in 40% of patients with WM at the time of diagnosis and is uncommon in PCM except with the POEMS variant.
    2. **Lymphadenopathy** occurs in 30% of patients with PCM but is rare in patients with PCM except late in the disease.
    3. **Bone tenderness** in patients with PCM often signifies recent fracture or subperiosteal infiltration with malignant cells.
    4. **Neurologic abnormalities** are frequent in PCM (see section II.D.6); neurologic abnormalities in WM are caused by hyperviscosity (see section VIII.A.1) or demyelination (see section VIII.B).
    5. **Purpura** signifies thrombocytopenia in PCM and hyperviscosity syndrome in WM.

C. **Laboratory studies.** The following studies should be obtained in the investigation of patients with suspected plasma cell neoplasms:
    1. **CBC.** Anemia is variable in MGUS and WM and present in 60% of patients with PCM. Neutropenia or thrombocytopenia are absent in MGUS and present in 15% of patients with PCM and 5% of patients with WM.
    2. **Biopsy.** Bone marrow, solitary osteolytic lesion, masses, skin nodules, or enlarged lymph nodes. Bone marrow findings are discussed in section II.A.
    3. **Serum biochemistry.** Blood urea nitrogen, creatinine, electrolytes, calcium, uric acid, total protein, and alkaline phosphatase levels
    4. **Serum proteins.** Protein electrophoresis (PEP), immunoelectrophoresis (IEP), and quantitative immunoglobulins (QIG)
    5. **Serum b_2-microglobulin (b2m) and C-reactive protein** (CRP) may be useful prognostic indicators.
    6. **Urine.** Twenty-four–hour excretion of protein and PEP and IEP of a concentrated specimen (urine dip sticks are usually not sensitive enough to detect light chains, and Bence-Jones protein assays are unreliable)
    7. **Skeleton studies**
        a. **Complete skeletal radiographic survey,** including skull and long bones
        b. **MRI** of spinal cord if there is a paraspinal mass or signs of cord or nerve root compression
        c. **Bone scans** are of limited usefulness in PCM because most lesions are osteolytic, and bone scans require perilesional osteoblastic activity to be positive. Positive bone scans in PCM usually indicate regions of fracture or arthritis, except in the rare event of osteoblastic myeloma.
        d. **Bone densitometry** studies may be useful in following patients with PCM. This study may help predict the risk for skeletal complications as well as the response to bisphosphonates among these patients.
    8. **Special studies.** Serum viscosity, cryoglobulins, and rectal biopsy or analysis of joint effusions for amyloid are obtained when indicated.

D. **Protein studies.** Some serum immunoglobulin properties that have clinical relevance are listed in Table 22.1. Kinetic studies of protein synthesis in animals and humans show tumor burden to be closely correlated with the quantity of paraprotein in the blood (about 1 g/dL of paraprotein corresponds to 100 g of tumor and 1×10^{11} plasma cells).
    1. **Protein electrophoresis** is extremely valuable for recognizing cases of monoclonal gammopathies and for following quantitative changes in spikes. PEP, however, is only a presumptive screening test; IEP must be done to establish the diagnosis of monoclonal gammopathy. Examples of serum and urine PEP patterns are shown in Fig. 22.1.

Figure 22.1 Electrophoresis patterns.

        a. **M-protein spikes** are usually located in the g or g-b region. Monoclonal peaks in the a or a-b region are usually not caused by paraproteins but by reactant proteins (see section VIII.C).
        b. **IgG spikes** are usually tall, narrow, and located in the b region. **IgA spikes** are usually broader because the molecule tends to form polymers of different sizes; they are located in the b region. **IgM spikes** are usually located near the point of origin. **IgD spikes** usually cause only slight deflections in the pattern because the protein is present in a relatively small concentration.
        c. **Light chains** are not ordinarily found in the serum because light chains are rapidly catabolized by the kidney or excreted in the urine. Light-chain spikes may be found in the serum of patients with renal insufficiency or in instances in which polymerization of light chains has occurred. The normal ratio of k to l chains in humans is 2:1. This normal ratio is usually maintained when excretion of light chains is due to renal disease but is significantly altered when the excretion is due to malignant gammopathies. Urinary excretion of monoclonal light chains is found in 50% to 60% of patients with PCM and in 10% to 20% of patients with WM. MGUS patients may also show light chains in the urine, but the amount of monoclonal urinary protein is usually less than 1 g per 24 hours.
    2. **IEP** determines the exact heavy-chain class (g, a, μ, D, e) and light-chain type (k, l) of the M protein and distinguishes polyclonal and monoclonal increases in gammaglobulins. IEP is more sensitive than PEP for low-concentration (e.g., IgI) or heterogeneous globulin mixtures.
    3. **QIG** estimations are excellent for measuring normal or decreased immunoglobulin levels and are useful for distinguishing MGUS from PCM. QIGs are unreliable, however, if levels are markedly increased or if protein aggregation has occurred. Additionally, using this test to determine the response to treatment is limited by the variability of the results.
    4. **Serum viscosity.** The rate of descent of serum at 37°C through a calibrated capillary tube is compared with that of distilled water. Plasma is not used because elevated levels of fibrinogen can markedly affect the results. Normal values for serum viscosity ratios range from 1.4 to 1.9. Symptoms usually do not develop unless the serum viscosity exceeds 4.

E. **Differentiation of plasma cell dyscrasias.** In the absence of biopsy proof of malignant disease, differentiating MGUS from early malignant disease may be impossible at the initial examination. To establish the diagnosis, serial evaluations of the patient and paraprotein level must be done for several months or years. Table 22.2 indicates the important data that need repeated observation. These data predict benign or malignant monoclonal gammopathy, but none is diagnostic by itself; patients with MGUS may slowly progress to PCM. About 25% of patients with MGUS progress to PCM or a related B-cell malignancy (WM, lymphoma, or amyloidosis). The most important findings that suggest malignant disease are significant and progressive increases in the serum paraprotein or urinary light-chain concentration.

Table 22.2 Protein variables for predicting benign versus malignant monoclonal gammopathy

    1. **IgM monoclonal gammopathies** may be benign or due to WM, lymphoproliferative disorders or epithelial tumors which can present with a serum abnormality years before the neoplasm becomes evident. Thus, the division of IgM gammopathies into MGUS, primary or Waldenström's macroglobulinemia, and secondary macroglobulinemia is at times arbitrary (see section II.C).
    2. **IgG, IgA, and IgD monoclonal gammopathies: diagnostic criteria for PCM.** To establish the diagnosis of PCM, invasion or destruction of normal tissues by the uncontrolled growth of plasma cells must be proved by biopsy. High concentrations of monoclonal serum immunoglobulins (more than 3.5 g/dL for IgG, more than 2 mg/dL for IgA) or urinary light chains (more than 1 g/day) are nearly diagnostic of PCM. However, PCM often remains subclinical or indolent (so-called smoldering myeloma) for many years. If the diagnosis of PCM cannot be proved, the working diagnosis becomes MGUS, and the patient is examined at regular intervals to detect changes in clinical or laboratory findings.

IV. Staging system and prognostic factors

A. **Staging system for PCM.** Distinguishing patients with low, intermediate, and high volumes of tumor mass before institution of therapy is useful for prognosis: 1

$\times 10^{12}$ cells correspond to 1 kg of tumor, and 3 to 5×10^{12} cells are usually incompatible with life in the average-sized patient. Some centers subdivide the stages that follow into **substage A** (serum creatinine less than 2 mg/dL) and **substage B** (serum creatinine more than 2 mg/dL).

Stage **Extent of disease**

I   Low tumor mass (<0.6 $\times 10^{12}$ plasma cells/m^2). Patients must have *all* of the following:

    Hemoglobin >10 gm/dl

    Serum calcium: normal or £12 mg/dl

    Low M-component production rates with

    IgG value <5 gm/dl

    IgA value <3 gm/dl

    UPEP M-component light chain <4 gm/24 hr

    Skeletal x-ray: normal or with a solitary plasmacytoma

II   Intermediate tumor mass (0.6–1.2 $\times 10^{12}$ plasma cells/m^2). Patients who qualify for neither stage I nor III

III   High tumor mass (>1.2 $\times 10^{12}$ plasma cells/m^2). Patients having *any one* of the following:

    Hemoglobin <8.5 gm/dl

    Serum calcium >12 mg/dl

    High M-component production rates

    IgG >7 gm/dl

    IgA >5 gm/dl

    UPEP M-component light chain >12 gm/24 hr

    Extensive lytic bone lesions

B. **Prognostic factors**
1. **MGUS.** If a patient with the presumptive diagnosis of MGUS remains stable for 2 years, the chance for malignant disease is about 20%.
2. **WM.** Median survival is about 3 to 4 years for patients who are unresponsive to treatment and about 5 to 7 years for responsive patients. Survival for 10 to 20 years, however, is not rare. The development of complications, such as hyperviscosity, hemorrhage, or infection, contributes to death. Age older than 60 years, male gender, and hemoglobin less than 10 g/dL are associated with shortened survival time.
3. **PCM.** The overall median survival time of patients with PCM is about 3 years. At diagnosis, the prognosis in PCM is usually determined by measurement of tumor mass as well as serum b2m and CRP. Studies suggest that loss of chromosome 13 in the malignant cells is also associated with a poor outcome.
   a. **Tumor mass.** Patients with a low tumor mass have a median survival of 3.5 to 10 years. Patients with a high tumor mass can expect a median survival time of 0.5 to 3 years.
   b. **Serum b2m** is the light-chain moiety of classic HLA antigens and is found on the surface membranes of most nucleolated cells. Patients with PCM and higher initial values of b2m appear to have a worse prognosis. Despite the high correlation of b2m levels with renal function, b2m has emerged as an important independent prognostic factor. Elevated b2m levels are also found in patients with acute or chronic myelocytic leukemia, lymphoproliferative disorders, myeloproliferative disorders, myelodysplastic syndromes, benign or malignant liver diseases, and autoimmune diseases.
   c. **CRP.** Elevated interleukin-6 (IL-6) levels may possibly portend a poor prognosis. CRP levels appear to reflect IL-6 serum levels, but most patients with PCM do not have elevated CRP levels.
   d. **Labeling index** (LI). The LI is indicative of the percentage of cells undergoing mitosis. A high LI (more than 3%) is associated with a poor prognosis in PCM.
   e. **Renal function** previously was thought to be an important prognostic factor. Increasing degrees of azotemia were associated with progressively shorter life expectancies. Advances in plasmapheresis, dialysis, and supportive care have made this a less important prognostic factor. The outcome for patients who normalize renal function with therapy is not different from that for patients who present with normal renal function.
   f. **Response to therapy.** Patients with a high tumor mass who have a reduction of the serum peak by more than 75% of the original value have a median survival time of 3 years or longer, whereas patients who have less than a 50% reduction in the peak have a median survival time of less than 1 year. Paradoxically, patients who respond too rapidly to therapy with melphalan and prednisone (more than 50% reduction in less than 3 months) have a poor prognosis.
   g. **Immunoglobulin class.** Although earlier studies suggested that patients with IgD or l light-chain disease had a worse prognosis, analyses of prognostic factors in large PCM trials have not shown the M-protein type to be a prognostic factor.
   h. **Other prognostic factors.** The presence of a *p53* deletion, plasmablastic morphology, higher numbers of circulating monoclonal plasma cells, or higher levels of soluble IL-6 receptor or syndecan-1 also predict a poor outcome. In early-stage disease, the pattern and number of MRI abnormalities predicts both progression to symptomatic disease and overall survival.

V. Prevention and early detection

The availability of PEP and of screening chemistry panels has probably resulted in earlier detection of monoclonal gammopathies. If IEP were used for screening populations, the incidence of MGUS might well double, but survival would not be affected.

VI. Management of MGUS and WM

A. **MGUS.** Patients should have PEP studies every 3 months for the first year, every 6 months for the next 2 years, and then yearly thereafter. Patients with MGUS should not be treated with cytotoxic agents. Only patients showing significant rises in M-protein levels should have additional diagnostic studies (bone marrow aspirate and biopsy, skeletal survey).

B. **WM.** The best management for WM has not been established. We recommend the following approach:
1. **Patients with asymptomatic disease,** without anemia, hyperviscosity, renal insufficiency, or neurologic abnormalities, should be monitored for clinical status and PEP until disease progression is confirmed.
2. **Patients with symptoms of progressive disease** are treated with a single agent.
   a. Chlorambucil is used in moderate doses (6 to 8 mg/day for 1 to 3 months, followed by 2 to 4 mg/day for maintenance). Most patients improve with treatment.
   b. Patients unresponsive to chlorambucil may respond to fludarabine or cladribine. Patients with WM should be treated with only several courses of these agents because decreases in M protein can occur for many months after discontinuing the drug.
   c. Rituximab therapy has been effective in some patients.
3. **Patients with hyperviscosity syndrome** (see section VIII.A)

VII. Management of PCM.

Maximizing ambulation, administration of chemotherapy, and RT are the mainstays of treatment.

A. **Surgery** for PCM is restricted to orthopedic procedures. Fractures of long bones usually require fixation with a medullary pin and postoperative irradiation. Sometimes, impending fractures with large osteolytic lesions of the femoral head are internally fixed prophylactically. If the diagnosis of the underlying disease is in doubt, acute spinal cord compression or vertebral fracture may make laminectomy necessary.

B. **RT** is useful for palliation of lesions that are localized or cause spinal cord or nerve root compression. Small subcutaneous tumors or small painful lesions in bone may be treated with only a single dose of 800 cGy. Large osteolytic lesions in long bones should be irradiated before a fracture occurs. Large lytic lesions or paraspinous masses rarely need more than 2000 cGy over 5 days.
1. **Solitary plasmacytomas** in bone or pharynx mandate more aggressive treatment, which may be curative.
2. **Back pain** is relieved by RT unless the pain is due to compression fracture. Because spinal cord compression is a common complication in PCM, the physician should not hesitate to order an MRI or myelogram in patients with PCM with new or changes in back pain. This should be treated emergently if it occurs (see Chapter 32, section III).

C. **Chemotherapy.** Several alkylating agents (melphalan, cyclophosphamide, nitrosoureas, and chlorambucil) are equally effective in producing responses in about 30% of patients. Refractoriness to one alkylating agent is often associated with responsiveness to another alkylating agent.
1. **Regimens**
   a. **M&P** (cycle frequency is 4 to 6 weeks)

   Melphalan: 10 mg/m^2 PO on days 1 through 4
   Prednisone: 60 mg/m^2 PO on days 1 through 4

   b. **VAD** (cycle frequency is 4 weeks)

   Vincristine: 0.4 mg/day for 4 days by continuous infusion through a central venous line

Doxorubicin (Adriamycin): 9 mg/m^2/day for 4 days by continuous infusion

Dexamethasone: 40 mg PO on days 1 to 4, 9 to 13, and 17 to 21

   c. **M-2 protocol** (cycle frequency is 5 to 6 weeks)

Melphalan: 0.25 mg/kg PO on days 1 through 4
Prednisone: 1.0 mg/kg PO on days 1 through 7
Vincristine: 0.03 mg/kg IV on day 1
BCNU: 1.0 mg/kg IV on day 1
Cyclophosphamide: 10 mg/kg IV on day 1

   d. **VBAP** (cycle frequency is 3 weeks)

Vincristine: 1 mg IV on day 1
BCNU (carmustine): 30 mg/m^2 IV on day 1
Doxorubicin (Adriamycin): 30 mg/m^2 IV on day 1
Prednisone: 100 mg PO on days 1 through 4

   e. **Dexamethasone alone:** 40 mg PO daily for 4 days every other week
   f. **Thalidomide:** 100 to 800 mg PO daily at night as tolerated
   g. **EC** (cycle frequency every 4 weeks)

Etoposide: 100 mg/m^2 IV on day 1 through 3
Cyclophosphamide: 1000 mg/m^2 IV on day 1

2. **Responses.** Response rates to daily low-dose, single-agent therapy appear to be equivalent to those to pulse therapy given every 4 to 6 weeks. The addition of prednisone to an alkylating agent regimen (e.g., M&P) increases the response rate from 30% to 40% or 50%. Responses to VAD occur more rapidly and are somewhat more frequent than to M&P. Steroids alone (dexamethasone) may produce response and survival rates nearly equivalent to those achieved with infusional VAD or M&P. Other combination chemotherapy regimens have not been proved to improve survival when compared with M&P.

3. **High-dose chemotherapy regimens** have generally contained either myeloablative doses of intravenous melphalan with or without total-body irradiation (TBI) or high doses of cyclophosphamide with either oral busulfan or TBI. With these high-dose regimens, the response rates are higher, and a significant proportion of patients show elimination of the M protein.
   a. **Allogeneic bone marrow support** is unfortunately associated with high treatment-related mortality rates (nearly 40%); thus, the use of this procedure has been reduced to primarily clinical trials. Studies have used **donor leukocyte infusions** with some reduction in M-protein levels but also with significant graft-versus-host disease toxicity.
   b. **Autologous BMT.** Because large numbers of tumor cells are found in the autograft, attempts have been made to "purge" autografts of tumor using stem cell selection. Although this procedure successfully eliminates tumor cells in the autograft, it does not improve overall survival, probably because of the relatively high tumor burden remaining in the patient even after myeloablative chemotherapy. Some centers are now performing **tandem (double) transplantations** for these patients, but the preliminary results from a large randomized French trial showed no difference in outcome compared with patients undergoing a single transplantation.
   c. **Autologous peripheral blood stem cell transplantation** is not curative, but improvements in supportive care have reduced the treatment-related mortality rate to 1% to 2% in most centers. A randomized trial comparing autologous transplantation to conventional therapy in patients younger than 60 years of age showed improvements in both response rate and survival with the high-dose procedure. Several other large randomized clinical trials are being conducted to confirm these results.

4. **Recommendations**
   a. In patients considered to be candidates for high-dose chemotherapy with hematopoietic support, initial therapy should begin with either infusional VAD or high-dose oral dexamethasone alone. This approach avoids the permanent stem cell cytotoxic effect of alkylator therapy.
   b. Otherwise, patients should begin therapy with steroids alone or pulse M&P, particularly those with low or intermediate tumor masses. If a rapid response is desired (e.g., patients with hypercalcemia, marrow failure, or renal dysfunction), initial therapy with VAD may be preferable.
   c. In patients who either relapse shortly after discontinuation of M&P therapy or are refractory to M&P, high-dose dexamethasone or VAD may be tried. If the relapse occurs late, another course of M&P may be effective therapy. In patients who fail VAD, M&P may help.
   d. Oral thalidomide, an anti-angiogenesis agent, leads to durable responses in one third of relapsing patients, even after high-dose therapy. Caution must be exercised in the use of this agent because of its known teratogenic effects and CNS toxicity (somnolence).
   e. The EC combination and single-agent therapy with topotecan or vinorelbine (Navelbine) show moderate activity in relapsing patients.
   f. Interferon alone has been shown to be effective in only a small percentage of relapsing patients, especially those with IgA paraproteins.

5. **Duration of therapy.** Patients should be treated until a plateau phase (stabilization of paraprotein levels for several months) is achieved. Continuation of chemotherapy beyond plateau phase has not been demonstrated to prolong survival but does increase the risk for secondary malignancies, especially acute leukemia.

6. **Maintenance therapy.** The use of prednisone (50 mg PO every other day) as maintenance therapy after even a minor response to VAD was shown to improve significantly both progression-free and overall survival without significant toxicity. Although remissions are sustained longer with the addition of interferon, a significant survival benefit for maintenance therapy with this cytokine after conventional therapy has not been demonstrated.

D. **Supportive care** is extremely important in PCM. Bed rest is often necessary because of the painful bony lesions or fractures. However, bed rest further promotes bone demineralization, which may lead to hypercalcemia.
   1. **Pain relief** may be achieved with focal radiotherapy. Analgesics should be prescribed in a regimen that gives the most consistent pain relief.
   2. **Ambulation** should be maximized as early as possible after the onset of fractures or pain. Corsets and braces are often effective in relieving back pain by stabilizing the spine until RT or chemotherapy becomes effective.
   3. **Hydration.** Patients must be repeatedly reminded to drink 2 to 3 L of fluids daily to promote urinary excretion of light chains, calcium, and uric acid. This simple reminder has been shown to improve survival greatly in some studies.
   4. **Infections** are the foremost cause of death in patients with PCM. Infections must be investigated and treated urgently. These patients have similar infections to other cancer patients treated with chemotherapy. In fact, the risk for infection is primarily during periods of chemotherapy-induced neutropenia or in the terminal stages of the disease. Although the use of prophylactic antibiotics and intravenous immunoglobulins may be attempted in patients with recurrent infections, most patients do not require these interventions.
   5. **Bone remineralization.** Fluoride and vitamin D are not effective in increasing bone remineralization in patients with PCM; fluoride treatment results only in increased bone density because of fluorosis. The use of the aminobisphosphonate pamidronate (Aredia, 90 mg IV monthly) has been shown to reduce the skeletal complications in patients with PCM. This treatment reduced pain and analgesic usage and prevented the deterioration of quality of life compared with placebo. This agent may also have an antimyeloma effect; results from a large randomized trial showed an improvement in survival when patients who had failed first-line treatment received pamidronate with chemotherapy, compared with patients receiving their chemotherapy with placebo.
   6. **Renal failure** is best prevented by hydration and treatment of hyperuricemia and hypercalcemia. Plasmapheresis may be a useful adjunct. When renal failure becomes severe, some patients may be candidates for hemodialysis treatment, especially if they have a reasonable prognosis and have not failed initial therapy. Azotemia improves slowly in these patients.

VIII. Special clinical problems

A. **Plasma alterations in patients with M proteins**
   1. **Hyperviscosity syndrome.** The blood cells normally contribute more to the whole blood viscosity than do plasma proteins. The development of hyperviscosity with M proteins depends on their concentration and their ability to aggregate or polymerize. WM is typically associated with hyperviscosity. Symptoms usually do not occur unless the serum paraprotein concentration exceeds 3 to 4 g/dL and the serum viscosity index exceeds 4.
      a. **Complications** of hyperviscosity include the following:
         1. **Bleeding diathesis** is manifested by spontaneous bruising, purpura, retinal hemorrhages, epistaxis, or mucosal bleeding. The hemorrhagic diathesis is compounded by thrombocytopenia. Bleeding in the hyperviscosity syndrome appears to be a result of the following:
            a. **Interference with coagulation,** especially the third stage of coagulation (polymerization of fibrin monomer), resulting in prolongation of clotting times

    b. **Impaired platelet function** resulting in abnormalities of bleeding times, clot retraction, and other platelet functions

  2. **Retinopathy** is manifested by venous dilation and segmentation ("link-sausage" appearance), retinal hemorrhages, and papilledema.

  3. **Neurologic symptoms** develop in about 25% of patients and include malaise, focal neurologic defects, stroke, and coma.

  4. **Hypervolemia** develops with an increase of M protein concentration, resulting in distention of peripheral blood vessels and increased vascular resistance. Plasma volume expansion may actually lessen the viscosity but may also precipitate congestive heart failure (which occurs in about 10% of patients who have hyperviscosity).

  b. **Management.** Hyperviscosity syndrome is treated by reducing the quantity of paraprotein in the serum. Reduction of paraprotein concentrations with cytotoxic agent therapy takes several weeks or months. Symptomatic patients should be treated with plasmapheresis, 4 to 6 units daily, until the viscosity index is less than 3. Patients with hyperviscosity caused by monoclonal IgM usually respond to plasmapheresis more rapidly than those with IgG or IgA gammopathies because IgM has a predominantly intravascular distribution ([Table 22.1](#)). Additionally, there is an exponential relationship between serum viscosity and IgM level, so that, for example, a 20% decrease in IgM concentration results in a 100% decrease in serum viscosity. Improvement should be monitored by noting changes in clinical findings, coagulation tests, and serum viscosity determinations.

2. **Cold sensitivity** may afflict patients with M proteins (especially IgM) that have physicochemical properties that permit cold precipitation. The cryoglobulins in plasma cell dyscrasias and lymphoproliferative disorders are monoclonal. The cryoglobulins in other disorders (such as collagen vascular diseases and viral infections) are circulating soluble immune complexes (IgM–IgG, IgA–IgG, IgG–IgG). Manifestations include cold urticaria, Raynaud's phenomenon, and vascular purpura in the absence of severe thrombocytopenia.

3. **Cold agglutinins** are IgMs with a specificity for specific red blood cell antigens (usually Ia) at temperatures less than 37°C. These proteins may be responsible for a mild extravascular complement-dependent hemolysis and acrocyanosis but not for other symptoms of cold sensitivity unless cryoglobulins are also present.

4. **Pseudohyponatremia** may be observed with high levels of M proteins (plasma water is displaced by the paraprotein).

5. **Anion gaps,** noted with measurement of serum electrolytes (serum concentration of sodium-chloride bicarbonate), may be decreased in patients with cationic monoclonal proteins. The decreased gap is produced by the increase of chloride and bicarbonate anions.

B. **Peripheral neuropathy** occurs especially in patients with IgM monoclonal gammopathies. About 5% of patients with a sensorimotor neuropathy have an associated monoclonal gammopathy. Nearly 10% of patients with WM or with MGUS and an IgM paraprotein develop a demyelinating peripheral neuropathy. Sural nerve biopsies demonstrate monoclonal IgM deposition on the outer myelin sheath. The antibody can be shown to react with myelin-associated glycoprotein (MAG) in half of cases. These patients usually have a mostly sensory or ataxic polyneuropathy, whereas patients with non–MAG-reactive antibodies usually have both a sensory and motor component to their neuropathy. Treatment with plasmapheresis may be effective in some cases. Other forms of treatment have included high doses of glucocorticosteroids or intravenous gammaglobulin.

C. **Pseudoparaproteinemia.** The PEP can detect serum proteins when the concentration exceeds 200 mg/dL. In certain situations, a nonimmunoglobulin homogeneous protein concentration may exceed 300 mg/dL and appear as a spike on PEP. The location of these spikes usually are in the a and b regions but may be in the b-g region. The differential diagnosis is clarified by review of the clinical picture, the location of the PEP spike, and IEP. Conditions that may produce pseudoparaproteinemia include the following:

1. Hyper-a_1-globulinemia (acute-phase reactant in many inflammatory and neoplastic diseases)
2. Hyper-a_2-globulinemia (nephrotic syndrome or hemolysis)
3. Hemoglobin–haptoglobin complexes (intravascular hemolysis)
4. Hyperlipidemia
5. Hypertransferrinemia (iron deficiency)
6. Bacterial products
7. Desiccated serum
8. Fibrinogen (if plasma is measured)

D. **Pseudomyeloma.** Several malignancies, including lymphoma and cancer of the breast, bowel, or biliary tract, may be associated with the production of a monoclonal paraprotein. These same malignancies may produce lytic lesions in the skeleton and induce marrow plasmacytosis. Pseudomyeloma must be distinguished from true myeloma.

E. **Therapy-linked acute leukemia** is discussed in Chapter 34, [Cytopenia, section I.D.](#)

F. **Heavy-chain diseases** (HCDs) are rare plasma cell lymphocytic neoplasms characterized by secretion of abnormal heavy chains (g, a, or µ) without light chains (k, l). a-HCD is the most common, and µ-HCD is the rarest. The heavy chains may also be excreted in the urine and detected by urine PEP. Normal immunoglobulin levels are usually suppressed. Diagnosis of these disorders necessitates detailed immunochemical investigation. IEP is the crucial test; it should demonstrate reaction of antisera with the appropriate heavy chain but not with light chains.

1. a-**HCD** nearly always involves only the a_1 subtype of heavy chain and is associated with gastrointestinal (GI) lymphomas.

2. g-**HCD** usually affects elderly patients. Generalized lymphadenopathy, hepatosplenomegaly, involvement of Waldeyer's ring, fever, pancytopenia, and eosinophilia are common features of the disease. The illness initially resembles granulomatous disease or Hodgkin's disease. Biopsies of lymph nodes and bone marrow are rarely diagnostic. The disease has a variable course, developing over a few months to several years. A satisfactory treatment plan has not been established.

3. µ-**HCD** nearly always occurs in patients with CLL, and the two disorders are treated in the same manner. However, in µ-HCD lymphadenopathy is infrequent, and in contrast to other HCDs, large amounts of k light chains are excreted in the urine. The rare disease may be suspected when a patient with CLL has unusual vacuolated plasma cells (characteristic of µ-HCD) in the bone marrow.

G. **Amyloidosis** may be primary (with or without associated plasma cell or lymphoid neoplasms), secondary to a variety of chronic inflammatory diseases or hereditary disorders (familial Mediterranean fever), or associated with the aging process. The disease is characterized by organ deposition of fibrillar substances of many different types. The fibrils are mostly or exclusively composed of immunoglobulin light chains (especially the l type) in amyloidosis associated with primary amyloidosis and myeloma, but the fibrils are composed of substances other than light chains in secondary amyloidosis.

1. **Organ distribution of amyloid.** The various forms of amyloidosis overlap considerably. **Secondary amyloidosis** affects the kidneys, spleen, liver, or adrenal glands and rarely involves the heart, GI tract, or musculoskeletal system. **Primary amyloidosis and amyloidosis associated with PCM** mostly affect the heart, GI tract, skeletal muscle, ligaments (carpal tunnel syndrome), and periarticular and synovial tissue (articular manifestations) as well as the tongue (macroglossia) and skin. Skin involvement most commonly is located in the periorbital and skin-fold regions and is manifested by spontaneous purpura and ecchymoses, which may be aggravated by coagulation factor X deficiency, which occasionally accompanies amyloidosis; postproctoscopic eyelid ecchymoses are characteristic. Involvement of the respiratory tract, endocrine glands, and peripheral and autonomic nervous systems also occurs.

2. **Diagnosis**

  a. **Biopsy** of an involved organ (especially the carpal ligament, sural nerve, rectum, or gingivae) must be performed to establish the diagnosis of amyloidosis; liver or renal biopsy may result in hemorrhage. Amyloid deposits have a homogenous eosinophilic appearance on light microscopy. Confirmation is made by the demonstration of specific birefringence by polarized microscopy of specimens stained with Congo red.

  b. **Monoclonal light chains** in the urine are found in both the primary type and amyloidosis associated with PCM. Many patients with primary amyloidosis are found to have developed plasma cell disease if they survive long enough.

3. **Prognosis.** Amyloid patients live a median of about 2 years, although the prognosis varies greatly depending on the type of amyloid and sites as well as extent of organ involvement. Patients with primary amyloidosis generally have the worst outcome. Amyloid patients with cardiac involvement have the worst prognosis, whereas patients with renal disease have a better outcome.

4. **Treatment** of amyloidosis is directed at both the affected organs and the underlying process producing the amyloid deposits. Large trials have shown that the use of intermittent oral M&P is superior to colchicine alone, and the addition of this latter agent to M&P does not improve outcome. High-dose therapy for primary amyloidosis is being evaluated.

H. **Papular mucinosis** (lichen myxedematosus) is a dermatologic condition characterized by cutaneous papules and plaques that result from the deposition of a mucinous material. The disease is often preceded by chronic pyoderma. It demonstrates a monoclonal paraprotein, usually IgG- l, with a characteristic mobility (slower than any other gammaglobulin component) and a strong affinity for normal dermis. Other manifestations of PCM (plasmacytosis, osteolysis, and excretion of light chains) are rare. Treatment with melphalan is often beneficial.

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Chapter 23 Chronic Leukemias

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Chronic Lymphocytic Leukemia

I. Epidemiology and etiology

A. **Incidence.** Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in Western countries, accounting for one third of cases. The disease is rare in Asians; 90% of patients are older than 50 years of age. Men are affected more often than women by a ratio of 2:1.

B. **Etiology**
   1. **Genetic factors.** Familial clusters of CLL have been described. The incidence in relatives of patients with leukemia is two- to three-fold greater than that of the general population. The great majority of cases are sporadic.
   2. **Immunologic factors.** Inherited and acquired immunodeficiency syndromes are often associated with CLL and other lymphoproliferative neoplasms. These observations suggest that defective immunosurveillance may result in proliferation of malignant cell clones and increased susceptibility to potential leukemogens, such as viruses.
   3. **Chromosomes, oncogenes, and viruses.** A variety of chromosome abnormalities have been described in patients with CLL. The most common abnormalities include trisomy 12 and 13q– with deletions involving the retinoblastoma gene. Rearrangements of three oncogenes are rarely associated with CLL. The t(11;14) translocation with rearrangement of the *BCL-1* oncogene is more common in mantle cell lymphomas. The t(14;18) translocation with rearrangement of the *BCL-2* oncogene is associated with 90% of follicular lymphomas and rarely with CLL, although overexpression of *BCL-2* is common in CLL. The t(14;19) translocation with rearrangement of the *BCL-3* oncogene appears unique to CLL but is rare.
   4. **Radiation.** Populations exposed to radiation do not have an increased incidence of CLL.

II. Pathology and natural history

A. **Pathology.** CLL is a clonal disease of immunologically incompetent, long-lived lymphocytes that express high levels of anti-apoptotic proteins, especially BCL-2. All cases involve CD5-B lymphocytes. CD5-B lymphocytes represent about 10% of normal B lymphocytes and appear to play a major role in autoimmunity.

B. **Natural history**
   1. **Immunologic abnormalities in CLL**
      a. Advanced disease is associated with hypogammaglobulinemia and decreased humoral responses to antigens.
      b. A variety of *in vitro* lymphocyte function tests are abnormal. Many studies have suggested decreased helper T-cell functions, and patients generally show an inversion of the normal helper T-cell– to–suppressor T-cell ratios.
      c. The leukemia cells have low levels of surface immunoglobulin and display a single heavy-chain class, typically μ; some cells display both μ and d; less commonly, g, a, or no heavy-chain determinant is found. The leukemia cells display either k or l light chains, but never both.
      d. Surface membrane antigens include the B-cell antigens CD19, CD20, and CD23. The CD11c and CD25 antigens are found on the cells in half of cases. CD5 is always present on CLL cells. See Appendix C4, Discriminatory Immunophenotypes for Lymphocytic Neoplasms and Appendix C5, Leukocyte Differentiation Antigens (CDs).
      e. Monoclonal paraproteins are not routinely identified; however, when one uses more sensitive techniques, it appears that most patients with CLL secrete small amounts of paraproteins (usually immunoglobulin M [IgM]). These paraproteins rarely produce symptoms of hyperviscosity.
      f. Coombs'-positive warm antibody hemolytic anemia occurs in about 10% of patients and immune thrombocytopenia in about 5%. Immune neutropenia and pure red blood cell aplasia are rare.
      g. Compared with the general population, the incidence of skin carcinoma is increased eight-fold and visceral cancers two-fold in patients with CLL.
   2. **Clinical course.** The natural history of CLL is highly variable. Survival is closely correlated with the stage of disease at the time of diagnosis. Because most patients are elderly, more than 30% die of diseases unrelated to leukemia.
      a. **Manifestations.** In 25% of patients, CLL is first recognized at routine physical examination or by a routine complete blood count (CBC). Clinical manifestations develop as the leukemic cells accumulate in the lymph nodes, spleen, liver, and bone marrow.
         1. **Osteolytic lesions and isolated mediastinal involvement** are unusual and suggest a diagnosis other than CLL.
         2. **Pulmonary leukemic infiltrates and pleural effusions** are common late in the course of disease.
         3. **Renal involvement** is common in CLL, but functional impairment is unusual in the absence of obstructive uropathy, pyelonephritis, or hyperuricemia secondary to tumor lysis from therapy.
         4. **Skin involvement** is rare.
         5. **Transformation** into a diffuse large cell lymphoma (Richter's syndrome) or "prolymphocytoid" leukemia occurs in less than 5% of patients.
      b. **Progressive disease** is accompanied by deterioration of both humoral and cell-mediated immunity.
         1. **Herpes zoster** is the cause of 10% of infections in CLL patients.
         2. **Bacterial pathogens** associated with hypogammaglobulinemia include *Streptococcus pneumoniae, Staphylococcus aureus,* and *Haemophilus influenzae.*

3. ***Pneumocystis carinii*** may be the causative infectious agent in patients with pulmonary infiltrates.
4. As the disease progresses, patients develop progressive pancytopenia, persistent fever, and inanition. During the latter stages of disease, cytotoxic chemotherapy is generally ineffective, and dosages are restricted because of pancytopenia. Death is usually caused by infection, bleeding, or other complications of the disease.

III. Diagnosis

A. **Symptoms and signs.** Patients with CLL that was discovered by chance are usually asymptomatic. Chronic fatigue and reduced exercise tolerance are the first symptoms to develop. Advanced and progressive disease are manifested by severe fatigue out of proportion to the degree of the patient's anemia, fever, bruising, and weight loss.

Lymphadenopathy, splenomegaly, and hepatomegaly should be carefully assessed. Edema or thrombophlebitis may result from obstruction of lymphatic or venous channels by enlarged lymph nodes.

B. **Laboratory studies**
   1. **Hemogram**
      a. **Erythrocytes.** Anemia may be caused by lymphocyte infiltration of the bone marrow, hypersplenism, autoimmune hemolysis, and other factors. Red blood cells are usually normocytic and normochromic in the absence of prominent hemolysis.
      b. **Lymphocytes.** The absolute lymphocyte count typically ranges from 10,000 to 200,000/μL but may exceed 500,000/μL. Lymphocytes are usually mature appearing with scanty cytoplasm and clumped nuclear chromatin. When blood smears are made, the cells are easily ruptured, producing typical "basket" or "smudge" cells.
      c. **Granulocytes.** Absolute granulocyte counts are normal or increased until late in the disease.
      d. **Platelets.** Thrombocytopenia may be produced by bone marrow infiltration, hypersplenism, or immune thrombocytopenia.
   2. **Other useful studies** that should be obtained in patients with CLL include the following:
      a. Renal and liver function tests
      b. Coombs' (antiglobulin) tests
      c. Serum protein electrophoresis
      d. Chest radiographs
      e. Computed tomography (CT) scans, which can be used to evaluate retroperitoneal, abdominal, and pelvic lymph nodes
   3. **Bone marrow examination** is usually not necessary to establish the diagnosis in patients with persistent lymphocytosis. The bone marrow of all patients with CLL contains at least 30% lymphocytes. The pattern of bone marrow infiltration is an important prognostic factor (see [section IV.A.2](#)). The indications for bone marrow aspiration and biopsy include the following:
      a. Borderline cases of lymphocytosis when the diagnosis is in doubt
      b. Thrombocytopenia, to distinguish immune thrombocytopenia from severe bone marrow infiltration
      c. Coombs'-negative, unexplained anemia
   4. **Lymph node biopsy** in patients with CLL shows malignant lymphoma of the small lymphocytic type. A lymph node biopsy is not indicated in CLL unless the cause of the lymph node involvement is in doubt, particularly when Richter's transformation is suspected.
C. **Establishing the diagnosis of CLL.** The National Cancer Institute (NCI) Working Group on CLL has established useful guidelines for the minimum diagnostic requirements for this disease, which are as follows:
   1. Absolute lymphocytosis (5000/μL or more) with mature-appearing lymphocytes that is sustained
   2. Characteristic immunophenotype of monoclonal B cells
      a. Expression of pan–B-cell antigens (CD19, CD20, and CD23)
      b. Coexpression of CD5 on the leukemic B cells
      c. Surface immunoglobulin of low intensity (most often IgM)
D. **Differential diagnosis**
   1. **Benign causes of lymphocytosis in adults**
      a. Viral infections, especially hepatitis, cytomegalovirus, and Epstein-Barr virus (EBV). Lymphadenopathy and hepatosplenomegaly are absent or mild in elderly patients with infectious mononucleosis. The presence of fever, liver function tests compatible with hepatitis, and positive EBV serologies should distinguish mononucleosis from CLL.
      b. Brucellosis, typhoid fever, paratyphoid, and chronic infections
      c. Autoimmune diseases; drug and allergic reactions
      d. Thyrotoxicosis and adrenal insufficiency
      e. Postsplenectomy
   2. **Hairy cell leukemia** must be differentiated from CLL because management of the two disorders is different. Diagnosis depends on recognizing the pathognomonic hairy cells.
   3. **Cutaneous T-cell lymphomas** are suspected if skin involvement is extensive. Differentiation from CLL is made by identifying the convoluted nuclei and helper T cells (with immunohistochemistry) that are characteristic of this disease.
   4. **Leukemic phase of non-Hodgkin lymphoma** (NHL) is usually distinguished from CLL morphologically and immunologically. NHL cells are often cleaved, whereas CLL cells are never cleaved. In addition, NHL cells demonstrate intense surface immunoglobulins without the CD5 antigen, and the opposite is generally true for CLL cells.
   5. **Prolymphocytic leukemia** has large lymphocytes with prominent nucleoli. Lymphadenopathy is minimal; splenomegaly is massive (see [section VI.B](#)).
   6. **Large granular lymphocyte leukemia** (LGLL) has a characteristic morphology with abundant pale to clear, sharply defined cytoplasm and multiple distinct azurophilic granules of varying size. The cells are true T cells, and most correspond to natural killer cells. The immunophenotype is positive for CD3, CD8, CD16, and CD57. LGLL is indolent and almost uniformly associated with neutropenia. Rheumatoid arthritis is peculiarly present in about one third of patients.

IV. Staging system and prognostic factors

A. **Prognostic factors.** Routine CBCs may detect asymptomatic cases of CLL, but this has no bearing on the overall survival of these patients. If survival has been improved (and, it is not clear that it has), effective treatment of complicating infections in CLL probably has been more responsible for the improvement than cytotoxic agents.
   1. **Clinical staging** is helpful for determining prognosis and deciding when to initiate treatment. Anemia and thrombocytopenia adversely affect prognosis when they are due to leukemic infiltration ("packing") of the bone marrow but not when due to autoimmune destruction of red blood cells or platelets.
   2. **The pattern of bone marrow infiltration** also appears to affect prognosis. Patients with nodular or interstitial patterns of bone marrow involvement have longer survival times than patients with diffuse ("packed") involvement.
   3. **Other adverse prognostic factors** appear to be a lymphocyte doubling time of less than 12 months and an elevated serum b_2-microglobulin level.
B. **Staging system.** The *modified Rai's classification* of CLL (see [section III.C](#) for differences with the NCI Working Group criteria) is shown in [Table 23.1](#).

[Table 23.1](#) The modified Rai classification of chronic lymphocytic leukemia

V. Management

A. **Indications for treatment.** CLL is usually indolent. Treatment of asymptomatic stable disease is not warranted. The blood lymphocyte count does not indicate the need to start therapy and generally is not useful to monitor therapy. The indications for instituting therapy in CLL are as follows:
   1. Persistent or progressive systemic symptoms (fever, sweats, weight loss)
   2. Lymphadenopathy that causes mechanical obstruction or bothersome cosmetic deformities
   3. Progressive enlargement of the lymph nodes, liver, or spleen

4. Stage III or IV (high-risk) disease that results from the replacement of bone marrow with lymphocytes
5. Immune hemolysis or immune thrombocytopenia
6. Rapid lymphocyte doubling time

B. **Chemotherapy.** Fludarabine is superior to alkylating agents in its associated complete response rate and duration of response but not overall survival. Fludarabine may be the initial treatment of choice for patients who would benefit from a rapid and sustained remission, such as cases designated for further aggressive therapy. Prolonged treatment with fludarabine and other nucleoside analogues (such as cladribine), however, is also associated with marked immunosuppression and an increased risk for opportunistic infections and autoimmune hemolysis.

1. **Guidelines**
   a. **The initiation of therapy** should be timed according to the clinically assessed pace of disease. Complete remission is not a necessary goal. Treatment is discontinued when the inciting problem has been controlled (after a few weeks to several months).
   b. **Immune hemolysis or thrombocytopenia** should be treated with prednisone alone, 60 mg PO daily, which is then tapered after achievement of control of blood cell counts.
   c. **Resistant disease** should be treated with alkylating agents if a nucleoside was first-line therapy. Third-line therapy includes combination chemotherapy regimens, such as CVP or CHOP (see Chapter 21, Non-Hodgkin Lymphoma).
2. **Drug dosages**
   a. **Alkylating agents**
      1. **Chlorambucil,** 0.1 to 0.2 mg/kg PO daily for 3 to 6 weeks as tolerated; the dose is usually tapered to 2 mg daily until the desired effect is achieved. Alternatively, 15 to 30 mg/m^2 PO may be given for 1 day (or divided over 4 days) every 14 to 21 days; the dose is adjusted to tolerance.
      2. **Cyclophosphamide,** 2 to 4 mg/kg PO daily for 10 days; the dose is then adjusted downward for continued therapy until the desired effect is achieved.
   b. **Nucleosides**
      1. **Fludarabine,** 25 to 30 mg/m^2 IV daily for 5 consecutive days every 4 weeks
      2. **Cladribine** (2-chlorodeoxyadenosine, 2-CdA), either 0.10 mg/kg daily by continuous IV infusion for 7 days, or 0.14 mg/kg daily IV over 2 hours for 5 consecutive days every 4 to 5 weeks

C. **Radiation therapy** (RT). Local irradiation is recommended only for reduction of lymph node masses that threaten vital organ function and that respond poorly to chemotherapy. Splenic irradiation may result in improvement of disease elsewhere and may temporarily improve signs of hypersplenism; however, the clinical usefulness of splenic irradiation has not been established. Total-body irradiation remains investigational and potentially dangerous.

D. **Surgery.** Splenectomy is indicated in CLL patients who have immune hemolytic anemia or thrombocytopenia that either fails to respond to corticosteroid therapy or must be treated with corticosteroids chronically. Splenectomy may also be helpful in patients with problematic hypersplenism.

VI. Special clinical problems in CLL

A. **Richter's syndrome.** About 5% of patients with CLL develop a diffuse large cell lymphoma with rapid clinical deterioration and death occurring within 1 to 6 months. The clinical features include fever, weight loss, increasing localized or generalized lymphadenopathy, lymphocytopenia (as well as other cytopenias), and dysglobulinemia. Combination chemotherapy with CHOP (see Appendix A-2) is usually tried but is rarely effective.

B. **Prolymphocytic leukemia** is a rare variant of CLL. The main clinical features are massive splenomegaly without substantial lymph node enlargement. Leukocytosis usually exceeds 100,000/µL and is characterized by large lymphoid cells with single prominent nucleoli. Tissue sections show almost no mitotic figures despite the immature appearance of the leukemic cells. Fludarabine or cladribine used as single agents or combination therapy with CHOP may be useful.

Eighty percent of cases involve B cells that have different surface markers than typical CLL (the B cells of prolymphocytic leukemia show intense surface immunoglobulin, the CD19 and CD20 B-cell antigens, but typically not the CD5 antigen). Twenty percent of cases are T cell, usually with the helper phenotype (CD3 and CD4 positive).

A small percentage of CLL patients develop a "prolymphocytoid" transformation, whereby more than 30% of the peripheral blood cells are prolymphocytic. This differs from *de novo* prolymphocytic leukemia in that the cells maintain the immune features of CLL and the clinical course resembles typical CLL, albeit in a late stage of the disease.

Hairy Cell Leukemia

I. Epidemiology and etiology Hairy cell leukemia (HCL; leukemic reticuloendotheliosis, lymphoid myelofibrosis) accounts for about 2% of all leukemias. Affected men outnumber women in a ratio of 5:1. The median age of patients is 55 years; patients younger than 30 years of age are unusual. The etiology is unknown.

II. Pathology and natural history

A. **Pathology.** The pathognomonic hairy cell can be identified in the peripheral blood, bone marrow, liver, and spleen of affected patients. The hairy cells are B lymphocytes in virtually every case (rare T-cell variants have been reported).

B. **Natural history.** The natural history is extremely variable, ranging from a relatively fulminant course, to a waxing and waning course of exacerbations and spontaneous improvements, and to prolonged survival measured in decades. Most patients are able to function normally throughout most of their illness. Patients with HCL usually present with an insidious development of nonspecific symptoms, splenomegaly, and pancytopenia. Progression of disease is manifested by bleeding because of thrombocytopenia, anemia requiring transfusions, and recurrent infections. Death is caused by severe infection in more than half of cases and (uncommonly) by hemorrhage.

III. Diagnosis

A. **Symptoms and signs.** Weakness and fatigue are the presenting complaints in about 40% of cases. A bleeding diathesis, recent infection, or abdominal discomfort is present in about 20% of patients.

Splenomegaly occurs in 95% of patients and is severe in most. Hepatomegaly is seen in about 40% of patients and is usually mild. Peripheral lymphadenopathy is rarely present in patients with HCL; however, CT scans of the abdomen may reveal retroperitoneal lymphadenopathy.

B. **Preliminary laboratory studies**
1. **CBC.** Anemia and thrombocytopenia occur in 85% of patients. About 60% of patients have leukopenia with granulocytopenia; 20% have increased hairy cells with a leukocytosis in the peripheral blood, usually associated with an absolute granulocytopenia.
2. **Blood chemistries.** Only 10% to 20% of patients have abnormal liver or renal function tests. Polyclonal hyperglobulinemia or decreased normal immunoglobulin concentrations occurs in 20% of patients.

C. **Special diagnostic studies.** The diagnosis of HCL is made by identifying the pathognomonic mononuclear cells in the peripheral blood or bone marrow. The cells have irregular and serrated borders with characteristic slender, hairlike cytoplasmic projections and round, eccentric nuclei with spongy chromatin. The cytoplasm is sky-blue without granules.
1. **Immune flow cytometry** demonstrates a characteristic pattern of CD19, CD20, CD22, CD11c, CD25, and CD103 positivity. Hairy cell variants may be CD25 or CD103 negative and typically do not have a favorable prognosis.
2. **Phase-contrast microscopy** with supravital staining of fresh preparations is extremely valuable for demonstrating the cellular characteristics because the cytoplasm of hairy cells is often poorly preserved in films mixed with Wright's stain.
3. **Tartrate-resistant acid phosphatase** (TRAP). HCL cells have a strong acid phosphatase activity, which is resistant to inhibition by 0.05 molar tartaric acid (due to the presence of isoenzyme 5 of acid phosphatase); the acid phosphatase in leukocytes from most patients with lymphomas and CLL is sensitive to tartrate. A strongly positive TRAP study is present in most patients with HCL but is not required for the diagnosis and can be detected in patients with other lymphoid malignancies.
4. **Bone marrow aspiration** frequently is unsuccessful ("dry tap"). Marrow biopsy shows a characteristic loose and spongy arrangement of cells, even with extensive infiltration with hairy cells. Fibrosis of the marrow with reticulin fibers is also characteristic in areas of HCL infiltration and accounts for the high frequency of dry taps.
5. **Splenic morphology.** The spleen is the most densely infiltrated organ in HCL. The red pulp of the spleen may contain a unique vascular lesion:

pseudosinuses lined by hairy cells.

    D. **Differential diagnosis.** It is important to distinguish HCL from other diseases because management is substantially different. HCL is most often confused with CLL, malignant lymphoma, histiocytic medullary reticulosis, myelofibrosis, or monocytic leukemia. Differentiation is made by identifying the pathognomonic cell, the characteristic immune profile, TRAP test, and pathologic findings of the bone marrow biopsy.

IV. Staging system and prognostic factors
The natural median survival time for HCL appears to be 5 to 10 years, but this has been dramatically altered by current therapies.

V. Management

    A. **The decision to treat.** Many cases tend to have an indolent course, and these patients have excellent survival times without therapy. Therapy may be deferred for asymptomatic patients until at least one of the following problems develops:
        1. Anemia (hemoglobin less than 10 g/dL)
        2. Granulocytopenia (less than 1000/μL)
        3. Severe thrombocytopenia (less than 100,000/μL)
    B. **Splenectomy** has achieved at least a partial response in 75% of patients and historically had been the standard therapy for HCL.
    C. **Cladribine** is now the treatment of choice for HCL. The drug is given by continuous intravenous infusion *once only* at a dose of 0.1 mg/kg per day for 7 days. More than 95% of patients respond to treatment, and 80% are complete responders. Twenty percent of patients may relapse, and most of them respond to an additional course of cladribine. Toxicity has been limited to transient fevers that are usually associated with neutropenia.
    D. **Interferon-a** (IFN-a) is a highly effective agent in reversing the pancytopenia and splenomegaly in HCL. Dosages of IFN ranging from 2 to 4 million U daily or three times weekly for 1 year achieve responses in 90% of patients with HCL. Complete responses with disappearance of hairy cells from the bone marrow, however, are unusual. Immune parameters, such as natural killer cells and cell-surface markers, normalize in association with the reversal in the hematologic parameters.
    E. **Pentostatin** (2'-deoxycoformicin) is also highly effective therapy for HCL. Most patients not only have normalization of their CBC but also have a complete response with disappearance of hairy cells from their bone marrow (rarely seen with IFN- a). Complications include skin rash and neurotoxicity. The dosage is 4 mg/m^2 IV every 2 weeks for 3 to 6 months.

Chronic Myelogenous Leukemia

I. Epidemiology and etiology
Chronic myelogenous leukemia (CML) is classified with the myeloproliferative disorders (see Chapter 24). The rate of transformation to acute leukemia and the presence of chromosomal markers and neutrophil alkaline phosphatase (NAP) abnormalities, however, clearly distinguish CML from the myeloproliferative disorders.

    A. **Incidence.** CML constitutes about 20% of adult leukemias in Western countries. People in their fourth decade are most often affected, although children and older adults are also affected.
    B. **Etiology.** The cause of CML is unknown. Radiation exposure is related to an increased incidence of CML but accounts for only a small portion of cases.

II. Pathology and natural history

    A. **The Philadelphia chromosome** (Ph[1]), designated t(9;22), arises from the translocation of the *C-ABL* gene from the long arm of chromosome 9 (band q34) to the long arm of chromosome 22 (band q11). The *C-ABL* gene is juxtaposed with the *BCR* gene on chromosome 22 in a head-to-tail fashion, forming a chimeric *BCR-ABL* gene that produces a chimeric protein of 210 kd (p210BCR-ABL). The mutation is somatic and is found in erythroblasts, megakaryocytes, granulocytes, monocytes, and most lymphocytes, but not in nonhematopoietic cells. This universal finding in CML can be detected by the polymerase chain reaction if it cannot be found by cytogenetics.
        1. **Ph1-negative CML** differs from typical CML and may be a different disease for the following reasons:
            a. The prognosis is poorer.
            b. The patient is usually a young child or an elderly person.
            c. The leukocyte and platelet counts are frequently lower.
            d. NAP scores tend to be higher.
            e. The bone marrow shows more immaturity in the myeloid series.
        2. **Ph[1] chromosome in acute leukemia.** The Ph[1] chromosome can be found in *de novo* acute leukemia. About 25% of adults with ALL and 2% of adults with AML present with the Ph[1] chromosome. These cases generally have an overall worse prognosis than similar cases that do not have a Ph[1] chromosome. Some of these cases represent CML that was never diagnosed in the chronic phase; effective treatment may reverse some cases to a chronic phase.
    B. **Clonality.** Clonal studies using the isoenzyme of glucose-6-phosphate dehydrogenase in black women who are heterogeneous for this enzyme have demonstrated that CML is a clonal disease of an abnormal stem cell. Myeloid, erythroid, megakaryocytic, and most lymphoid cells are involved in the malignant clone.
    C. **Clinical course.** The major clinical manifestations in CML relate to the unrestrained growth of granulocytes. Chronic, accelerated, and acute phases are recognized. Death is usually caused by hemorrhage or infection.
        1. **Chronic phase.** The chronic phase, which usually lasts about 3 to 4 years, is manifested by mild systemic symptoms, hepatosplenomegaly, and leukocytosis. Granulocyte production proceeds at a more or less steady rate; a few patients exhibit spontaneous cyclic fluctuations in the granulocyte count. The clinical and laboratory abnormalities are readily controlled by chemotherapy, and most patients are able to lead normal lives.
        2. **Accelerated phase.** About 15% of patients enter an accelerated phase, which is resistant to therapy. Cytopenias, increasing splenomegaly, osseous and extraosseous collections of leukemic cells, fever, anorexia, and weight loss are common. Patients may die of any of a variety of problems.
        3. **Acute phase.** About 85% of patients develop acute leukemia ("blast crisis"), either abruptly or after 3 to 6 months of an accelerated phase. The risk for blast crisis is 25% in each year, whether it be the first year or the tenth year since the time of diagnosis. Blast crisis is recognized when 30% or more of the myeloid cells in the bone marrow or blood are myeloblasts or promyelocytes.
            a. Cytogenetic changes, other than the Ph[1] abnormality, develop in more than 75% of patients, often several months before clinical evidence of acute transformation.
            b. About 30% of cases of acute leukemic transformation occur as ALL. The blasts morphologically, immunologically, and enzymatically (terminal deoxynucleotidyl transferase activity) are characteristic of lymphoid cells.
            c. The clinical course after acute transformation is virtually identical to that of *de novo* acute leukemia, except that the blast crisis phase of CML is usually refractory to treatment.

III. Diagnosis.
The diagnosis of CML is usually made easily on the basis of a constellation of findings. No single test is pathognomonic of CML.

    A. **Symptoms and signs**
        1. **Chronic phase**
            a. About 20% of patients do not have symptoms; disease is discovered by the incidental finding of leukocytosis.
            b. Fatigue, malaise, anorexia, or weight loss occur in about 80% of patients. Fever, sweats, and other manifestations of hypermetabolism are common and roughly proportional to the degree of anemia and organomegaly.
            c. Bone pain and sternal or other bony tenderness, from expanding leukemic mass in the marrow
            d. Abdominal fullness or easy satiety usually reflect splenomegaly. Splenomegaly, which may be massive, is present in 95% of cases, and hepatomegaly is present in 50%.
            e. Unusual hemorrhagic or thrombotic episodes reflect abnormalities in platelet number and function.
        2. **Acute phase**
            a. Fever, which occasionally is high and spiking
            b. Rapid weight loss
            c. Recurrence of bone pain or tenderness after successful treatment
            d. Splenic pain because of a rapidly enlarging spleen or splenic infarcts
            e. Signs of infection or bleeding

      f. Lymphadenopathy, cutaneous infiltrations, meningeal leukemia
B. **Laboratory studies**
  1. **Erythrocytes.** A mild to moderate normocytic, normochromic anemia is usually present. Erythrocytosis may occasionally occur. Often, a few nucleated red blood cells are seen on the peripheral blood smear. As myeloid overgrowth progresses, erythrocytes show considerable variation in size and shape.
  2. **Leukocytes.** The granulocyte count exceeds 30,000/µL and usually ranges from 100,000 to 300,000/µL at the time of diagnosis. The blood smear is dramatic and represents a shift of the cells out of the overcrowded marrow; it is often described as peripheral blood that looks like bone marrow. The granulocytes are normal in appearance and functional. Myeloblasts and promyelocytes constitute less than 10% of the leukocytes. In contrast to acute leukemia, discontinuity of maturation in the granulocyte series is absent. Eosinophil and basophil counts are often elevated.
  3. **Platelets.** About half of patients have thrombocytosis, which may exceed 1,000,000/µL at presentation. Thrombocytopenia is unusual early in the disease. Platelet aggregation and other platelet function tests are commonly abnormal, especially with markedly elevated counts.
  4. **Uric acid.** Hyperuricemia and hyperuricosuria are the rule, both with and without treatment.
  5. **Bone marrow.** The marrow is markedly hypercellular as a result of massive granulocytic hyperplasia; consequently, the myeloid-to-erythroid ratio is markedly increased. Megakaryocyte numbers are occasionally increased. Fibrosis is present in variable amounts but is rarely profound. Maturation of the granulocytes is normal. Gaucher's-like cells are seen in some patients because of the prominent phagocytic activity of marrow macrophages.
  6. **Ph[1] chromosome analysis** should be performed at the time of bone marrow examination. If cells capable of division (myelocytes and less mature forms) are present in the circulation in sufficient numbers, however, chromosome analysis may be performed on peripheral blood samples.
  7. *BCR-ABL* **gene rearrangement** can be detected by widely available sensitive techniques, such as Southern blotting or polymerase chain reaction.
  8. **NAP** activity in circulating granulocytes is substantially decreased or absent. Five fresh blood smears are submitted for special staining. The intensity of staining of the neutrophils is graded on a scale of 0 to 4+, and 100 neutrophils are scored and counted (normal range is 40 to 100). The NAP score in cases of CML usually is 0 to 10. The NAP score may occasionally be low in myelodysplastic syndromes and is usually elevated in myeloproliferative disorders.
  9. **Helpful studies in special circumstances**
    a. **Serum vitamin B$_{12}$ concentrations and B$_{12}$-binding capacity** are markedly elevated because of increased levels of transcobalamin I, which is synthesized by granulocytes.
    b. **Chromosome analysis** by sensitive banding techniques may demonstrate a second Ph[1] chromosome, an extra chromosome 8, or other changes in 75% of patients in an imminently acute phase.
C. **Differential diagnosis** mainly involves distinguishing CML from myeloproliferative disorders and leukemoid reactions (see Table 24.1 in Chapter 24).

IV. Staging system and prognostic factors

A. **Staging system.** Single risk factors are only of limited value for CML. Some centers have adopted risk profiles (such as the modified Sokal's Risk Index), the impact of which often overrides that of therapy. Several factors are *combined and weighted* in the calculation of risk. **Risk factors that adversely affect prognosis** include the following:
  1. Age 50 years or older
  2. Increasing spleen size on physical examination
  3. Increased percentage of blasts in the peripheral blood
  4. Increased percentage of eosinophils
  5. Increased percentage of basophils (3% or more)
  6. Increased platelet count (1,500,000/µL or more)
B. **Transformation.** Patients with CML usually pursue a normal lifestyle during the chronic phase. Virtually anything that changes the stable pattern may signal transformation into the accelerated or acute phase. Changes that may herald blastic transformation include the following:
  1. Signs or symptoms of the acute phase (see section III.A.2)
  2. Anemia, thrombocytopenia, granulocytopenia, progressive basophilia, rising NAP score, or more rapidly increasing granulocytosis in a patient whose disease was previously under control
  3. Myelofibrosis with nucleated red blood cells in the peripheral blood
  4. Osteolytic bone lesions
  5. Chromosome abnormalities other than a single Ph[1] chromosome (usually multiple Ph[1] chromosomes or aneuploidy)
C. **Survival.** Using a risk index scale, the median survival times are 3.5 years in the high-risk group, 5 years in intermediate-risk group, and more than 8 years in the low-risk group. The median time survival for Ph[1]-negative CML is only 9 to 15 months. Survival after the development of blast crisis is usually 2 to 4 months.

V. Management

A. **Perspective.** The choices for therapy in newly diagnosed cases of CML include busulfan, hydroxyurea, IFN- a with or without an antimetabolite, and bone marrow transplantation (BMT). IFN-a is associated with cytogenetic complete remissions (CRs) but is accompanied by significant side effects and does not appear to increase the probability of cure. BMT is viewed as the gold standard of therapy for CML but is associated with substantial morbidity and mortality.

Cytogenetic remissions are substantially more common after BMT than after IFN therapy and are rare after hydroxyurea or busulfan therapy. At least half of patients remain in CR 5 to 10 years after treatment, suggesting that BMT cures CML. Patients in BMT studies, however, are often 10 years younger than subjects in IFN studies and are less likely to have other adverse risk factors. Numerous potential biases in existing evidence could exaggerate the apparent efficacy of BMT. Outcome estimates must be looked on with caution.

The decision for initial and ultimate treatment in patients with CML must be individualized, with detailed information provided to the patient. It must be remembered that therapy with IFN-a or BMT is most successful when administered soon after the diagnosis is established. The patient's input for desired quality of life, as well as potential duration of life, is essential. Examine the trade-offs: the potential long-term benefits against immediate short-term risks.

B. **BMT** is the treatment of choice and should be initiated as soon as possible for patients in the chronic phase who are younger than 50 years of age and have an HLA-identical allogeneic sibling donor. Results of BMT are best when transplantation is performed during the first year of diagnosis. Disappearance of the Ph[1] chromosome and long-term (5 to 10 years) disease-free survival are reported in more than half of patients who are treated with BMT. Reported relapse rates are less than 20%. Survival advantage for BMT becomes statistically significant after 5.5 years when compared with hydroxyurea or IFN therapy, especially for high-risk patients and those who underwent transplantation early. Projected survival rates after BMT appear to plateau after 3 to 7 years, suggesting that allogeneic BMT offers eligible patients their best prospects for cure. Results of treating CML with unrelated donor marrow have been considerably less favorable than those with related donor marrow.

Patients undergoing BMT face a 20% to 40% probability of transplant-related death within 1 year of the procedure. Significant graft-versus-host disease occurs in 10% to 60% of cases and is the cause of death in 5% to 15% of patients. Giving IFN before BMT risks a lower probability of cure because the success rate decreases as the time elapsed after the diagnosis of CML increases.

C. **IFN-a** has achieved hematologic and cytogenetic remissions in a significant number of patients. Patients treated with IFN appear to live 20 months longer than those treated with conventional chemotherapy but continue to relapse as time goes on. The potential survival advantage must be weighed against the significant side effects with IFN. There is inadequate evidence to recommend IFN over conventional chemotherapy for patients, especially if elderly, with advanced (high-risk) chronic-phase disease. If IFN is selected, patients with good prognostic factors should be offered IFN combined with other agents (hydroxyurea or cytarabine).
  1. **Dosage.** IFN-a is typically initiated at 3 to 5 million U/m^2 SC daily. A controversial lower dose regimen is 2 million U/m^2 SC daily for 1 month, then three times weekly. Leukopenia (white blood cell [WBC] count less than 4000/µL) is a target for effective treatment. The dose may have to be adjusted downward because of toxicity or gradually increased to a maximally tolerated dose to achieve a satisfactory hematologic response. An option is adding cytarabine (20 mg/m^2 per day for 10 days per month) or hydroxyurea (0.5 to 2 g/day).
  2. **The duration of IFN therapy** in patients who achieve complete response (or, unsatisfactory response) is uncertain.
D. **Chemotherapy for chronic-phase disease** is not associated with cytogenetic remissions but does significantly improve the quality of life. Hydroxyurea and busulfan have been used comfortably for both the patient and physician for decades. The goals of therapy are to relieve symptoms and to control disease. All signs, symptoms, physical findings, and laboratory abnormalities usually parallel the WBC count. Hydroxyurea has the advantage of a more rapid onset of action, shorter period of activity, and fewer side effects than busulfan. Therapy with hydroxyurea appears to have a survival advantage over therapy with busulfan.

1. **Starting daily doses** are 2 to 4 g PO for hydroxyurea and 4 to 8 mg PO for busulfan. Treatment is usually initiated when the WBC count exceeds 50,000/µL. As the patient demonstrates response to treatment, doses are decreased to 1 to 2 g for hydroxyurea and 2 to 4 mg for busulfan. The WBC count continues to fall after stopping busulfan but rises again shortly after stopping hydroxyurea. Estimating the WBC doubling time is often useful in planning treatments.
2. **Indicators of response.** Within a few weeks, a response to treatment is demonstrated in most patients in the chronic phase of CML by disappearance of symptoms, improving anemia, control of granulocytosis and thrombocytosis, reduction in spleen size, and increase in the NAP score.
3. **Inhibitors of the BCR-ABL fusion protein.** Since the main transforming property of the BCR-ABL protein is exerted through its constitutive tyrosine kinase activity, direct inhibition of such activity seems to be a logical means of "silencing" the oncoprotein. Synthetic compounds known as *tyrphostins* were developed to compete for the binding site in the catalytic center of the kinase. The most promising of the tyrphostins is 2- phenylaminopyrimidine STI-571, which specifically inhibits ABL tyrosine kinase at micromolar concentrations. Inhibition of the BCR-ABL kinase activity by this compound results in transcriptional modulation of various genes, leading the Ph-positive cell to an apoptotic death. STI-571 is undergoing extensive clinical investigation for the treatment of CML. The potentially harmful side effects of tyrosine kinase inhibitors have not yet been elucidated.

E. **Other treatment modalities**
1. **Allopurinol,** 300 mg/day PO, is given to all patients continuously and should be instituted before chemotherapy is started.
2. **Leukapheresis** rapidly decreases the granulocyte count for short periods of time but is time-consuming and expensive. This procedure is useful in the following circumstances:
   a. Patients with central nervous system or pulmonary symptoms from leukostasis, which usually develops when the WBC count exceeds 100,000/µL, especially with significant proportions of blasts. Leukapheresis is implemented emergently in combination with hydroxyurea.
   b. Patients with priapism
   c. Pregnant patients when cytotoxic agents are contraindicated
3. **RT.** Splenic irradiation may be transiently useful in patients with symptomatic splenomegaly. Radioactive phosphorus may be effective in CML but is rarely used.
4. **Splenectomy** during the chronic phase of CML may be beneficial for hypersplenism, but it neither delays the onset of blastic transformation nor prolongs survival. The complications (postoperative infections and thromboembolism) are formidable. Splenectomy during the accelerated phase is not indicated.

F. **Management of the accelerated or acute phase.** After the accelerated phase has developed, other agents may be tried but without much hope for success. Patients usually require blood component therapy and other supportive measures. Extramedullary sites of symptomatic disease may be controlled with RT. Management of the myeloblastic acute phase of CML is virtually the same as for *de novo* adult acute leukemia. Chances for durable CR, however, are dim for all treatment regimens. High-dose cladribine therapy is associated with some success.

VI. Special clinical problems in CML

A. **False platelet counts.** Patients with accelerated or acute-phase CML usually develop severe, refractory thrombocytopenia. Platelet counts that incorrectly show improvement may be found in patients with marked leukocytosis and advancing disease. The false platelet count happens because the granulocytes become disrupted in the test tube, and automatic platelet counting machines enumerate the larger leukocyte granules as platelets. The paradox is resolved by reviewing the peripheral blood smear and estimating platelet numbers.
B. **Other false laboratory results.** Pseudohyperkalemia, pseudohypoglycemia, and pseudohypoxemia are discussed in Chapter 24, Comparative Aspects, section III.A.8.

Chronic Myelomonocytic Leukemia

I. Terminology. Chronic myelomonocytic leukemia (CMML) has also been described as "smoldering leukemia." CMML was previously classified with the myelodysplastic syndromes (see Chapter 25.I.C).

II. Diagnosis

A. **Physical examination.** CMML most commonly affects the elderly. Splenomegaly is commonly present and tends to increase as the disease progresses. Hepatomegaly is uncommon, and lymphadenopathy is rare.
B. **Blood studies.** Patients usually have unexplained monocytosis with granulocytosis or thrombocytopenia.
1. **Erythrocytes.** Anemia is usually mild unless complicated by iron deficiency.
2. **Platelets** are moderately decreased in most patients, normal in 15%, severely decreased in 15%, and occasionally elevated.
3. **Leukocytes.** Leukocytosis in the range of 11,000 to 50,000/µL (because of increased numbers of both granulocytes and monocytes) is present in most patients; leukopenia occasionally occurs. The morphology of leukocytes is characteristically indeterminate and abnormal. Nucleolated cells in the peripheral blood are uncommon.
4. **Serum lysozyme** levels are usually elevated.
5. **NAP** values are variable but rarely as low as those in CML.
C. **Bone marrow aspirates** in CMML are very hypercellular. Granulocytic hyperplasia with increased numbers of promyelocytes and myeloblasts (5% to 20% of nucleated cells) is prominent. The myeloid series in the marrow often has monocytoid features, but pure monocytosis is unusual. Features of myelodysplasia are also seen. In cytogenetic studies, the Ph^1 chromosome is absent, but other noncharacteristic abnormalities are common.

III. Clinical course. Distinguishing CMML from acute myelomonocytic leukemia is essential. CMML often has an insidious onset and an indolent course. Most patients live 2 years or longer, and about 30% survive more than 5 years. Eventually, most patients die of acute monoblastic or myeloblastic leukemia.

IV. Management. Early treatment for CMML does not forestall the development of acute leukemia and is usually ineffective. Supportive and blood component therapies are often the only necessary interventions. Tissue infiltration and marrow proliferation may be controlled with oral etoposide, hydroxyurea, or 6-thioguanine or with subcutaneous low-dose cytarabine. Intensive therapy is best not considered until and unless acute leukemia becomes overt, particularly in elderly patients.

Hypereosinophilic Syndrome

Hypereosinophilic syndrome (HES) is a group of disorders marked by the sustained overproduction of eosinophils and a distinct predilection to damage multiple organs, including the heart.

I. Epidemiology and etiology

A. **Epidemiology.** More than 90% of patients with HES are men, usually between the ages of 20 and 50 years. Both pediatric and elderly patients have also been described.
B. **Etiology.** The etiology of HES is unknown. Granulocyte-macrophage colony-stimulating factor, interleukin-5 (IL-5), and IL-7 may be involved in the dysregulated overproduction of eosinophils. Furthermore, despite the major propensity of thrombosis development, no consistent systemic alterations in coagulation or fibrinolysis have been found.

II. Pathology and natural history Most authorities recognize HES to be part of a spectrum of disease characterized by blood and bone marrow eosinophilia, *tissue infiltration* by relatively mature eosinophils, and multisystem organ dysfunction.

A. **Hematopoietic system involvement**
1. **Leukocytes.** All patients with HES have eosinophilic leukocytosis from the outset. The WBC count usually ranges from 10,000 to 35,000/µL, with 30% to more than 70% being eosinophils. The eosinophils are usually mature but often contain decreased numbers of granules that are small in size or cytoplasmic vacuoles.
2. **Erythrocytes.** Half of patients have a persistent normocytic, normochromic anemia, but "teardrop" and nucleated red blood cells can be seen.
3. **Platelets** are usually normal, but they may be decreased in about 30% of patients or increased in 15%.
4. **Bone marrow cytology** shows myeloid hyperplasia, and 25% to 75% of these cells are eosinophils, which are shifted to the left in maturation. Increased

numbers of myeloblasts are absent.
5. **Chromosome analysis.** Those cases showing a cytogenetic abnormality should be classified as eosinophilic leukemia rather than HES.
B. **Cardiac involvement** occurs in 55% to 75% of cases. Cardiac damage emanates from the presence of increased numbers of eosinophils (seen on endomyocardial biopsy) and other poorly defined factors in eosinophil physiology; this damage occurs identically whether the eosinophilia is caused by HES or many other etiologies.
1. **Three stages of cardiac involvement** in HES
a. **Acute, necrotic stage.** Myocardial necrosis is of short duration (about 1.5 months). Echocardiography and angiography are normal, and diagnosis is made by endomyocardial biopsy.
b. **Thrombotic stage.** Thrombosis in the ventricles or atria develops after a mean duration of eosinophilia of 10 months.
c. **Fibrotic stage.** Mitral or tricuspid valvular regurgitation and restrictive cardiomyopathy due to endomyocardial fibrosis develop after a mean duration of eosinophilia of 24 months.
2. **Clinical findings.** Patients with HES usually present in the thrombotic or fibrotic stages with chest pain, mitral regurgitation, and congestive heart failure from restrictive cardiomyopathy.
C. **Neurologic involvement** occurs in about 40% to 70% of cases; biopsy findings are inconsistent. The three clinical manifestations are as follows:
1. **Cerebral thromboemboli** originating in the heart or in local arterioles
2. **A distinct encephalopathy** with behavioral changes, confusion, ataxia, memory loss, and upper motor neuron signs. Impaired cognitive abilities may persist for months. Seizures, dementia, and organic psychoses occur less frequently.
3. **Peripheral neuropathies** account for half of the neurologic abnormalities associated with HES and manifest as symmetric or asymmetric sensory polyneuropathies.
D. **Cutaneous involvement.** Skin rashes develop in more than half of cases. Three types of manifestations occur.
1. **Angioedematous and urticarial lesions.** Affected patients are likely to have a benign course without cardiac or neurologic complications. These cases usually respond to prednisone or require no treatment.
2. **Erythematous, pruritic papules and nodules** show a mixed cellular infiltrate in the skin and perivascular tissue devoid of vasculitis on biopsy. These tend to respond to psoralen with ultraviolet light (PUVA), dapsone, or sodium chromoglycate.
3. **Mucocutaneous manifestations** may occur anywhere with incapacitating mucosal ulcers; these respond poorly to treatment.
E. **Lung involvement** occurs in about 40% to 50% of cases. The chest radiograph is usually clear despite a chronic nonproductive cough. Bronchial asthma is a rare occurrence in HES. Diffuse or focal infiltrations develop in 15% to 25% of patients. Pulmonary function test abnormalities are rare in the absence of congestive heart failure or pulmonary emboli arising from the right ventricle.
F. **Involvement of other organs**
1. **Splenomegaly,** which develops in 40% of cases, is caused by eosinophilic infiltrates.
2. **Ocular manifestations,** usually visual blurring, are caused by microemboli or local thrombosis.
3. **Rheumatologic manifestations** include arthralgias, effusions, and cold-induced Raynaud's phenomenon with digital ischemia or necrosis.
4. **Gastroenterologic manifestations.** Eosinophilic gastritis, enterocolitis, or colitis may occur. Chronic active hepatitis and Budd-Chiari syndrome have also been observed in HES.
5. **Renal manifestations.** Pyuria or microscopic hematuria are apparent in about 25% of cases. Azotemia is a late event that is usually associated with congestive heart failure.

III. Diagnosis

A. **Diagnostic criteria for HES**
1. Persistently increased absolute eosinophil count greater than 1500/μL (the upper limit of normal is 600/μL) for longer than 6 months
2. Absence of parasites, allergies, or other causes of eosinophilia
3. Evidence of organ system involvement
B. **Helpful studies**
1. Complete history and physical examination, CBC, liver and renal function tests, and urinalysis
2. IgE levels and serologic tests for collagen vascular disorders
3. Chest radiograph
4. Electrocardiogram and echocardiogram
5. Bone marrow aspirate, biopsy, and chromosome analysis
6. Several stool samples for ova and parasites
7. Duodenal aspirates and blood serology to exclude *Strongyloides* species infection
8. Cultures for fungi, mycobacteria, and bacteria to exclude infection
9. Biopsy of skin lesions
C. **Differential diagnosis.** The differential diagnosis of eosinophilia is discussed in Chapter 34, Increased Blood Cell Counts, section IV.
1. **Eosinophilic leukemia** can be distinguished by a marked increase in immature eosinophils in the blood or marrow, more than 10% blasts in the marrow, infiltration of tissues with immature eosinophils, pronounced cytopenias, chromosomal abnormalities, and a clinical course similar to other acute leukemias.
2. **Myeloproliferative disorders.** Patients with HES rarely have expansions of other cell lines besides eosinophils to the extent seen in myeloproliferative disorders and do not develop severe myelofibrosis.
3. **Eosinophilic syndromes limited to specific organs** characteristically do not extend beyond their own target organ and hence lack the multiplicity of organ involvement often found in HES.
4. **Churg-Strauss syndrome** is the major vasculitis associated with eosinophilia. It is characterized by asthma, pulmonary infiltrates, eosinophilia, paranasal sinus abnormalities, neuropathy, and blood vessels showing extravascular eosinophils. Asthma is usually absent in HES and may be the only feature that distinguishes it from Churg-Strauss syndrome.
5. **Episodic angioedema with eosinophilia** is characterized by recurring episodes of angioedema, urticaria, fever, and marked eosinophilia. This syndrome is distinguished from HES by its periodicity and its lack of associated cardiac damage.
6. **Other cutaneous diseases associated with eosinophilia** can usually be distinguished by biopsy.
7. **Eosinophilia-myalgia syndrome** caused by ingestion of contaminated l-tryptophan should be excluded.
8. **Parasites.** Helminthic parasites, particularly strongyloidiasis, filarial infections, and enteric protozoans, particularly *Isospora belli* and *Dientamoeba fragilis,* should be carefully excluded.

IV. Prognostic factors. More than 75% of patients survive 5 years, and 40% survive 10 and 15 years. If the sequelae of organ damage, especially to the heart, can be managed, the course of HES can be prolonged over decades. A poor prognosis is indicated by refractory congestive heart failure, WBC count greater than 90,000/μL, and the presence of blasts in the peripheral blood.

V. Prevention and early detection Early recognition, management, and close follow-up of cardiac disease can significantly prolong longevity.

VI. Management

A. **Observation.** Treatment should be withheld until there is evidence of progressive organ system involvement and dysfunction.
B. **Corticosteroids** have been the most effective agents. A suggested regimen is prednisone, 60 mg daily for 1 month, then every other day for 3 months. More prolonged therapy may be necessary. Therapy is discontinued if organ dysfunction improves and if the eosinophil count is reduced to or near the normal range. A good response to corticosteroids is associated with a better prognosis.
C. **Cytotoxic agents**
1. **Hydroxyurea** is used in patients with organ involvement and eosinophilia who do not respond to prednisone.
2. **Vincristine** is especially useful for acutely reducing eosinophil counts and may be useful for controlling HES and thrombocytopenia.
3. **Other cytotoxic agents.** Chlorambucil has been useful in HES. Cyclosporine and IFN-a are also effective occasionally. Toxic regimens should be avoided.
D. **Leukapheresis** is not helpful because eosinophil counts rebound to pretreatment levels within 1 day.
E. **Antithrombotic agents,** such as aspirin or warfarin, have been frequently used because of the occurrence of thromboembolic disease, but their role has not been established.

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Chapter 24 Myeloproliferative Disorders

Dennis A. Casciato

Comparative Aspects

The myeloproliferative disorders (MPDs) include polycythemia vera (PV), myelofibrosis with myeloid metaplasia (MMM), and essential thrombocythemia (ET). All bone marrow cells proliferate *en masse,* producing a "panmyelosis." The individual diseases are distinguished by the predominant proliferation of one of the marrow cell lines. Table 24.1 compares important clinical and distinguishing features of MPD and chronic myelogenous leukemia (CML), which is discussed in Chapter 23.

Table 24.1 Clinical features of the myeloproliferative disorders and chronic myelogenous leukemia

I. Epidemiology and etiology

A. **Incidence.** The MPDs are uncommon illnesses; their frequencies in the general population are uncertain. Both PV and ET each affect about 1 per 100,000 population. The peak incidence occurs in patients 50 to 60 years of age, but the diseases also occur in children. The MPDs affect men and women equally, except in young patients with ET, where female patients predominate.

B. **Etiology.** Radiation exposure is associated with an increased incidence of MMM but accounts for only a small percentage of cases. Exposure over many years to tuff (a building material used in central and southern Italy) or to dark hair dyes is reported to be associated with an increased risk for ET. No other etiologic factors have been determined for MPDs. Familial cases occur in PV and MMM.

C. **The Polycythemia Vera Study Group** was founded in 1967 to study the natural history of MPDs and the effects of therapies on them. More than 1000 patients were entered into protocols. Modern modifications of diagnostic criteria proposed by the PV Study Group have been incorporated into this chapter.

II. Pathogenesis. The MPDs usually have insidious onsets, and manifestations evolve at varying rates.

A. **Clonality of MPDs.** The MPDs arise from a single pluripotential hematopoietic stem cell. Thus, they are clonal and, hence, neoplastic. The description of clonality is based on studies of women with these MPDs who were also heterozygous for isotypes A and B of glucose-6-phosphate dehydrogenase.

Chromosome analyses have established that a clonal cytogenetic abnormality is present in erythroblasts, neutrophils, basophils, macrophages, megakaryocytes, and subsets of B lymphocytes, but *not* in fibroblasts. Abnormal karyotypes are associated with PV in about 30% of cases, del(20q) being most common. In MMM, abnormal karyotypes are found in 35% of cases; del(20q), del(13q), and partial trisomy 1q account for 70% of the abnormal karyotypes found.

B. **Hematopoiesis in the MPDs** is generally characterized by autonomous growth and hypersensitivity of progenitor cells to growth factors.
 1. **Erythropoiesis** *in vitro* in semisolid media normally requires exogenous erythropoietin (EPO). Blood or bone marrow from patients with PV forms erythroid colony-forming units (CFUs) without exogenous EPO. Serum EPO levels are low in PV and are elevated in most cases of secondary polycythemia. In PV, erythropoiesis is either autonomous or excessively sensitive to extremely low levels of EPO. Increased erythroid burst-forming units (BFU-E) or endogenous erythroid colonies (EEC) are demonstrable *in vitro* in PV, and in ET and MMM as well. Deregulated expression of an apoptosis inhibitor, *Bcl-x,* also appears to contribute to the EPO-independent survival of erythroid lineage cells in PV and thereby contributes to the pathogenesis of the disease.
 2. **Granulocytopoiesis** is frequently increased in all MPDs to varying degrees and is manifested by neutrophilia and myeloid hyperplasia in the marrow.
 3. **Megakaryocyte CFUs** in ET are not only increased in number but are also able to grow autonomously without added growth factor. The pathogenetic roles of released growth factors are incompletely understood. In ET thrombopoietin levels are usually inappropriately elevated or normal. Reduced expression of the thrombopoietin receptor Mpl is characteristic of PV, MMM, and ET.
 4. **Extramedullary hematopoiesis** is consistently present in the liver and spleen in patients with MMM and contributes to organ enlargement. This does not result in quantitatively significant hematopoiesis outside of the marrow. The splenomegaly in patients with PV does not represent extramedullary hematopoiesis except in late stages of the disease.

C. **Bone marrows in MPDs** demonstrate hypercellularity that is often trilineage but are diagnostic of a specific disorder only in MMM. Megakaryocytes are greatly increased in number and size in ET and MMM at all stages of disease and to a lesser degree in PV. Reticulin is increased in all MPDs, but collagen fibrosis occurs only in MMM and in PV that has converted to MMM. Morphology, however, is still too indistinct to permit marrow histology from being incorporated as major diagnostic criterion for PV and ET.
 1. **Fibrosis of the marrow,** which develops in all patients with MMM, in many patients with PV, and in some patients with ET, is *not* an intrinsic part of clonal expansion in the MPDs. Marrow fibrosis is most closely related to increased numbers of dysplastic megakaryocytes and results from the inappropriate release of growth factors from clonal megakaryocytes and platelets. These growth factors cause an increased deposition of various interstitial and basement membrane glycoproteins, including collagen types I, III, IV, V, and VI, fibronectin, vitronectin, laminin, and tenascin. The fine reticulin fibers that are visible with silver stains are principally type III collagen and do not stain with trichrome dyes.
 2. **MMM.** Marrow fibrosis is prominent in MMM. Megakaryocytes are increased in number, and they are atypical, enlarged, and immature. Neutrophilic granulopoiesis is hyperplastic. A marked neovascularization is also present, even in the early proliferative phase of the disease.
 3. **PV.** Erythroid hyperplasia is prominent in PV. Enlarged and clustered mature and pleomorphic megakaryocytes with multilobulated nuclei, and hyperplasia of dilated sinuses in a moderately to markedly hypercellular bone marrow constitute the hallmarks of untreated PV. In secondary erythrocytosis, erythroid hyperplasia may be present, but megakaryocytes remain small and normal with no tendency to cluster. Iron stores are absent or decreased in most untreated patients. Spontaneous BFU-E or EEC is present in virtually all patients with PV but in none with secondary erythrocytosis (except some patients with a rare mutation of EPO receptor).
 4. **ET.** Increased numbers of enlarged megakaryocytes with mature cytoplasm and multilobulated nuclei and a tendency to cluster in a normal or slightly increased cellular bone marrow constitute the hallmarks of ET. In reactive thrombocytosis, increased numbers of megakaryocytes may be present, but they have normal size and morphology and no tendency to cluster. Spontaneous megakaryocyte or erythroid growth can be shown in most patients with ET, but in none with reactive thrombocytosis.

D. **Interconversions of the MPDs** are probably uncommon. The only consistent transformation is the conversion of PV into MMM (5% of cases).
E. **Complications**
1. **Thrombotic phenomena,** both venous and arterial, are common in uncontrolled PV and ET and are frequently the cause of death. Myocardial or cerebrovascular ischemia is the most feared developments, but thrombosis anywhere in the venous or arterial tree can occur.

   For example, PV is the most common cause of hepatic vein thrombosis (Budd-Chiari syndrome). In PV, two thirds of thrombotic events occur either at presentation or before diagnosis (particularly in the 2 years preceding diagnosis), and one third occur during follow-up. The risk for thrombosis is higher in patients who are older or who had a history of thrombosis.

   In patients with asymptomatic ET, the risk for thrombosis cannot be predicted by platelet counts or platelet function. Most patients with ET who had CVAs also have had at least one atherosclerotic risk factor (hypertension, obesity, and particularly heavy smoking).

2. **Erythromelalgia,** the most characteristic vaso-occlusive manifestation in MPDs, is caused by the toxic effects of platelet arachidonic acid on arterioles. Localized painful erythema and warmth occur in the distal portions of the extremities and may progress to cyanosis or necrosis of toes or fingers. This microvascular syndrome is most often associated with PV and ET and is easily and best controlled by low-dose ASA or by reduction of platelet count to normal with low-dose myelosuppressive agents.
3. **Hemorrhagic phenomena** occur in PV, ET, and late MMM, but they occur far less commonly than with thrombotic events. Easy bruisability and purpura are the usual manifestations. Gastrointestinal (GI) hemorrhage can be catastrophic, but the incidence of peptic ulcer disease is not increased in any of the MPDs. Bleeding can occur spontaneously without relationship to the platelet count, especially in uncontrolled myeloproliferation, and can be promoted by the use on nonsteroidal antiinflammatory agents, such as aspirin.
4. **Acquired von Willebrand disease** develops occasionally in the MPDs. This coagulopathy is characterized by a *very high platelet count,* a normal or prolonged bleeding time, normal factor VIII and normal von Willebrand factor (vWF) antigen levels, but with decreased vWF– ristocetin cofactor activity, decreased collagen-binding activity, and a decrease or absence of large vWF-multimers. This condition simulates type II vWF deficiency. The increased number of platelets appears to be directly responsible for the observed decrease of large vWF multimers in plasma that leads to the tendency for spontaneous bleeding at very high platelet counts.
5. **Hypercatabolism.** Hyperuricemia and hyperuricosuria are present in nearly all patients with active MPD. Treatment with allopurinol can prevent gouty arthritis, uric acid nephropathy, and nephrolithiasis, but its necessity is unproved and controversial. Pruritus is a frequent problem, particularly in PV. Fever, heat tolerance, and weight loss ensue when the disease becomes rapidly progressive.
6. **Transformation to acute myelogenous leukemia** (AML). The chance that an MPD will convert to leukemia depends on the treatment given and the reported series. AML is almost nonexistent in untreated ET and occurs in 0% to 15% of patients with MMM, in 5% to 25% of those those with PV, and in 20% of patients who convert from PV to MMM. The development of AML is clearly increased after treatment of MPD with alkylating agents (chlorambucil) or radioactive phosphorus (^{32}P).

   Hydroxyurea (HU) has also become suspect but has not been proven to enhance transformation to AML. The risk for AML in patients treated with HU alone is about 3% to 4% in those with ET and 10% in those with PV. The risk with HU appears to be about double the rate of patients who are not treated with myelosuppressive agents and half the rate of patients who are treated with alkylating agents or ^{32}P. A high proportion of AML and myelodysplasia occurring in patients with ET treated with HU alone have morphologic, cytogenetic, and molecular characteristics of the *17p⁻ syndrome* (namely, typical dysgranulopoiesis combining pseudo-Pelger-Huët hypolobulation, vacuoles in neutrophils, rearrangements of chromosome 17, and *p53* mutation).

   The risk for blast transformation also appears to be significantly increased in subjects with MMM who underwent splenectomy, independent of factors leading to the splenectomy. More blast transformations occurred in those patients with MMM who underwent splenectomy (25%) than in those who did not (12%).

III. Diagnosis

A. **Laboratory studies**
1. **Hemogram** results are discussed under each specific entity.
2. **Platelet function.** Neither the severity of thrombocytosis nor the results of platelet function tests correlate with thrombotic or hemorrhagic events in the MPDs. Platelet dysfunction is common in all MPDs and is manifested by lack of aggregation in response to epinephrine and by abnormal surface membrane properties. Template bleeding times are usually normal in PV and ET and prolonged only in CML and late MMM.
3. **Neutrophil alkaline phosphatase** (NAP) scores are normal or increased in MPDs and decreased in CML.
4. **Vitamin B$_{12}$.** Transcobalamins I and III are synthesized by granulocytes. The total-body granulocyte mass, when increased, is reflected by increased serum levels of vitamin B$_{12}$ and unsaturated B$_{12}$-binding capacity (UBBC). These levels are usually elevated in patients with MPD and CML and normal in patients with erythrocytosis or granulocytosis of other causes. Transcobalamin I is increased in CML, and transcobalamin III is increased in PV.
5. **Bone marrow findings** in MPDs are discussed in section II.C.
6. **Growth factors.** Serum EPO levels are characteristically undetectable (50% of cases) or low (50%) in patients with untreated PV. Serum thrombopoietin levels in patients with ET are expected to be downregulated (low or inappropriately normal), but reported results have not been consistent.
7. **Cytogenetics.** Many types of nonrandom structural and numeric chromosomal abnormalities are common in PV and MMM at any stage of disease, particularly in patients treated with myelosuppressive therapy (see section II.A and section II.E.6). These abnormalities may be helpful in differentiating secondary conditions associated with elevated blood counts or in determining prognosis. Cases with a positive Philadelphia chromosome should be excluded from classification with the MPDs because they probably represent CML in evolution.
8. **False laboratory results**
   a. **Pseudocoagulopathy.** Prolonged clotting times in patients with marked erythrocytosis are usually the result of excessive amounts of anticoagulant relative to the small plasma volume in the test tube. Accurate determinations can be made if the volume of anticoagulant is adjusted for the hematocrit.
   b. **Pseudohyperkalemia.** Marked thrombocytosis may result in elevated serum potassium concentrations because platelets release potassium during the clotting reaction. The true level is determined by reviewing the electrocardiogram for evidence of hyperkalemia and by measuring the potassium concentration in plasma rather than serum.
   c. **Pseudo–hyperacid-phosphatemia.** Platelets are rich in acid phosphatase. Marked thrombocytosis may result in spurious elevations of enzyme levels measured in serum and plasma.
   d. **Pseudohypoglycemia.** Leukocytes metabolize glucose from serum in test tubes. Dramatically low blood glucose concentrations may result from marked granulocytosis. More accurate glucose levels can be measured if the clot with entrapped leukocytes is removed immediately.
   e. **Pseudohypoxemia.** Oxidative respiration is used by monocytes and immature leukocytes to a greater extent than by mature leukocytes and platelets and is not used by mature erythrocytes. Falsely low oxygen tensions may be seen in patients with severe thrombocytosis or granulocytosis because of oxygen consumption within the test tubes. The presence of hypoxemia may be clarified if specimens are collected in test tubes containing fluoride and are immediately placed in ice.
B. **Differential diagnosis**
1. **Elevated blood counts** (see Chapter 34, Increased Blood Cell Counts, sections I to V for discussion of polycythemia, neutrophilia, eosinophilia, basophilia, and thrombocytosis)
2. **Marrow fibrosis** (see Chapter 34, Cytopenia, section I.B)
3. **Differentiation of the MPDs** necessitates attention to the characteristics listed in Table 24.1 and the diagnostic criteria for each disorder. Long-term observation often clarifies the diagnosis. Patients must have iron and folate deficiencies corrected before the specific disorder can be accurately diagnosed.
4. **MPD, undifferentiated type** is the best designation for patients who have leukoerythroblastic blood smears, normal red blood cell mass, and a hypercellular marrow that shows only mild fibrosis. The diagnosis of MPD is made by exclusion.

IV. Staging system and prognosis
No staging system exists for the MPDs. Prognosis depends on the pace of disease, the ability of treatment to control manifestations, and the development of complications. With modern therapy, survival for patients with ET appears to be the same as for age-matched controls. Survival for patients with PV is somewhat decreased and with MMM is substantially decreased.

Polycythemia Vera

See Comparative Aspects at the beginning of this chapter for epidemiology, etiology, pathogenesis, comparative laboratory results, false laboratory results, and

I. Diagnosis. The erythroid series is the predominant proliferating cell line in the panmyelosis of (PV).

- A. **Diagnostic criteria for PV.** The PV Study Group developed a group of criteria to use available laboratory measurements and to study treatment options that were available in 1967. Some of these criteria (NAP score, vitamin B$_{12}$ levels, and UBBC) are no longer considered sensitive enough. Modern revisions of these criteria use newer technologies and refine important diagnostic criteria. Recognizing that some cases still require the designation of *idiopathic erythrocytosis,* the following modifications for the diagnosis of PV should prove useful:
  - 1. **Category A criteria**
    - A1 Increased red blood cell mass measured with ^{51}Cr-labeled red blood cells: more than 25% above mean normal predicted value
    - A2 Absence of causes of secondary polycythemia
    - A3 Palpable splenomegaly
    - A4 Clonality marker (e.g., abnormal karyotype)
  - 2. **Category B criteria**
    - B1 Thrombocytosis: platelets more than 400,000/μL
    - B2 Neutrophilia: Neutrophil count more than 10,000/μL
    - B3 Splenomegaly demonstrated on isotope or ultrasound scanning (interpret results with caution)
    - B4 Reduced serum erythropoietin or characteristic BFU-E growth (if available)
  - 3. **The diagnosis of PV** is established by the presence of the following:
    Category A1 and A2 and either A3 or A4,
    or
    Category A1 and A2 and any two from Category B
- B. **Laboratory abnormalities**
  - 1. **Erythrocytes.** To establish the diagnosis of PV, an increased red blood cell mass must be demonstrated by using ^{51}Cr at some time during the course of disease unless the hematocrit is 60% or more. Erythrocytes are usually normocytic and normochromic unless iron deficiency is present. Poikilocytosis and anisocytosis reflect the transition into MMM late in the disease course. Some cases have increased amounts of fetal hemoglobin.
  - 2. **Granulocytes.** Granulocytosis in the range of 12,000 to 25,000/μL occurs in two thirds of patients at presentation. Early forms may be present but are not prominent. Two thirds of patients have basophilia.
  - 3. **Platelets.** Platelet counts usually are in the range of 450,000 to 800,000/μL, occasionally with abnormal morphology.
  - 4. **NAP score** is increased (70% of patients) or normal.
  - 5. **Serum B$_{12}$ and UBBC.** The serum B$_{12}$ concentration is increased in 35% of patients. The UBBC is increased in 75% and is mostly transcobalamin III.
  - 6. **Bone marrow examinations.** See Comparative Aspects, section II.C.
  - 7. **Immunologic abnormalities** occur in one third of PV patients.
- C. **Differential diagnosis** includes the other MPDs (particularly for patients with PV who are anemic because of blood loss) and relative and secondary erythrocytosis (see Chapter 34, Increased Blood Cell Counts, section I). Although not necessary for most patients, bone marrow biopsy, measurement of the serum EPO level, or assessment of CFU or EEC in semisolid media may be helpful in difficult cases.

II. Clinical course. The survival of patients with PV approaches that of a matched otherwise healthy population with modern therapy. Previously, the mortality rate was twice the control population; untreated patients often died within 18 months of diagnosis. Reported median survival times now exceed 12 years.

- A. **Predominant signs and symptoms** early in the disease are secondary to increased red blood cell mass that results in plethora and hyperviscosity. Modest splenomegaly is present in 75% of cases and hepatomegaly in 40%. Splenomegaly is caused by an increased splenic red blood cell pool and not by extramedullary hematopoiesis, which is absent early in the disease. Pruritus develops in 15% to 50% of cases, urticaria in 10%, and gout in 5% to 10%.
  - 1. **Hyperviscosity** results in decreased blood flow and, consequently, in tissue hypoxia. Manifestations include headache, dizziness, vertigo, tinnitus, visual disturbances, stroke, angina pectoris, claudication, and myocardial infarction.
  - 2. **Hemorrhagic manifestations** (10% to 20% of patients) include epistaxis, ecchymosis, and GI bleeding. Minor mucosal bleeding is most common. Acquired abnormalities of vWF (see Comparative Aspects section II.E.4) and coagulation factors V and XII frequently occur in PV.
  - 3. **Thrombotic manifestations** in patients treated with phlebotomy alone develop in 15% of patients during the first 2 years and in 33% during the first 7 years after diagnosis.
    - a. **Types of events.** Both arterial and venous thrombosis occur in PV. About two thirds of thrombotic events are life-threatening and are associated with a 25% mortality rate. Half of these events are cerebrovascular accidents, and half comprise myocardial infarction, pulmonary infarction, and axillary, hepatic, or mesenteric vein thrombosis. The remaining one third of events are uncomplicated deep-vein or other thromboses. PV accounts for half of the hepatic, portal, splenic, or mesenteric vein thrombosis cases that occur.
    - b. **Thrombosis-related risk factors** in PV include the degree of hematocrit elevation advanced age, history of prior thrombosis, treatment with phlebotomy alone, and the rate of phlebotomy, *but not the platelet count or platelet function tests*.
- B. **Phases of disease**
  - 1. **Erythrocytic phase.** The phase of persistent erythrocytosis that necessitates regular phlebotomies lasts from 5 to 25 years. The manifestations of erythrocytosis and severity of complications depend on comorbid conditions.
  - 2. **Burned-out phase.** Eventually, the patient enters a "spent" or "burned-out" phase; the need for phlebotomies is greatly reduced, or the patient enters a long period of apparent "remission." Anemia eventually supervenes, but thrombocytosis and leukocytosis usually persist. The spleen increases in size, but little marrow fibrosis is present.
  - 3. **Myelofibrotic phase.** Myelofibrosis develops in 10% of patients and increases over the course of PV. When cytopenias and progressive splenomegaly develop, the clinical manifestations and course become similar to that of myelofibrosis with myeloid metaplasia.
  - 4. **Terminal phase.** In 35% to 50% of patients with PV, death results from thrombotic or hemorrhagic complications. Death is attributed to myelofibrosis in less than 15% of cases. The risk for acute leukemia is greatly increased when patients are treated with radioactive phosphorus or alkylating agents compared with treatment by phlebotomy alone.
- C. **Pregnancy and PV.** Pregnant patients with PV have an increased incidence of premature births, fetal wastage, preeclampsia, and postpartum hemorrhage. Pregnancy does not affect the course of PV.

III. Management. The therapeutic dilemma in PV is balancing the control of manifestations with the risks for thrombosis, hemorrhage, and leukemic transformation. Phlebotomy alone is associated with poor compliance and an increased risk for thrombosis during the first 3 to 5 years, whereas chemotherapy may induce AML after 7 to 10 years of follow-up.

- A. **Principles of treatment**
  - 1. Reduction of hematocrit and control of erythropoiesis with phlebotomy
  - 2. Avoidance of elective surgery
  - 3. Avoidance of overtreatment
  - 4. Avoidance of myelosuppressive agents in patients younger than 65 years of age, if possible
  - 5. Control of panmyelosis with hydroxyurea in patients who have one of the following characteristics:
    - a. A history of a prior thrombotic event, a high risk for thrombotic complications, or a very high requirement for phlebotomy (more frequently than every 2 months)
    - b. Problematic splenomegaly
    - c. Uncontrolled systemic symptoms (e.g., intractable pruritus, weight loss) or poor venous access
    - d. Pathologic bleeding in the presence of thrombocytosis
- B. **Medical management**
  - 1. **Phlebotomy** alone may be adequate for many years. The hematocrit is maintained between 42% and 47%.
    - a. Initially, 500 mL of blood may be removed every other day (only 250 mL of blood should be removed in patients with serious vascular disease).
    - b. About 200 mg of iron is removed with each 500 mL of blood (the normal total-body iron content is about 5 g). Iron deficiency is a goal of chronic phlebotomy treatment. Symptomatic iron deficiency (glossitis, cheilosis, dysphagia, asthenia, pruritus) resolves rapidly with iron administration.

2. **Myelosuppressive therapy** controls the complete blood count, minimizes complications from increased circulating elements, reduces symptomatic organomegaly, improves pruritus, and ameliorates problems with poor venous access.
   a. **Hydroxyurea** (HU), 10 to 30 mg/kg daily PO, controls the panmyelosis in 85% of patients within 12 weeks and reduces the incidence of thrombotic events by 50% in patients with PV. No drug has been shown to be superior to HU. This drug, however, is now suspected to be leukemogenic; the risk is not yet determined (perhaps three-fold). HU must be given continuously, and patient compliance must be excellent. Occasional side effects of HU include fever, rash, stomatitis, leg ulcers, gastric discomfort, and possible renal dysfunction.
   b. **Radioactive phosphorus** (^{32}P), 2 to 5 mCi, controls panmyelosis in 80% of patients within 2 months and may be effective for 2 years or longer. Doses may be repeated every 12 weeks if necessary. Serious cytopenias are rare. Treatment with ^{32}P reduces the incidence of thrombotic complications but also increases the incidence of acute leukemia (five-fold), lymphomas, and cancers of the skin and GI tract. This agent is most suitable for elderly patients, especially those who are poorly compliant.
   c. **Alkylating agents** (chlorambucil, busulfan, and melphalan) successfully control panmyelosis and reduce the incidence of thrombosis but unacceptably increase the incidence of acute leukemia (13-fold) and other malignancies. These drugs are not recommended for the management of PV.
   d. **Interferon-a** (IFN-a), 3 million U SQ three times weekly, can control myeloproliferation, reduce splenomegaly, ablate pruritus, and possibly delay fibrosis. IFN-a, however, is costly and associated with problematic side effects, which include a flu-like syndrome, severe weakness late in treatment, altered mental status, depression, and exacerbation or development of autoimmune disease. This drug appears to be nonmutagenic, but its effect on reducing thrombotic events is uncertain.
   e. **Anagrelide,** an inhibitor of platelet production that does not suppress erythrocyte or granulocyte production, has successfully lowered platelet counts in more than 80% of MPD patients with problematic thrombocytosis when other available agents have failed, usually within 1 or 2 weeks. The mechanism of how anagrelide lowers platelet counts is unknown. The maintenance dosage is usually 2 to 2.5 mg/day in two to four divided doses. The main side effects of anagrelide are headache (2 weeks or less in duration), palpitations, fluid retention, and other neurologic, GI, and cardiac manifestations. It should be used with caution in patients with heart disease. Anagrelide appears to be nonmutagenic, but its effect on reducing thrombotic events is uncertain.
   f. **Pipobroman,** 1 mg/kg/day, has been used extensively in Europe, effectively controls panmyelosis, and may be less leukemogenic than HU.
3. **Antiplatelet drugs.** Low-dose aspirin (81 mg/day) is helpful for patients with erythromelalgia or other microvasculature problems. Using aspirin in high doses (1000 mg/day) alone or together with dipyridamole (Persantine) does not prevent thrombotic complications in PV, can result in serious hemorrhage, and is not recommended.
4. **Supportive care**
   a. **Hyperuricemia,** if associated with complications, is treated with allopurinol, 100 to 600 mg/day PO. Other measures are discussed in Chapter 27, section IX.
   b. **Platelet transfusions** are given for important bleeding, even if the platelet count is normal or elevated, because platelet function abnormalities may be present and are not predictable by laboratory tests.
   c. **Anticoagulation** with heparin or low-molecular-weight heparin and then warfarin is used for acute thrombotic complications.
   d. **Pruritus** is multifactorial and often resistant to therapy.
      1. Histamine blockers, such as cyproheptadine (4 mg PO t.i.d.) or cimetidine (300 mg PO t.i.d.) should be tried initially.
      2. Combined histamine and serotonin blockage can be tried by using doxepin or trifluoroperazine and cyproheptadine.
      3. Low-dose ferrous sulfate supplementation to treat pruritus that may be caused by iron deficiency should be considered. In these cases, the hematocrit must be closely monitored for the expected increase in requirement for phlebotomy.
      4. Cholestyramine is helpful in some cases.
      5. If the above measures fail, HU or IFN-a may be necessary.
   e. **Burned-out PV** is managed as for MMM.
C. **Surgery**
1. **Elective surgery** should be avoided whenever possible in patients with PV. More than 75% of patients with uncontrolled PV who undergo surgery develop hemorrhagic or thrombotic complications, and about one third of patients die as a result. The longer the disease is controlled, the fewer the complications that will occur. The following approach is recommended:
   a. **Phlebotomy.** The hematocrit should be reduced to 45%. If there is evidence of clinically significant arterial disease, reducing the hematocrit to 35% to 40% appears to be justified. The blood obtained by phlebotomy may be saved for autologous transfusion.
   b. **Prevention of perioperative thromboembolism**
      1. Elastic stockings or pulsating boots should be used to speed blood flow through the calf.
      2. Low-dose heparin, 5000 U SC every 8 to 12 hours, or low-molecular-weight heparin can be given until the patient returns to normal activity, if there are no contraindications.
2. **Emergency surgery.** Aggressive phlebotomy with reinfusion of the patient's plasma or colloid may be lifesaving.
3. **Splenectomy** is extremely hazardous in all phases of PV and should be restricted to highly selected patients. Progressive hepatomegaly from extramedullary hematopoiesis and increased risk for transformation to AML typically follow splenectomy performed for massive splenomegaly in the myelofibrotic phase of disease.

Essential Thrombocythemia

See Comparative Aspects at the beginning of this chapter for epidemiology, etiology, pathogenesis, comparative laboratory results, false laboratory results, and differential diagnosis of the MPDs.

I. Diagnosis. The megakaryocyte is the predominant proliferating cell line in the panmyelosis of ET (essential, hemorrhagic, idiopathic, or primary thrombocythemia or thrombocytosis). Distinguishing PV from ET may be difficult in the early stages of disease.

A. **Diagnostic criteria for ET** are predominantly those which exclude other conditions.
   1. **Platelet counts** persistently greater than 1,000,000/µL (some authorities accept greater than 600,000/µL)
   2. **Absence of other causes of thrombocytosis**
      a. No prior splenectomy
      b. No iron deficiency as assessed by the red blood cell mean corpuscular volume, serum ferritin, and if necessary, marrow hemosiderin (which may not be reliable). Re-evaluation after replacement therapy with ferrous sulfate may be necessary.
      c. No evidence of malignancy, of recent GI bleeding, or of other causes of thrombocytosis
   3. **Bone marrow examination** shows hypercellularity, markedly increased numbers of megakaryocytes, and clumps of platelets and megakaryocytes (see Comparative Aspects, section II.C).
      a. Cytogenetic studies show no Philadelphia chromosome and no *BCR/ABL* gene rearrangement (to exclude CML).
      b. Cytogenetic and morphologic studies show no evidence of myelodysplasia.
B. **Laboratory abnormalities**
   1. **Erythrocytes.** Hypochromic, microcytic anemia is present in more than 60% of patients. Other abnormalities of red blood cell shape and size are mild. Howell-Jolly bodies are found in 20% of patients and indicate splenic atrophy from repeated infarctions.
   2. **Granulocytosis** is present in half of cases, usually in the range of 15,000 to 30,000/µL. Myelocytes and earlier forms are rare, and basophilia is mild.
   3. **Platelet counts** always exceed 600,000/µL and are often present as clumps or megakaryocytic fragments. Counts may reach 15,000,000/µL.
   4. **NAP scores** are nearly always normal. Elevated scores probably indicate that the patient will eventually manifest PV. Low values are seen occasionally.
   5. **Serum B$_{12}$ and UBBC** levels are usually normal.
C. **Differential diagnosis** of ET includes reactive thrombocytosis, familial cases of thrombocytosis related to increased levels of thrombopoietin, the other MPDs, CML, and myelodysplastic syndromes. Myelodysplastic syndromes with thrombocytosis usually manifest more severe anemia, macrocytosis, ringed sideroblasts, or the 5q– chromosomal abnormality. Reactive thrombocytosis is discussed in Chapter 34, Increased Blood Cell Counts, section III.

II. Clinical course

A. **Predominant signs and symptoms.** Two thirds of patients do not have symptoms when ET is discovered. The spleen may be enlarged (one third of cases) or atrophic. Hepatomegaly is absent. Extramedullary hematopoiesis is not a major feature of ET; surgically removed spleens usually demonstrate only chronic passive congestion. Pruritus develops in 10% to 15% of patients. Diminished arterial pulses do not typically accompany signs of arterial insufficiency.
B. **Thrombotic, embolic, or hemorrhagic episodes** of varying severity are the most common spontaneous manifestations of ET. Despite extensive study, it is not known why some patients bleed. Neither platelet counts nor platelet function tests correlate with clinical events, except that the risk for hemorrhage is increased

when the platelet count exceeds 2,000,000/μL. Increased platelet turnover appears to be present in ET when assessed by a variety of methods. Cardiovascular risk factors (obesity, hypertension, and particularly smoking tobacco) significantly increase the risk for thrombosis.

1. **Thrombotic episodes** are most frequently venous and deep-vein thrombosis, with pulmonary emboli as the most frequent manifestation. Splenic, hepatic, portal, and cerebral veins are also often affected. Arterial thromboses most frequently result in digital ischemia or infarction or in symptoms relative to occlusion of small and medium-sized vessels. Cerebrovascular ischemia may present as recurrent or transient headaches (peculiarly similar to migraines), visual disturbances, confusion, or manifestations of acute thrombotic stroke or transient ischemic attacks; signs and symptoms are often nonspecific and not well localized. Central nervous system manifestations are subsequent to sludging or occlusion of the cerebral arterial microvasculature.
2. **Hemorrhage episodes** occur most frequently in the mucous membranes or skin. Life-threatening hemorrhage rarely occurs except after trauma or surgery or in the presence of higher doses of aspirin and other antiplatelet drugs.
3. **Pregnancy** is associated with increased occurrence of spontaneous abortions in patients with ET because of thrombosis of placental vessels.

C. **Survival** approaches that of matched, otherwise healthy controls. The median survival exceeds 10 years, and the 5-year survival rate is greater than 80%. Transformation of ET into acute leukemia is rare if leukemogenic agents are not used.

III. Management

A. **Principles.** The mainstays of treatment for ET are observation without treatment or myelosuppression and avoidance of splenectomy. It is important to remember that most patients with ET who are to have a catastrophic thrombosis either have it at the time of diagnosis or after a preceding thrombotic event and that the natural history of ET is consistent with a nearly normal life expectancy. All patients with ET and hemorrhagic or vasoocclusive disease should be treated promptly to lower the platelet count.

B. **Medical management**
   1. **Observation without treatment.** There is no evidence in the literature to show that myelosuppressive therapy should be used simply because the platelet count is high. No myelosuppressive therapy remains a perfectly viable option, particularly for the young patient and for the older patient with low thrombotic risk. Young patients without symptoms can do well without sequelae for many years and probably should be observed without initiating treatment unless complications of the disease occur. The risk factors for thrombosis and probable indications for myelosuppressive therapy in patients with ET include the following:
      a. Age older than 70 years
      b. History of thrombotic complications
      c. Heavy smoking of tobacco
      d. The presence of other cardiovascular disease risk factors (e.g., hypertension, obesity)
   2. **Myelosuppressive therapy.** Drugs are administered to achieve platelet counts less than 600,000/μL. If thrombotic events still occur, dosages are adjusted to maintain platelet counts well within the normal range.
      a. **Hydroxyurea** is effective in controlling thrombocytosis and pruritus and in reducing thrombotic complications for patients who are at high risk. HU is most commonly employed in the treatment of ET. No agent has been shown to be superior to HU. (See Polycythemia Vera, section III.B.2.a.)
      b. **Anagrelide** controls thrombocytosis in more than 80% of patients. Its role in preventing recurrence of thromboembolic complications is not completely defined. Anagrelide (or IFN-a) is indicated when patients develop problematic side effects from HU. (See Polycythemia Vera, section III.B.2.e.)
      c. **IFN-a** is effective in controlling thrombocytosis and pruritus when HU fails. It does not ablate clonal hematopoiesis. The role of IFN- a in preventing recurrence of thromboembolic complications is uncertain. (See Polycythemia Vera, section III.B.2.d.)
      d. **Radioactive phosphorus** is probably the simplest form of therapy to administer but should be restricted to elderly patients who are not compliant. (See Polycythemia Vera, section III.B.2.b.)
      e. **Alkylating agents** (melphalan, busulfan, chlorambucil, or thiotepa) effectively reduce platelet counts but are carcinogenic. Avoid their use in ET if possible, particularly in younger patients.
   3. **Antiplatelet drugs.** Erythromelalgic distress, ischemic neurologic attacks, and ocular disturbances in ET are completely abolished by control of platelet function with low-dose aspirin (81 mg/day). The benefit of low-dose aspirin, however, is still uncertain in the primary prevention of thrombosis in ET. The use of aspirin, dipyridamole, and other antiplatelet drugs in other situations and in higher dosages is controversial and potentially risk bleeding, particularly when the platelet count exceeds 1,000,000/μL. Use aspirin with caution in patients with dyspeptic symptoms or a history of peptic ulceration or bronchospasm.
   4. **Plateletpheresis** is indicated for emergency treatment of life-threatening complications of severe thrombocytosis and is nearly always associated with improvement in hemorrhagic and thrombotic symptoms.
   5. **Cardiovascular risk factors** should be optimized. All patients with ET must stop smoking tobacco.

C. **Splenectomy** greatly aggravates thrombocytosis, often leads to death, and is contraindicated in patients with ET.

D. **Pregnancy with ET** is successful in 55% of cases and is most frequently complicated by spontaneous abortion during the first trimester (35% of pregnancies). Maternal complications occur in about 5% of pregnancies. Abortion cannot be predicted by history or therapy or platelet counts, although a decline in the platelet count has been observed in some patients with successful pregnancies. Specific therapies for ET during pregnancy, including platelet apheresis, do not appear to modify the clinical outcome. The ideal management for women with ET during pregnancy is speculative.

Myelofibrosis With Myeloid Metaplasia

See Comparative Aspects at the beginning of this chapter for epidemiology, etiology, pathogenesis, comparative laboratory results, false laboratory results, and differential diagnosis of the MPDs.

I. Diagnosis. Monoclonal megakaryocytes and polyclonal fibroblasts are the predominant proliferating cell lines in the panmyelosis of myeloid metaplasia (MMM, agnogenic myeloid metaplasia, osteosclerosis, myelosclerosis).

A. **Diagnostic criteria for MMM** (according to the PV Study Group) consist of the following:
   1. Splenomegaly
   2. Leukoerythroblastic blood smear (nucleated red blood cells and granulocytosis) with prominent anisocytosis and poikilocytosis
   3. Normal red blood cell mass
   4. Bone marrow examination that demonstrates fibrosis involving more than one third of the cross-sectional area and the fibrosis is not secondary to some identifiable cause (see Chapter 34, Cytopenia, section I.B).
   5. Absence of Ph[1] chromosome and of dyserythropoiesis

B. **Diagnostic criteria for osteosclerosis** consist of sclerotic lesions demonstrated on radiographs of the pelvis, spine, and long bones plus the criteria for diagnosis of MMM. Radiographic film evidence of patchy osteosclerosis occurs in half of patients with MMM and may resemble metastases from carcinoma.

C. **Laboratory abnormalities**
   1. **Erythrocytes.** At presentation, anemia is moderate in two thirds of patients. Macrocytosis may reflect the presence of folic acid deficiency. Dacrocytes ("teardrop" cells), ovalocytes, pronounced anisocytosis, polychromasia, and nucleated red blood cells make up the characteristic and nearly pathognomonic blood picture of patients with MMM. The anemia is usually due to ineffective erythropoiesis but may be caused by acquired versions of autoimmune hemolysis, hemoglobin H disease, or a paroxysmal nocturnal hemoglobinuria-like syndrome.
   2. **Granulocytes** usually range from 10,000 to 30,000/μL. Blasts and promyelocytes constitute less than 10% of the granulocytes. Granulocytopenia occurs in 15% of patients. Basophils are only slightly increased.
   3. **Platelet count** is increased in one third, normal in one third, and decreased in one third of patients with MMM, depending on the stage of disease. Platelets usually have abnormal morphology.
   4. **NAP score** is normal or increased but may be decreased late in the course.
   5. **Serum B_{12} and UBBC** are slightly increased in many patients but not to the degree observed in patients with PV or CML.
   6. **Bone marrow examination** shows decreased fat content, granulocytic hyperplasia, and markedly increased numbers of dysplastic megakaryocytes. Fibrosis is patchy and variable in distribution; reticulin is always increased and is striking in half of patients. The extent or progression of fibrosis is *not correlated* with the duration of disease, splenic size, or degree of splenic myeloid metaplasia. See Comparative Aspects, section II.C.
   7. **Immunologic abnormalities,** such as monoclonal antibodies (10%), positive direct Coombs' tests (20%), polyclonal hyperglobulinemia, rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies, or circulating immune complexes are found in more than half of patients with MMM.

D. **Differential diagnosis** of MMM includes the other MPDs, CML, hairy cell leukemia, metastatic carcinoma associated with marrow fibrosis (desmoplastic reaction), and disseminated mycobacterial infection. A long list of other disorders associated with secondary myelofibrosis include collagen vascular diseases and are discussed in Chapter 33, Cytopenias, section I.B.

II. Clinical course

A. **Predominant signs and symptoms** relate to the severity of anemia and splenomegaly. Virtually all patients have splenomegaly, which may be massive in one third of cases, and three quarters of patients have enlarged livers. One fourth of patients do not have symptoms at the time of diagnosis. Progressive disease is commonly manifested by fever, weight loss, and debilitating bone pain from periostitis.

B. **Chronic myelofibrosis.** The clinical course of MMM is extremely variable. Some patients are symptom free for long periods without treatment. Hemorrhagic manifestations rarely develop until late in the disease when severe thrombocytopenia develops. Death is due to heart failure, infection, hemorrhage, postsplenectomy mortality, or transformation to acute leukemia. The transition rate of MMM into acute leukemia ranges from less than 5% to 10%.

The overall median survival time in patients with MMM is 4 to 5 years. Expected survival time, however, can range from less than 2 years for patients at "high risk" to more than 10 years (20 years in some reports) for patients at "low risk." Several scoring systems to quantify risk in MMM have been offered, but without consensus. Splenic size and bone marrow findings have been found not to be significant prognostic factors. The expected survival, however, is poorer with each of the major risk factors that a patient demonstrates.

1. **Accepted risk factors in MMM**

Hemoglobin less than 10 g/dL
White blood cell count less than 4000/μL or more than 30,000/μL
Presence of more than 10% circulating precursors (blasts, promyelocytes, myelocytes)

2. **Probable risk factors in MMM**

Abnormal karyotype
Age older than 65 years
Presence of constitutional symptoms

C. **Associated syndromes**
1. **"Acute myelofibrosis"** is now recognized to be AML (type M7).
2. **Portal hypertension and varices in MMM** are caused by massive increases in splenoportal blood flow and decreased hepatic vascular compliance. The decreased compliance is due to extramedullary hematopoiesis and its secondary collagen deposition.
3. **Extramedullary hematopoietic tumors** can develop in any organ and are most problematic in the epidural space. Foci of these tumors on serosal surfaces can result in massive effusions containing immature hematopoietic cells.
4. **Neutrophilic dermatoses,** which are skin lesions with intense polymorphonuclear neutrophil infiltration, can be a presenting or complicating feature of MMM. The resultant raised tender plaques can progress to bullae or pyoderma gangrenosum.

III. Management

A. **Medical management.** Therapy for MMM may not significantly improve survival. Treatment is therefore postponed until patients develop symptoms.
1. **Transfusions of packed red blood cells** is the major form of treatment and are given often enough to maintain tissue oxygenation above levels that produce symptoms.
2. **Androgens,** such as fluoxymesterone (Halotestin; 10 mg PO b.i.d.) or danazol (200 to 400 mg PO twice daily), may improve the anemia in many patients (see Chapter 4, section VII.C). Several months of treatment are necessary before improvement is evident. Androgens may be combined with glucocorticoids for improved results.
3. **Glucocorticoids,** such as prednisone (20 to 30 mg/day), sometimes ameliorate systemic symptoms and are useful for immunologic complications.
4. **Folic acid,** 1 mg/day PO, is often prescribed, particularly for patients with weight loss or marked splenomegaly.
5. **Erythropoietin** rarely helps these patients.
6. **Chemotherapy** with low doses of hydroxyurea most commonly (also, busulfan or 6-thioguanine) has been used for patients with high leukocyte and platelet counts, symptomatic splenomegaly, or symptoms of hypercatabolism (fever, sweats, or weight loss). The response to treatment is unpredictable. Cytotoxic agents must be used cautiously because these patients have marginal hematopoietic reserves. 2-Chlorodeoxyadenosine (2-CdA) in usual doses may be palliative in noncytopenic MMM patients with progressive hepatomegaly after splenectomy.
7. **IFN-a** is useful in some but not most patients with MMM. (See Polycythemia Vera, section III.B.2.d.)
8. **Anagrelide** is not helpful in the clinical or pathologic aspects of MMM other than reducing the platelet count.
9. **^{32}P** has no clear role in the management of MMM.
10. **Bone marrow transplantation** should be considered for patients who are younger than 40 years of age and who have a histocompatible sibling.
B. **Splenectomy,** when decided on cautiously in a timely fashion, is beneficial in nearly all patients who have painful splenomegaly, in about 40% of patients who have serious cytopenias, and in many patients with hypercatabolism. The mortality rate is less than 10% if the procedure is performed by experienced surgeons; postoperative morbidity exceeds 30%. Progressive hepatomegaly and an increased risk for blast transformation after splenectomy are major concerns. The indications for splenectomy in medically suitable patients with MMM are as follows:
1. Persistent discomfort because of a grossly enlarged or infarcted spleen
2. Refractory hemolytic anemia as manifested by the need for increasingly more frequent transfusions
3. Refractory, severe thrombocytopenia in the absence of evidence of disseminated intravascular coagulation
4. Hypercatabolic symptoms that are not responsive to HU
5. Portal hypertension associated with bleeding varices. Based on circulatory dynamic studies performed at the time of surgery, the following procedures should be performed:
   a. Splenectomy alone for portal hypertension secondary to markedly increased blood flow from the liver to the spleen
   b. Portosystemic shunt for portal hypertension secondary to intrahepatic obstruction to blood flow
C. **Radiation therapy**
1. Small doses (20 to 300 cGy per course given in daily fractions of 20 cGy) of RT to the spleen can relieve pain and early satiety secondary to massive splenomegaly in MMM, usually for a few months, when splenectomy is contraindicated. Blood counts must be monitored carefully during splenic RT because severe cytopenias can develop rapidly.
2. RT may also palliate focal areas of periostitis, extramedullary hematopoietic tumors, and ascites secondary to myeloid metaplasia of the peritoneum.

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Chapter 25 Acute Leukemia

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I. Epidemiology and etiology

A. **Incidence.** Acute leukemia afflicts 3 to 4 per 100,000 population annually (11,000 new cases per year) in the United States. Children account for 25% of cases. Acute leukemia is the most common malignant disease of childhood (see Chapter 18, Incidence, Leukemia, and Lymphoma, section II).

   1. **Cell type.** Eighty percent of cases of acute lymphoblastic leukemia (ALL) occur in children, and 90% of cases of acute myelogenous leukemia (AML) occur in adults.

   2. **Age.** The peak incidence of ALL occurs at 3 to 4 years of age; the incidence steadily decreases after 9 years of age and is rare after 40 years of age. The incidence of AML gradually increases with age; the median age of patients is 60 years.

   3. **Sex.** Acute leukemia shows a male predilection only in very young and elderly patients.

B. **Etiology**

   1. **Radiation** is the leukemogenic factor in humans that has been best documented. Increased incidence of leukemia proportional to the cumulative radiation dose has been demonstrated in populations exposed to atomic bombs, in patients irradiated for ankylosing spondylitis, and in radiologists (before current protective precautions). Doses of less than 100 cGy are not associated with the development of leukemia. The types of leukemia induced by radiation are ALL, AML, and chronic myelogenous leukemia (CML), but not chronic lymphocytic leukemia.

   2. **Viruses** have not been associated with acute leukemia in humans.

   3. **Chemicals.** The ability of chemicals to produce acute leukemia and pancytopenia is likely related to their ability to mutate or ablate the bone marrow stem cells.

      a. **Benzene and toluene** are well-documented causes of acute leukemia. Acute leukemia develops 1 to 5 years after exposure and is often preceded by bone marrow hypoplasia and pancytopenia.

      b. **Drugs.** Drug-induced acute leukemia is usually preceded by myelodysplasia. Alkylating agents given for prolonged periods are associated with a markedly increased risk for AML (see Chapter 34, Cytopenia, section I.D). Other drugs that have been implicated include arsenicals, phenylbutazone, and chloramphenicol.

   4. **Heredity**

      a. **Hereditary syndromes** that are associated with chromosomal abnormalities and high risk for acute leukemia include the following:

         1. **Bloom's syndrome,** which is a recessively transmitted disease occurring predominantly in people of Jewish ancestry. Chromosome breaks are readily found in cytogenetic studies. The syndrome is characterized by short and thin stature, delicate features, telangiectatic lesions over the malar eminences of the face, photosensitivity, and a variety of other cutaneous abnormalities (acanthosis nigricans, hypertrichosis, ichthyosis, and café-au-lait spots). AML is the type of leukemia that develops in these patients.

         2. **Fanconi's congenital pancytopenia** (Fanconi's aplasia), which is an autosomal recessive disease associated with multiple chromosomal abnormalities. Clinical features include skeletal abnormalities (absence of radii, hypoplasia of the thumbs), squinting, microcephaly, small stature, and hypogonadism. AML, as well as skin carcinoma, often complicates this syndrome.

         3. **Down's syndrome** (mongolism, trisomy 21), which is associated with an increased risk for both AML and ALL.

      b. **Siblings** of patients with acute leukemia have a five-fold increased risk. If one member of a monozygotic twinship develops acute leukemia, the risk that the other twin will also be affected is 1:4, especially if the patient is younger than 8 years old and it is within 1 year of the first diagnosis of leukemia.

   5. **Hematologic diseases.** CML transforms into acute leukemia ("blast crisis") in more than 80% of cases. Patients with myelodysplastic syndromes (see section I.C) clearly are at increased likelihood for acute leukemia. The incidence of acute leukemia in myeloproliferative disorders, myeloma, and certain solid tumors is increased by the use of chemotherapy.

C. **Idiopathic myelodysplastic syndromes** ("preleukemia," "refractory anemias"). Patients who have idiopathic myelodysplastic syndromes (MDSs) are at high risk for developing AML. Theoretically, defects in stem cells account for ineffective hematopoiesis and for the wide variety of abnormalities. The diagnosis of a primary MDS may be made only in the absence of conditions that produce *secondary myelodysplasia,* namely, radiation exposure and cytotoxic agent therapy. Folic acid and vitamin B_{12} deficiencies produce a reversible myelodysplastic picture.

   1. **Clinical features.** MDSs usually affect patients older than 65 years of age, particularly men. Symptoms are absent or nonspecific and usually reflect the degree of anemia. Physical examination is usually normal. Various cytopenias, usually including anemia, may persist for months to years. The bone marrow is always abnormal.

   2. **Dyspoiesis** is manifested by cytopenias in the presence of a normocellular or hypercellular bone marrow. Components and features of dyspoiesis, which occur in various combinations for each syndrome, are as follows:

      a. **Dyserythropoiesis**

         1. **Peripheral blood.** Anemia and reticulocytopenia from ineffective erythropoiesis; anisocytosis, poikilocytosis, basophilic stippling; macrocytosis (when megaloblastoid maturation is present); dimorphic (normocytic, normochromic, and microcytic, hypochromic) red blood cell populations (when ringed sideroblasts are present)

         2. **Bone marrow.** Erythroid hyperplasia or hypoplasia; ringed sideroblasts; megaloblastoid maturation (multinuclearity, nuclear fragments, or cytoplasmic abnormalities)

         3. **Other assays.** Positive Ham's test (paroxysmal nocturnal hemoglobinuria-like defect) and increased fetal hemoglobin levels may be detected.

      b. **Dysgranulocytopoiesis**

         1. **Peripheral blood.** Neutropenia; decreased or abnormal neutrophil granules; neutrophil nuclear changes with hyposegmentation (pseudo-Pelger-Huët anomaly), hypersegmentation, or bizarre shapes

         2. **Bone marrow.** Granulocytic hyperplasia; abnormal or decreased granules in neutrophil precursors; increased numbers of blast cells

         3. **Other assays.** Decreased neutrophil alkaline phosphatase and myeloperoxidase activity

      c. **Dysmegakaryocytopoiesis**

         1. **Peripheral blood.** Thrombocytopenia; large platelets with abnormal and decreased granularity

         2. **Bone marrow.** Reduced numbers of megakaryocytes; micromegakaryocytes; megakaryocytes with large, single nuclei or multiple, small nuclei

         3. **Other assays.** Abnormal platelet function tests

   3. **Classification of the MDSs** into one of four groups (on the basis of the French-American-British Cooperative Group Criteria [FAB]) is accomplished by assessing the spectrum of hematologic abnormalities. Distinguishing features are shown in Table 25.1. In general, the risk for transformation to AML is proportional to the number of cell lines affected by cytopenia, the percentage of blasts in the marrow, and the complexity of chromosomal abnormalities.

Table 25.1 Distinguishing features of the idiopathic myelodysplastic syndromes

   a. **Refractory anemia** (RA) applies to patients who do not fit precisely into any of the groups below. They present with anemia, neutropenia, or thrombocytopenia and a normocellular or hypercellular bone marrow. Dyserythropoiesis is present, but ringed sideroblasts are either absent or less than 15% of nucleated cells in the marrow. The incidence of infection and hemorrhage depends on the severity of neutropenia and thrombocytopenia. The incidence of AML is not defined.

   b. **Refractory anemia with ringed sideroblasts** (RA-S) differs from RA by having more ringed sideroblasts (more than 15% of all nucleated cells in the bone marrow). Neutropenia and thrombocytopenia are uncommon. Less than 10% of cases develop AML.

c. **Refractory anemia with excess blasts** (RAEB) shows conspicuous abnormalities in all three cell lines and cytopenias in at least two cell lines. Blast cells are increased in the marrow. AML develops in about 30% of cases. Some patients die from bone marrow failure caused by ineffective myelopoiesis or from unrelated causes because this disorder affects the elderly.

d. **RAEB in transformation** (RAEB-T) includes cases, often with a brief period of symptoms, that cannot clearly be classified as RAEB or AML. Auer rods or increased numbers of blasts are seen. Nearly all cases develop into AML.

e. **Other categories** that do not fit strictly into these FAB categories include refractory cytopenias with trilineage dysplasia, MDS with hypoplasia or myelofibrosis, and therapy-linked MDS. Chronic myelomonocytic leukemia is no longer included among the MDSs.

4. **Cytogenetic abnormalities** are nonrandom and occur in 40% to 60% of patients. Most combinations include whole or partial losses of chromosomes 5, 7, or 20 (5q–, –7, 20q–) or gains of chromosomes 1 or 8 (+1, +8). The unbalanced translocation between chromosomes 1 and 7 [t(1;7) (p11;p11)] results in trisomy for the long arm of chromosome 1 and monosomy for the long arm of chromosome 7 and may be causally related to therapy-related MDS. *RAS* oncogene activation occurs early in the pathogenesis of MDS in about 15% of patients. The development of cytogenetic abnormalities in patients with MDS, and previously normal karyotypes portends rapid transformation to AML.

5. **The 5q– syndrome** is a unique MDS that is characterized by macrocytosis, hypolobulated micromegakaryocytic hyperplasia, and a clonal interstitial deletion of the long arm of chromosome 5 (5q–). The platelet counts are normal or increased, and granulocytopenia is rare. Patients have a median age of 68 years, and female cases predominate by a ratio of 2:1. Survival tends to be better than for other MDS types because of the lower occurrence of hemorrhage and infection, but 15% develop AML.

6. **Management.** MDSs are usually managed conservatively unless and until acute leukemia supervenes.

a. Supportive care includes packed red blood cell transfusion as necessary, platelets for thrombocytopenic bleeding, and broad-spectrum antibiotics for neutropenic fever. Iron chelation therapy could be considered for patients who require red blood cell transfusions frequently and whose MDS has an indolent course.

b. Androgens, pyridoxine, folate, danazol, and derivatives of vitamins A and D have been effective rarely and have not improved survival. High doses of erythropoietin (5000 to 10,000 U/day) may improve the red blood cell count in 10% to 20% of patients. Combining growth factors, such as erythropoietin and granulocyte colony-stimulating factor (G-CSF; 30 to 150 µg/day SC), has been suggested to be synergistic and potentially helpful.

c. Cytotoxic agents are usually not recommended in these patients. Some patients have benefited temporarily from "low-dose cytarabine" therapy (3 to 20 mg/m^2 per day for 14 to 21 days) or topotecan.

d. Bone marrow transplantation (BMT) should be considered in patients younger than 45 years of age who have an HLA-compatible sibling (less than 10% of MDS patients) and who do not have "low-risk" MDS.

II. Pathology and natural history

A. **Classification.** The FAB classification of acute leukemia is summarized in Table 25.2.

Table 25.2 Classification of acute leukemias

1. **Auer rods** are abnormal condensations of cytoplasmic granules. Their presence in the immature cells distinguishes AML from ALL; their absence is not diagnostically helpful.

2. **Immunologic markers** distinguish subsets of ALL with similar morphologies (usually L1 or L1/L2) and usually distinguish ALL and AML. These markers are summarized in Table 25.3. Antiplatelet antibodies (e.g., to CD41 or CD61) are useful in differentiating megakaryoblastic (M7) leukemia. In some centers, flow cytometry has largely replaced cytochemistry.

Table 25.3 Immunologic cell-surface markers in acute leukemias

3. **Cytochemistry.** Identifying the type of early cell may be difficult but is facilitated by readily available and traditionally used histochemical techniques (Table 25.4).

Table 25.4 Cytologic reactions in acute leukemia [a]

4. **Quantitative bone marrow differential** based on a 500-cell count differentiates M1, M2, M4, M5, and M6 subtypes of AML (Table 25.5).

Table 25.5 Quantitative bone marrow differential counts in acute myelogenous leukemia [a]

B. **Pathology.** Bone marrow examination in acute leukemia shows hypercellularity with a monotonous infiltration of immature cells. Normal marrow elements are markedly decreased. Erythroblast maturation is commonly megaloblastoid in all types of AML, especially subtype M6.

C. **Natural history.** Leukemic cells generally replicate more slowly than their normal counterparts. Hematopoiesis is abnormal even before the proportion of blast cells in the marrow is conspicuously increased. Immature and malfunctioning leukocyte progenitors progressively replace the normal bone marrow and infiltrate other tissues. Unless complete remission after therapy lasts 4 or more years, relapse is inevitable. Relapse is associated with progressively poorer response to therapy and progressively shorter duration of remission. Unsuccessful therapy is usually followed by death within 2 months. Death in acute leukemia is usually caused by either infection or hemorrhage.

III. Diagnosis

A. **Symptoms**

1. **Nonspecific fatigue and weakness** are the most common symptoms. Bruising, fever, and weight loss are also frequent.
2. **Central nervous system** (CNS) **involvement** may be manifested by headaches, nausea, vomiting, blurred vision, or cranial nerve dysfunction.
3. **Bone pain** is more common in ALL than in AML.
4. **Abdominal fullness** usually reflects hepatosplenomegaly, which is more common in ALL.
5. **Oliguria** may result from dehydration, uric acid nephropathy, or disseminated intravascular coagulation (DIC).
6. **Obstipation** may signify disorders of calcium or magnesium metabolism.

B. **Physical findings**

1. **Pallor, petechiae, and purpura** are the most frequent findings in acute leukemia.
2. **Sternal tenderness to palpation, lymphadenopathy, and hepatosplenomegaly** are much more common in ALL than in AML.
3. **Meningismus** may indicate CNS involvement. CNS leukemia is most common in ALL, less common in M4 (particularly with abnormal bone marrow eosinophils) and M5 AML, and rare in the other subtypes of AML.
4. **Leukemic infiltrates in the optic fundus** appear as Roth's-like spots with flame hemorrhages.
5. **Gingival enlargement** is seen in ALL and M5 AML. Extranodal masses, especially involving the skin, orbits, breasts, or testes, are also most likely to occur in monocytic leukemias and ALL.
6. **Other organs.** At the time of diagnosis, the kidneys are clinically involved in about 25% of cases; the lung, joints, or gastrointestinal tract in 5% of cases; and the heart in 2% of cases. At postmortem examination, virtually all organs are infiltrated with leukemic cells.
7. **Bleeding** out of proportion to the degree of thrombocytopenia suggests the presence of DIC, especially in type M3 acute leukemia.

8. **Signs of infection** should be carefully sought.

C. **Laboratory studies.** The diagnosis of acute leukemia is established by bone marrow examination. Borderline cases are observed and the diagnosis of acute leukemia deferred until progressive bone marrow infiltration and clinical deterioration are demonstrated.

1. **Bone marrow findings** are discussed in section II.A and section II.B. Blasts must account for more than 30% of the nucleated cells to establish the diagnosis. Cytochemistries should be performed in all cases of acute leukemia. Immunologic cell-surface markers should be evaluated in all cases suspected of being ALL.

2. **Cytogenetic abnormalities** associated with the various subtypes of AML (see Appendix D-1, Glossary of Cytogenetic Nomenclature) are as follows:
   a. M0 with lymphoid markers: t(9;22)
   b. M2: t(8;21)
   c. M3: t(15;17); this translocation uniquely disrupts the gene encoding for the retinoic acid receptor a on chromosome 17q21
   d. M4 with eosinophilia: del(16)(q22) or inv(16)(p13q22)
   e. M5: 11q–
   f. M6 with dysplastic background: 7 or del(7q), and/or –5 or del(5q)
   g. M7: frequent in children with trisomy 21

3. **Hemogram**
   a. **Erythrocytes.** Ninety percent of patients have a normocytic, normochromatic anemia, which is usually severe. Reticulocytes are nearly always decreased. Macrocytosis usually reflects megaloblastoid maturation. Nucleated red blood cells are often observed in the peripheral blood.
   b. **Leukocytes.** The white blood cell (WBC) count is elevated in 60% of cases, normal in 15%, and decreased in 25%. Circulating blasts are demonstrable in virtually every case of acute leukemia. Blasts account for most of the circulating cells in patients with elevated WBC counts.
   c. **Platelet counts** are decreased in 90% of cases and are less than 50,000/μL in about 50%.

4. **Biochemical tests** that should be obtained include the following:
   a. Serum uric acid, calcium, phosphorus, and magnesium levels
   b. Serum renal and liver function tests
   c. Serum lysozyme concentration with M4 and M5 types of AML
   d. Coagulation tests for DIC (see Chapter 34, Coagulopathy, section II)

5. **Radiologic studies** that should be obtained include the following:
   a. Chest radiograph to look for leukemic or infectious infiltrates
   b. Bone radiographic study of painful or tender areas to look for periosteal elevation or bony destruction

6. **Cerebrospinal fluid** (CSF) examination should be performed in patients with meningismus or CNS abnormalities. The fluid should be cultured routinely for acid-fast bacilli, fungi, and bacteria. Meningeal involvement with leukemia is associated with decreased sugar and increased protein concentrations, pleocytosis, and leukemic cells found by cytologic examination (see section VII.B). Cytarabine or methotrexate should be injected into the CSF at the completion of the examination because of the possibility of leukemic contamination from blood.

7. **Surveillance bacterial cultures** of the nose, pharynx, axillae, and perianal regions identify organisms that may have colonized the patient. These cultures, however, are not commonly helpful in predicting etiologic organisms for serious infection.

IV. Staging system and prognostic factors

A staging system for acute leukemia does not exist. Complete remission (CR) is the paramount prognostic factor in all forms of acute leukemia. A CR is defined as all of the following:

Bone marrow contains less than 5% blasts.
Erythrocyte, granulocyte, and platelet counts are normal.
Organomegaly is resolved.
Performance status has returned to normal.

A. **Adverse prognostic factors in AML**
   1. Secondary AML (after cytotoxic drugs, benzene, or irradiation)
   2. AML after a prolonged MDS
   3. Age older than 55 years
   4. Presence of the Philadelphia chromosome, t(9;22)

B. **Adverse prognostic factors in ALL**
   1. **Age** less than 1 year or more than 9 years (prognosis is poorer in older children and poorest in adults, especially those older than 60 years of age)
   2. **WBC** count greater than 50,000/μL in children, or 30,000/μL in adults
   3. **Immunophenotype** true B-cell ALL (L3, surface immunoglobulin positive) and B-cell myeloid ALL have the worst prognosis. CD10-positive B-cell ALL has a better prognosis than T-cell ALL and CD10-negative B-cell ALL. CD10 was previously known as "CALLA."
   4. **Cytogenetic abnormalities:** t(9;22), the Ph[1] chromosome, which occurs in 10% of children and 30% of adults with ALL; its associated *BCR/ABL* fusion gene; t(4;11) in children.
   5. **The presence of** CNS leukemia, hepatosplenomegaly, lymphadenopathy, or mediastinal mass (the *absence* of a mediastinal mass may be unfavorable in adults).
   6. **Slow response to treatment** (more than 4 to 5 weeks to achieve CR in adults)

C. **Survival rates**
   1. **AML.** About two thirds of patients achieve a CR. The median survival is 12 to 24 months for patients who achieve CR; the median duration of first remission is 10 to 12 months. About 20% of patients who achieve CR (5% to 15% of all patients) survive 5 or more years, and many of these patients may be cured. Most relapses occur within 3 years.
   2. **ALL**
      a. **"Standard-risk" children** (1 to 9 years, of age WBC count less than 50,000/μL, precursor B-cell subtype, and without adverse prognostic factors). Less than 20% of cases relapse if properly treated. More than 80% of cases have a 5-year disease-free survival. Relapse or death is unusual in these patients after 4 years of continuous CR.
      b. **High-risk children** (those with adverse prognostic factors) have remission duration and survival similar rates to those of adults, yet some series report 70% of patients surviving disease free for 4 years. The survival time for infants is less than 2 years.
      c. **Adolescents and adults** have a median first CR duration of 12 to 24 months and a median survival time of 24 to 30 months. Late adolescents (17 to 21 years old) appear to have a substantially improved survival time if treated with aggressive pediatric protocols. The median survival time is less than 18 months for patients who are older than 60 years of age with an elevated WBC count.

V. Management of acute myelogenous leukemia

A. **Remission induction.** Intensive chemotherapy, nearly always to the point of severe bone marrow aplasia (which generally occurs about 12 days after treatment is begun), is necessary to achieve CR in patients with AML. Cytarabine and an anthracycline are usually administered. Cytarabine has been given in daily dosages ranging from 100 to 6000 mg/m^2, but it is not clear that higher dosages give better results. Daunorubicin, idarubicin, and mitoxantrone at equivalent doses also appear to give similar results.

If the blasts are not cleared from the blood and bone marrow after the first course of treatment, and if the patient can tolerate such intensive treatment, the combination therapy is repeated once or twice more. A CR is achieved in 60% to 75% of patients with good medical support, usually about 1 month after initiating treatment. More than 95% of CRs are achieved with one or two courses of induction chemotherapy. A typical regimen is as follows:

Cytarabine, 100 mg/m^2/day by *continuous IV infusion* for 7 days, *and*
Idarubicin, 12 mg/m^2 IV push on either days 1, 2, and 3, or days 5, 6, and 7 (daunorubicin at a dose of 45 to 60 mg/m^2 daily for 3 days may be substituted for idarubicin)

An alternative regimen for AML is as follows:

Cytarabine, 3 g/m^2 IV over 3 hours every 12 hours on days 1, 3, 5, and 7 (8 doses), *and*
Idarubicin, 12 mg/m^2 IV push on days 1, 2, and 3 (daunorubicin may be substituted), *and*

Etoposide, 75 mg/m^2 IV on days 1 to 7

1. **Toxicity of induction therapy**
   a. Hyperuricemia; all patients should be begun on treatment with allopurinol, 300 to 600 mg daily, 12 to 48 hours before starting antileukemic therapy.
   b. Severe marrow depression with life-threatening pancytopenia
   c. Nausea, vomiting, severe stomatitis
   d. Anthracyclines may be associated with electrocardiographic changes, arrhythmias, or congestive heart failure.
   e. Self-limited alopecia; tissue necrosis if the anthracycline is infiltrated outside the vein
   f. High-dose cytosine arabinoside (3.0 g/m^2 IV over 3 hours) is associated with a greater incidence of cerebellar, ophthalmologic, and gastrointestinal, toxicity, particularly in patients older than 60 years of age. These toxicities occur in much lower frequency when given in lower dosages (1.5 g/m^2 IV over 3 hours) or when the drug is infused over longer periods of time (100 to 400 mg/m^2 by continuous IV infusion).

2. **Promyelocytic (M3) leukemia**
   a. **All-*trans* retinoic acid** (ATRA, 45 mg/m^2 per day PO divided into two doses for up to 2 months) induces differentiation and a nonmyelosuppressive remission in virtually all cases of type M3 AML. Concurrent chemotherapy involving an anthracycline (perhaps alone with ATRA), however, is required to reduce the relapse rate. Maintenance therapy with ATRA is necessary, but the best consolidation and maintenance regimens have not been established. About 70% of patients with M3 AML remain disease free at 4 years.
   b. **Coagulopathy** previously occurred in more than 90% of patients with subtype M3 AML and resulted in severe hemorrhagic manifestations in excess of that expected for the degree of thrombocytopenia. Both the incidence and severity of DIC have substantially decreased with ATRA therapy. Laboratory abnormalities include not only features associated with DIC (decreased fibrinogen and increased fibrin and fibrinogen degradation products) but also evidence of increased fibrinolysis (acquired deficiency of the fibrinolysis inhibitor, a$_2$—antitrypsin).

   Patients should be monitored closely for the development of DIC (see Chapter 34, Coagulopathy, section II) and treated at the first sign of DIC. Continuous infusion of heparin (10,000 to 30,000 U/ day) and transfusions with platelets and cryoprecipitate (to sustain fibrinogen levels) are the mainstays of therapy. Heparin may be discontinued after induction therapy is completed, provided there is no evidence of DIC. An alternative to heparin therapy is the use of antifibrinolytic agents, such as epsilon aminocaproic acid.

   c. **Retinoic acid syndrome** is the most serious and life-threatening complication of differentiation therapy. This respiratory distress syndrome is manifested by fever, hypoxemia, interstitial pulmonary infiltrates, pleural or pericardial effusions, episodic hypotension, and otherwise unexplained weight gain. It often occurs in association with the rapid development of hyperleukocytosis that can be observed during ATRA induction therapy. The syndrome usually resolves rapidly if dexamethasone, 10 mg IV twice daily, is administered at the earliest sign or symptom.

3. **Elderly patients.** The treatment of patients 65 years of age or older is controversial. Some authorities argue that intensive chemotherapy should be used because the rate of CR is the same as for younger patients. Other experts disagree. An antecedent MDS is often seen in elderly patients, who cannot tolerate the toxic effects of intensive induction therapy as well as can younger patients; the death rate from hematotoxicity in these patients is about 30% with intensive regimens.

   Less intensive treatment using attenuated dosages of drugs, oral agents (hydroxyurea or etoposide), or "low-dose cytarabine" (10 mg/m^2 SC daily) have been shown to be associated with less myelosuppression, fewer early deaths, and longer quality (outpatient) survival than standard intensive induction therapy. The use of supportive care alone is a reasonable option for many elderly patients with AML, particularly for patients who are not in good general medical condition. Two useful, less intensive regimens for elderly patients who are in good general medical condition are the following:

   a. Cytarabine, 100 mg/m^2 per day for 5 days given by continuous IV infusion; and idarubicin, 12 mg/m^2 IV for one dose only.
   b. Cytarabine, 100 mg/m^2 IV push or SC twice daily for 5 days; and mitoxantrone, 10 mg/m^2 IV for one dose only.

B. **Postremission therapy.** After CR is achieved, the most important goal is to prevent recurrence. Leukemic cells that are not clinically apparent remain. Therapy to eradicate residual leukemia is required, or recurrence is inevitable. The best form of postremission therapy, however, remains controversial.

1. **Postremission chemotherapy.** Relatively high doses of drugs are given shortly after the patient has achieved CR, has regained normal hematologic function, and has clinically completely recovered. Cytarabine alone is commonly used; dosages range from 100 to 400 mg/m^2 by continuous IV infusion for 5 to 6 days to 1.5 to 3 g/m^2 IV over 3 hours every 12 hours for 6 to 12 doses, depending on the age of the patient and the intent to follow with allogeneic or autologous marrow transplantation. One course of consolidation chemotherapy is usually given if allogeneic transplantation is feasible. Two to four courses are often given if no form of transplantation is feasible. The dosage of cytarabine is usually restricted to 1.5 g/m^2 for six doses in patients who are older than 65 years of age. Other regimens use cytarabine with other drugs.

   Results of consolidation therapy are best in patients who have favorable cytogenetics and are younger than 60 years of age. None of the dosage schemes have proved to be superior in patients who have unfavorable cytogenetics or who are older. The number of required courses for postremission chemotherapy is uncertain.

2. **Allogeneic BMT** is considered when an HLA-identical sibling donor can be identified in a patient younger than 50 years of age. Allogeneic BMT has the theoretical potential benefit of a graft-versus-leukemia effect but also has a higher treatment-related mortality rate than autologous transplantation or consolidation chemotherapy. Results are best in children, teenagers, and young adults.

3. **Autologous BMT** with intensive chemotherapy and radiation therapy (RT) followed by infusion of bone marrow that is either untreated or "purged" with drugs or antibodies may be used rather than chemotherapy alone. Similarly, autologous stem cell transplantation may be performed. These therapies permit escalation of chemotherapy doses but lack the graft-versus-leukemia effect associated with allogeneic transplantation; they also have the potential of infusing residual leukemic cells. Autologous BMT and postremission consolidation chemotherapy have similar outcomes.

C. **Controversial therapies**
1. **Maintenance therapy** has not been shown to prolong survival in adults with AML.
2. **CNS prophylaxis** with cranial irradiation and intrathecal chemotherapy may be effective in preventing meningeal leukemia but has not prolonged the length of remission because nearly all of these cases relapse in the bone marrow. CNS relapse is most common in the M4 and M5 subtypes. CNS therapy *is indicated* when AML cells are detected in the CSF.
3. **Cycling AML** cells with G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) before cytarabine to make then more susceptible is under investigation.

D. **Treatment of relapses.** Relapses in AML are typically systemic (i.e., in the marrow and elsewhere). Some cases are heralded by extramedullary relapse (e.g., chloromas in skin or lymph nodes) but are followed by systemic relapse. Up to half of patients achieve a second CR using either the same drugs as were used to induce first remission or investigational drugs. Investigational drugs are often prescribed because the second remission is so short, usually less than 6 months, and is so difficult to achieve with agents that are available commercially.

VI. Management of acute lymphoblastic leukemia

A. **Remission induction.** All patients should be begun on treatment with allopurinol, 300 to 600 mg daily, 12 to 48 hours before starting antileukemic therapy.
1. **Children.** The combination of vincristine and prednisone (V + P regimen) produce CR in 85% to 90% of cases of childhood ALL. The addition of l-asparaginase improves the duration of CR. Most children achieve CR within 4 weeks of therapy; if CR is not achieved within 6 weeks, there is no value in continuing the drugs. Children often achieve CR without prolonged myelosuppression. Those who achieve CR and experience the least morbidity most often have the longest remissions.
   a. **Standard-risk patients** are treated with V + P and l-asparaginase for 4 to 6 weeks:

   Vincristine, 1.5 mg/m^2 (maximum 2 mg) IV push weekly
   Prednisone, 40 mg/m^2 PO daily
   l-asparaginase, 6000 U/m^2 (maximum 10,000 U) IM three times weekly for a total of nine doses

   b. **High-risk patients** are treated with V + P, l-asparaginase, and daunorubicin (25 mg/m^2 IV weekly for two doses).
2. **Adults.** The V + P regimen results in CR in 45% to 65% of adults with ALL. The addition of an anthracycline with or without l-asparaginase increases the CR rate to 70% to 85%. Complex multiagent protocols may be more effective.
3. **Toxicity of induction therapy**
   a. **V + P**

      1. Intestinal colic and constipation (bulk laxatives should be used prophylactically).
      2. Peripheral neuropathy (usually reversible).
      3. Hematosuppression and alopecia are uncommon.
    b. **V + P and an anthracycline.** Same as in section 3.a, along with nausea, vomiting, stomatitis, alopecia, hematosuppression, and possibly cardiac toxicity
    c. **V + P and l-asparaginase.** Same as in section 3.a, with the addition of coagulation defects, allergic reactions, and encephalopathy

B. **CNS prophylaxis** prevents early CNS relapse and is mandatory in children with ALL after CR is induced. The CNS is the initial site of relapse in more than half of patients unless prophylaxis is given. However, this treatment has not been shown to improve remission duration or survival in adolescents or adults because the likelihood of isolated CNS relapse in adults is about 5%.
  1. **Regimens.** The form of CNS prophylaxis is controversial. Many authorities recommend intrathecal methotrexate (6 to 12 mg/m^2 up to a maximum of 15 mg/dose of preservative-free methotrexate, twice weekly for five to eight doses) combined with craniospinal irradiation (about 2400 cGy in 12 fractions over 2.5 weeks) for patients older than 1 year of age. Intrathecal methotrexate alone is recommended by some authorities for patients at low risk for relapse (age 2 to 9 years, WBC less than 10,000/μL, and CD10 positivity).
  2. **Toxicity of CNS prophylaxis**
    a. **Transient encephalopathy,** which can be fatal, develops in up to 67% of patients for 4 to 8 weeks after completion of cranial irradiation, especially if methotrexate is given in the maintenance program. Symptoms of encephalopathy include somnolence, headache, vomiting, and low-grade fever. Spinal fluid examination shows pleocytosis with neutrophils and mononuclear cells. The differential diagnosis includes CNS infection, cerebrovascular accidents, and leukemic meningitis, which should be distinguishable by MRI scans and by spinal fluid culture and cytology.
    b. **Alopecia** after cranial irradiation
    c. **Headache** after intrathecal drug administration
    d. **Chemical arachnoiditis** with meningismus and back pain on account of epidural extravasation of methotrexate
    e. **Leukoencephalopathy** may develop in patients given large doses of intravenous methotrexate after brain irradiation.
    f. **Neuropsychological effects** of treatment are common, especially in children younger than 6 years of age. Memory and mathematic and motor skills may be impaired. CNS prophylaxis and the drugs that have activity in the CNS (methotrexate, prednisone, vincristine, and l-asparaginase) are thought to cause these problems. However, the disease itself may contribute: ALL disrupts the patient's family, social, and school life and alters attitudes of others toward the patient.

C. **Intensive postremission therapy**
  1. **Consolidation treatment** has not been shown to improve remission duration or survival in ALL. High-dose cytarabine may be beneficial for T-cell ALL and some high-risk subgroups. High-dose methotrexate may be useful in B-cell–lineage ALL.
  2. **BMT** is not recommended during first CR for adults with ALL or for children with standard-risk ALL. BMT may be important for specific subgroups of ALL or for those who relapse after initial remission.

D. **Maintenance therapy** for 2 to 3 years is *mandatory* in childhood ALL.
  1. **Effective drugs.** Methotrexate (20 mg/m^2 PO weekly) and mercaptopurine (50 to 75 mg/m^2 PO daily) are the cornerstones of maintenance therapy in ALL. It is important that the drugs be given in dosages sufficient to produce hematosuppression; otherwise, the risk for relapse is substantially increased. Monthly pulses of V + P are also given. Intrathecal chemotherapy is administered every 90 days.
  2. **Toxicity of maintenance therapy.** Late side effects of maintenance therapy in patients cured of ALL are not established. All of the following side effects resolve after therapy is stopped.
    a. Therapy is interrupted if any of the following occurs:
      1. Significant hematosuppression (which is dose-limiting but is a necessary goal)
      2. Abnormal liver function tests
      3. Stomatitis, diarrhea
      4. Renal tubular necrosis because of methotrexate (renal function is closely monitored)
    b. Immunosuppression (increased susceptibility to infection, particularly varicella and *Pneumocystis carini*)
    c. Growth inhibition
    d. Skin disorders
    e. Osteoporosis with long-term methotrexate treatment
  3. **When to stop maintenance therapy**
    a. **Children.** Prolonged chemotherapy is of greatest consequence in children because adverse, very late, side effects may develop. Most children in remission are treated for 30 to 36 months; 20% of children taken off treatment relapse, most within the first year. Elective testicular biopsy of boys before stopping maintenance therapy has been shown to be of no clinical value.
    b. **Adults.** Most adults with ALL or AML relapse despite maintenance therapy. We recommend maintenance therapy for 3 years in adults with ALL based on the experience with children.

E. **Treatment of relapses.** ALL may relapse systemically or in sanctuary sites (testicle or CNS).
  1. **Extramedullary relapse.** Without CNS prophylaxis, relapse in just the CNS is common. Relapse in only the testis occurs but is unusual. Patients who have solitary extramedullary relapse and absolutely normal bone marrow may be treated with local therapy alone (i.e., CNS irradiation plus intrathecal chemotherapy for CNS relapse or RT to the testicle for testicular relapse).
  2. **Systemic relapse.** In half of cases, systemic relapse may be successfully treated with the agents used to induce the original remission.
  3. **Subsequent remissions.** Each subsequent remission becomes progressively shorter, and drugs available for maintenance therapy are progressively limited. Patients who relapse after cessation of maintenance therapy have a better prognosis than those who relapse during continuous therapy.

VII. Management of acute leukemias: other issues

A. **Supportive care**
  1. **Indwelling Silastic right atrial catheters** are used during the induction phase to facilitate the administration of intravenous therapies and the sampling of blood for laboratory tests (see Chapter 5, section XI).
  2. **Blood component therapy**
    a. **Platelet transfusions** are clearly indicated for patients with thrombocytopenia of any severity when there is active bleeding. Without petechiae or bleeding, platelets are transfused "prophylactically" when counts are 10,000/μL or less.
    b. **Packed red blood cell transfusions** are used to treat symptomatic anemia and active hemorrhage (see Chapter 34, Cytopenia, section VI).
    c. **Granulocyte transfusions** are not recommended. The chance of survival depends on recovery of the patient's own granulocytes.
    d. **G-CSF or GM-CSF** given on completion of administration of the induction drugs may shorten the duration of neutropenia by 2 to 4 days and appear to lessen morbidity. These hematopoietic growth factors do not exacerbate leukemia, but they also do not improve CR rate or survival.
  3. **Infections.** Emergency empiric treatment of fever with intravenous antibiotics is mandatory in neutropenic patients with acute leukemia (see Chapter 35, section I).
  4. **Prophylaxis against infection.** See Chapter 35, section I.E.3.
  5. **Tumor lysis syndrome.** See Chapter 27, section XIII.

B. **Treatment of meningeal leukemia**
  1. **Manifestations.** Meningeal leukemia is manifested by a variety of neurologic signs (see also Chapter 32, section II) and by blast cells that are identified by cytologic evaluation of the CSF.
  2. **Treatment.** Optimal treatment has not been determined. Most patients are given cranial or craniospinal irradiation over a 3-week period plus intrathecal chemotherapy. Intrathecal therapy alone may be insufficient.
    a. **Drugs.** Preservative-free methotrexate (6 to 12 mg/m^2, maximum of 15 mg) or cytarabine (50 to 100 mg) is used for intrathecal therapy. Toxic effects of methotrexate may be prevented by giving leucovorin, 1 mg per each milligram of methotrexate, 24 hours after intrathecal administration.
    b. **Diluent.** Artificial spinal fluid (Elliott's B solution) is available at some institutions to dilute the cytotoxic agents.
    c. **Technique.** Intrathecal chemotherapy is given isovolumetrically and gradually by serial withdrawal and injection of spinal fluid with a syringe containing the chemotherapeutic agent. The drugs may be administered by lumbar puncture, by cisternal puncture, or through an inserted intraventricular reservoir.
    d. **Duration.** Intrathecal chemotherapy is given at 3- to 7-day intervals until abnormal cells and excess protein are cleared from the spinal fluid. Therapy is often continued at 1- to 2-month intervals for a period thereafter.

C. **Special clinical problems**
  1. **Leukostasis** is more common in AML than ALL and frequently occurs in patients with WBC greater than 100,000/μL. Sludging impairs circulation and results in organ dysfunction. The circulating blast count can be rapidly reduced with leukapheresis, thereby reducing the risks of leukostasis, DIC, and metabolic abnormalities associated with tumor lysis. Hydroxyurea (3 g/day) should be instituted with leukapheresis.
  2. **Ocular and gingival involvement.** Irradiating eyes involved with leukemic infiltrates may prevent blindness. Gingival enlargements in patients with monocytic leukemia does not require special treatment because it should resolve with induction chemotherapy.

3. **Patients exposed to varicella zoster infections** should be given zoster immune globulin (see Chapter 35, section IV.C).
4. **Acute leukemia during pregnancy.** See Chapter 26, section IV.
D. **Investigational therapies,** which have not been proved to improve CR duration or survival (not recommended except in research protocols), include the following:
1. **Intensification therapy,** which uses high doses of new drugs that the patient has not previously received. *Early intensification* is given within a few months of achieving CR. *Late intensification* is given to patients who have been in continuous CR for 1 year or longer.
2. **Immunotherapy,** which has most often been studied in patients who achieve CR. It theoretically preferentially kills leukemic cells and spares normal cells. CD33 is present on most early myeloid cells and in more than 90% of AML cases. Anti-CD33 antibody, either unmodified or conjugated with ^{131}I or toxins (such as calicheamicin) shows promise. Anti-CD52 monoclonal antibody is being investigated for ALL.
3. **BMT.** Results of allogeneic BMT are disappointing for patients with resistant acute leukemia but are most promising in patients undergoing BMT during CR (during the first CR for patients with AML and during the second CR for patients with ALL). Major limitations of BMT include the following:
   a. Only about 25% of patients have compatible donors.
   b. The best survival rates are achieved in patients younger than 22 years of age; most patients with AML are older.
   c. The complications of BMT in surviving patients remain substantial.
   d. The results of investigations of BMT are still preliminary.
4. **Cytotoxic drugs.** High doses of interleukin-2, antisense oligodeoxynucleotides, cyclosporine, arsenic trioxide (for M3 AML), and compound 506U (for T-cell ALL) are under investigation.

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Chapter 26 Sexual Function and Pregnancy

Mimi Mott-Smith and Lawrence Stolberg

I. Sexual function in patients with cancer

A. **Background.** The ability to enjoy intimate relationships and to express oneself as a sexual being is a prominent determinant of quality of life for many survivors of cancer. Pre-treatment sexual function strongly influences post-treatment status. The desire phase of the sexual response cycle is highly sensitive to a variety of adverse conditions. Orgasmic response is much more resistant to damage than are desire and arousal. Factors affecting sexual function in cancer patients include the following:

1. **Depression,** which is the most common reason for loss of interest in sex.
2. **Guilt.** Some patients experience cancer as punishment for past behavior and resolve to give up sex and other pleasures in exchange for survival.
3. **Anxiety and fear.** Fears of contagiousness, pain, disability, death, or financial disaster may overwhelm the patient.
4. **Self-image changes.** Hair loss, loss of body parts or function, appliances, colostomy, or tracheostomy may result in loss of self-esteem or loss of one's sense of femininity or masculinity. Losses of earning power and roles in the family and community also threaten self-esteem.
5. **Personal philosophy and style of coping with disaster.** Responses vary from determination and positive attitude to resignation and despair.
6. **Concomitants of chronic disease.** Pain, other systemic symptoms, and side effects of drug and cancer therapy.

B. **Sexual problems specific to women**

1. **Germ cell depletion** is discussed in section III. Indirect indicators of menopause are amenorrhea, increased serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, and symptoms of estrogen deficiency. Symptoms include hot flashes, loss of vaginal lubrication, atrophy of genital structures, and discomfort with intercourse.
2. **Tamoxifen therapy,** commonly used in women with breast cancer, may have a positive estrogenic effect on the vaginal mucosa or may contribute to vaginal atrophy and dyspareunia. Patients who are taking tamoxifen often experience hot flashes or vaginal discharge. Tamoxifen does appear to have a somewhat proestrogenic effect on serum lipids and bone density.
3. **Chemotherapy** may cause ovarian failure (see section III.B). Emotional and physical changes can also adversely affect sexual function. The effect of chemotherapy on ovarian androgen output is unknown. Diminished androgen production affects libido.
4. **Radiation therapy** (RT). Effects of ionizing radiation on sexual function depend on age, field, and dose (see section III.A). RT for cervical cancer leads to vaginal fibrosis, dyspareunia, and ovarian failure. Symptoms may not become apparent until 1 year after treatment.
5. **Pelvic surgery**
   a. **Cervical conization** does not impair desire, arousal, or orgasm.
   b. **Radical hysterectomy** results in a shallower vagina. Women may need to experiment with different positions to experience comfortable penetration.
   c. **Radical cystectomy** leads to decreased vaginal lubrication and dyspareunia.
   d. **Abdominal-perineal** (A-P) **resection** commonly causes dyspareunia, but orgasmic function is preserved.
   e. **Total pelvic exenteration** with vaginal reconstruction results in loss of vaginal lubrication, loss of some erotic zones, dyspareunia, decreased intensity of orgasm, and the need to relearn how to achieve orgasm.
6. **Mastectomy.** Women often feel less feminine and less physically attractive after mastectomy. About one third experience significant anxiety or depression and are unable to enjoy or tolerate making love. A similar percentage of patients' partners reported decreased sexual activity after mastectomy and fears of causing pain during intercourse. Men's reactions to seeing their partner's incision and chest wall area appear to have prognostic value: if the reaction is primarily empathic rather than negative, the prognosis for good sexual adjustment appears favorable. Women treated with lumpectomy and breast irradiation have improved self-image compared with those treated with mastectomy. Women who undergo breast reconstruction have a better body image than those who do not.

C. **Sexual problems specific to men.** Men treated for testicular cancer, prostate cancer, and Hodgkin lymphoma (HL) are particularly at risk for sexual dysfunction (see section II.A). Twenty percent of surviving testicular cancer patients have reported that they have been sexually inactive; many have reported decreased sense of pleasure with orgasm, anxiety, and marital unhappiness.

1. **Germ cell depletion.** Clinical indicators of germ cell depletion include decreased testicular size, severe oligospermia or azoospermia, infertility with elevated serum LH and FSH levels, and decreased testosterone level.
2. **Impotence.** The reported incidence of impotence in the general population is about 10%: 8% at 50 years of age, 20% at 60 years of age, and 80% at 80 years of age. The incidence of impotence in men treated for cancer is increased, particularly for men with tumors involving the pelvis and genital tract. Often, men emotionally relate impotence to a loss of masculinity, with attendant fear, anxiety, depression, and feelings of diminished self-worth.

   Temporary or permanent erectile impotence is the most common symptom of sexual dysfunction in men with cancer. Recovery of erectile function is more likely in men younger than 60 years of age and may take months to years. Preexisting conditions, such as diabetes, cardiovascular disease, and antihypertensive medication, exacerbate the risk for erectile dysfunction. Ejaculatory dysfunction occurs less frequently and may be due to retrograde ejaculation or dry orgasm. The presence of nocturnal tumescence is helpful in differentiating nonorganic from organic causes of impotence.

3. **Systemic therapy.** Fatigue, nausea, alopecia, anxiety, and other general effects of chemotherapy interact to diminish libido during treatment.
   a. **Chemotherapy** is thought to suppress Leydig's cell function, resulting in decreased serum testosterone, increased serum LH levels, and resultant loss of desire and erectile function. Chemotherapeutic agents associated with neuropathy (e.g., vinca alkaloids) can cause dry orgasm with preservation of pleasurable sensation. The effect of chemotherapy on spermatogenesis is discussed in section II.C.
   b. **Hormonal therapy** for prostate cancer can impair all phases of the sexual response cycle. Gonadotropin-releasing hormone agonists (leuprolide acetate, flutamide, diethylstilbestrol [DES]) all reduce serum testosterone to prepubertal levels and lead to loss of libido, difficulty with arousal, and diminished intensity of orgasm. Hot flashes may occur. In addition, DES and flutamide can cause gynecomastia.
4. **RT**
   a. **Prostate cancer.** RT can result in loss of erectile function in 20% to 80% of patients treated for prostate cancer. Younger men with intact sexual function before RT are most likely to regain adequate erectile function. Semen volume is also reduced with RT, leading to little or no ejaculatory fluid.
   b. **Testicular cancer.** Patients who receive radiation to the pelvis and retroperitoneum have an increased incidence of erectile dysfunction. The effects of RT on sperm count are discussed in section II.B.
   c. **Testicular shielding** should be used if the distance between the testes and the radiation field boundary is less than 30 cm. Radiation dose to the testes is reduced to less than 10% of the total dose if this method is used.
5. **Surgery.** After the recovery period from pelvic surgery itself, the desire phase generally remains intact. Orgasmic function may be normal or reduced.
   a. **Radical prostatectomy** causes impotence or impaired erection in most patients, although partial recovery of erectile function is possible. Parasympathetic stimulation causes tumescence; sympathetic stimulation causes detumescence. One or both of these autonomic bundles are at risk during radical prostatectomy.
   b. **Nerve-sparing techniques during radical prostatectomy** allow a greater percentage of men to recover erectile function (reportedly up to 85%). Closer analysis, however, has disclosed that many men do not have erections firm enough for vaginal penetration.
   c. **Radical cystectomy** results in erectile dysfunction and dry orgasm. With nerve-sparing procedures, up to 67% may recover erectile function.
   d. **A-P resection** leads to problems with erection (55%) and dry orgasm as a result of nerve damage.
   e. **Total pelvic exenteration** results in permanent impotence and dry orgasm.
   f. **Retroperitoneal lymph node dissection** (RPLND) leads to retrograde ejaculation. With *modified* RPLND in clinical stage I nonseminomatous germ cell tumor patients, ejaculatory function can be preserved in about 90% of cases.

D. **Guidelines for treatment of sexual problems**

1. **Initial history** should include information about the patient's sexual function before diagnosis. Patients at particular risk for dysfunction include those in relationships characterized by conflict and poor emotional adjustment, younger patients, those who want more children, and those with a history of rape or

incest.

2. **Brief counseling** can alleviate most problems. Physicians should include the sex partner in discussions and recognize and deal with feelings and fears. In addition, clinicians should specifically tell patients that it is all right to resume sexual activity and that cancer is not contagious.

3. **Refer for expert assistance** if needed: occasionally, patients need the services of a sex therapist, marital counseling, or referral to a urologist. An invaluable resource is the pamphlet *Sexuality and Cancer* (separate pamphlets for women and men) available from the American Cancer Society.

4. **Control pain and treat depression**

5. **For men with erectile dysfunction**
   a. Intracavernous injections of papaverine and phentolamine, or prostaglandin E (fibrosis may result from long-term use)
   b. Vacuum erection device or penile prosthesis
   c. Oral therapy with sildenafil (Viagra) is efficacious in half of patients or more regardless of the underlying cause. This drug is contraindicated in patients taking nitrates.

6. **For men with testicular cancer**
   a. Depotesterone, 200 to 300 mg IM every 3 weeks, for hypotestosteronism (check serum testosterone levels)
   b. Imipramine, 25 to 50 mg daily PO, may induce antegrade ejaculation in those who have undergone RPLND.

7. **For women with dyspareunia and vaginal fibrosis**
   a. Vaginal dilators of graduated sizes can help women learn to relax voluntary muscles progressively until penetration can be achieved without pain.
   b. Water-based lubricants and vaginal moisturizers can be used.

8. **For women with dyspareunia and vaginal dryness,** administer estrogen replacement therapy or creams.

9. **For women with breast cancer**
   a. The dictum that estrogen replacement therapy is contraindicated is being seriously challenged. A decision for such replacement therapy must be individualized.
   b. Early discussion of the option of breast reconstruction may alleviate feelings of loss and poor self-image. A prosthesis should be fitted as soon as feasible for a normal silhouette in clothing. The "Reach to Recovery" program of the American Cancer Society exposes the patient to women with breast cancer who have made successful adjustments.

II. Reproductive function in men with cancer

A. **Pretreatment hypogonadism in cancer patients**
   1. **Testicular cancer.** More than 80% of men with disseminated germ cell tumors are oligospermic or azoospermic before therapy, probably owing to effects of the disease itself and abnormalities of the malignancy-prone testis.
   2. **HL.** More than half of men with HL have low sperm counts and poor motility before treatment.
   3. **Metastatic cancer** of any type may be associated with low levels of testosterone in up to two thirds of male patients. Malnutrition is believed to play a significant role.

B. **Effects of RT in men.** The testes are exquisitely sensitive to radiation (see section I.C.4). Doses as low as 15 cGy result in transient suppression of spermatogenesis. The duration of azoospermia is proportional to the magnitude of the RT dose. At 200 to 300 cGy, recovery takes 3 years, and at 400 to 600 cGy, azoospermia can persist for 5 years. A dose of 600 cGy or more results in permanent sterility.

C. **Effects of chemotherapy in men.** Spermatogenesis is highly susceptible to toxic effects of certain chemotherapeutic agents.
   1. **Alkylating agents** cause germ cell depletion in a dose-related fashion. Drugs reported to be definitely associated with azoospermia include chlorambucil (possibly reversible if total dose is less than 400 mg), cyclophosphamide (possibly reversible if total dose is less than 6 to 10 g), nitrogen mustard, busulfan, procarbazine, and nitrosoureas.
   2. **Other drugs** probably associated with germ cell depletion include doxorubicin, vinblastine, cytosine arabinoside, and cisplatin. Effects of methotrexate, 5-fluorouracil, 6-mercaptopurine, vincristine, and bleomycin are either unknown or unlikely to cause damage.
   3. **Combination regimens.** Therapy with MOPP (mustargen, vincrisitine, procarbazine and prednisone) for HL leads to testicular atrophy in 80% of patients. The ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) is an alternative to MOPP with a reported 35% occurrence of azoospermia during therapy but eventual return of spermatogenesis in nearly 100% of cases; similar regimens based on mitoxantrone show similar results. About half of patients treated with cisplatin, vinblastine, and bleomycin for nonseminomatous testicular cancer regain spermatogenesis within 2 to 3 years.

D. **Measures to protect reproductive function in men**
   1. **Sperm banking** can be offered to men who are likely to suffer prolonged or permanent sterility. Between 50% and 80% of patients with HL or testicular cancer, however, have low sperm counts (less than 20 million/mL) with poor motility (less than 50%) before treatment. Sperm banking should be offered to all patients at risk for treatment-related infertility. Surveillance in lieu of chemotherapy or RT may be offered to men with good-prognosis testicular cancer, which optimizes fertility.
   2. **Artificial insemination** may be tried in women whose partner's posttreatment sperm quality is good despite low sperm count.
   3. *In vitro* **fertilization** (IVF) techniques in men with very low sperm counts can result in successful production of an embryo with relatively few sperm. In addition, IVF can be carried out before cancer therapy with cryopreservation of embryos. Intracytoplasmic sperm injection enables even apparently azoospermic men to achieve fertilization. Only a single viable sperm is needed for micropipette insertion into an ovum.
   4. Nerve-sparing procedures for prostatectomy, modified RPLND to reduce retrograde ejaculation, and testicular shielding for RT are discussed in section I.C.4.c. and section I.C.5.b.

III. Reproductive function in women with cancer

A. **Effects of RT in women.** The effects of radiation on fertility are strongly influenced by age as well as by RT field and total dose. Cessation of menses for variable periods of time occurs at doses above 150 cGy. A dose of 500 to 600 cGy to the ovaries usually results in permanent ovarian failure. After total nodal irradiation, 70% of women younger than 20 years of age resume normal menses, whereas 80% of women older than 30 years of age do not.

Oophoropexy, or sequestering the ovaries surgically in midline behind the uterus, reduces the risk for infertility in half of women undergoing inverted-Y field irradiation. Sparing one ovary in women younger than 40 years of age prevents premature menopause.

B. **Effects of chemotherapy in women.** The likelihood of permanent ovarian failure after chemotherapy increases with age. Menses rarely return after age 35 to 40 years.
   1. **Alkylating agents.** Cyclophosphamide, nitrogen mustard, alkeran, busulfan, and procarbazine are clearly associated with ovarian failure.
   2. **Other drugs.** Methotrexate, 5-fluorouracil, and 6-mercaptopurine are unlikely to cause ovarian dysfunction. Agents with unknown effects on the ovary include doxorubicin, bleomycin, vinca alkaloids, cisplatin, nitrosoureas, cytosine arabinoside, etoposide, vinorelbine, paclitaxel, and interferon.
   3. **Combination regimens.** MOPP leads to ovarian dysfunction in 40% to 50% of women treated for HL. Nearly all patients younger than 25 years of age experience a return of normal menses, but these patients may experience very early menopause (before 30 years of age). ABVD is associated with a much lower incidence of infertility than is MOPP.

IV. Pregnancy and cancer

A. **Background**
   1. **Epidemiology.** Cervical cancer is the most common malignancy complicating pregnancy, occurring in 1 in 1000 pregnancies, followed by breast cancer (1 in 3000), melanoma and ovarian cancer (1 in 10,000), and colon cancer, leukemia, and lymphoma (1 in 50,000 to 1 in 100,000).
   2. **Natural history.** The incidence of malignancy is not increased in pregnancy. Pregnancy neither alters the biologic behavior or prognosis of cancer nor reactivates cancer in remission. Metastasis to the placenta or fetus is very rare.
   3. **Teratogenesis.** The definition of teratogenesis has been broadened to encompass not merely morphologic abnormalities readily apparent at birth but also other types of malformation, growth retardation, fetal death, and developmental disability. The incidence of major malformations apparent at birth in the general population is about 3% to 4%. Damage from chemotherapeutic agents in the first trimester is more likely to cause morphologic abnormalities and spontaneous abortion. Exposure during the second and third trimesters is more likely to cause intrauterine growth retardation, microcephaly, and developmental delay with attendant risks for mental retardation and learning problems.

B. **Diagnostic studies during pregnancy**
   1. **Biopsies** under local anesthesia carry essentially no risk to the fetus. Biopsy procedures using general anesthesia present minimal risk to the fetus.
   2. **Studies to avoid:** radionuclide scans, contrast studies of the gastrointestinal and urinary tracts, abdominal and chest computed tomography (CT) scans, pelvic and lumbosacral spine films, and full lymphan- giograms. In general, studies should only be done if results would have a significant effect on treatment

decisions.

3. **Mammograms** lack sensitivity in pregnancy because of to breast engorgement and histologic changes. Up to half of pregnant women with a breast mass have a negative mammogram.
4. **Chest radiographs** can be done safely with proper abdominal shielding. The dose of ionizing radiation to the fetus is about 0.008 cGy.
5. **Bone scans** are relatively contraindicated in pregnancy. The fetus receives a dose of about 0.1 cGy. Because of low yield, bone scans are not justified in asymptomatic stage I and II breast cancer patients and can be deferred until postpartum.
6. **Ultrasonography** does not involve ionizing radiation and is safe.
7. **Other permissible radiologic studies.** Brain CT scans and radiographs of the cervical spine or long bones are probably associated with radiation doses to the fetus of less than 0.5 cGy if the abdomen and uterus are properly shielded.
8. **Magnetic resonance imaging** (MRI) has unknown effects on the fetus. Because of theoretical risks of increased temperature during organogenesis, MRI should be employed only when the diagnostic benefit outweighs the theoretical risks and other imaging modalities are either nondiagnostic or will expose the fetus to an unacceptable dose of radiation.

C. **Principles of cancer therapy during pregnancy**
1. Pregnancy prevention should be emphasized in all women of childbearing age with cancer and in the context of the patient's personal goals. All options, including pregnancy termination, should be discussed.
2. Accurate determination of gestational age should be made before commencing diagnostic studies or therapy.
3. When maternal cure is possible and delay would compromise this goal, therapy should be instituted as soon as possible. If feasible, chemotherapy should be delayed until the second or third trimester or after delivery.
4. Therapeutic abortion (TAB) may be performed up to the 24th week of gestation. TAB should be offered to the patient if her fetus has received a dose of ionizing radiation in excess of 10 cGy during the first trimester.
5. Breastfeeding is usually contraindicated because chemotherapeutic agents are excreted into human milk and have caused neutropenia in infants.

D. **Surgery during pregnancy.** Surgical treatment is far less likely to affect pregnancy adversely than is chemotherapy or RT. General anesthesia is an uncommon cause of teratogenesis. The fetus is exquisitely sensitive to hypoxia; the anesthesiologist and surgeon must take special precautions to ensure adequate oxygenation.

E. **RT during pregnancy**
1. A dose of 10 cGy to the fetus during the first trimester carries a substantial risk for fetal damage. No increase in the incidence of spontaneous abortion, growth retardation, or congenital malformations has been noted when the dose of radiation is less than 5 cGy at any time during pregnancy.
2. Defects most commonly seen with radiation damage include microcephaly, growth retardation, and ocular abnormalities. Late effects of radiation in early pregnancy include an increased incidence of thyroid cancer and leukemia.

F. **Chemotherapy during pregnancy**
1. **Pharmacokinetics.** Absorption, distribution, and metabolism of chemotherapeutic agents are undoubtedly altered by the multiplicity of physiologic changes accompanying pregnancy. Because the effects of pregnancy on pharmacokinetics are unknown, standard drug dosages are used. It can be assumed that most antineoplastic drugs cross the placenta.
2. **First-trimester exposure.** When folic acid antagonists and concomitant RT are excluded, single agents lead to congenital defects in 6% of infants exposed in the first trimester.
   a. **Antimetabolites.** Folic acid antagonists are the agents most frequently associated with teratogenesis and should not be used in the first trimester. Aminopterin and methotrexate are abortifacient and teratogenic. The aminopterin syndrome consists of facial anomalies, bone and limb deformities, and variable intellectual impairment. Although other antimetabolites, including cytarabine and 5-fluorouracil, have been associated with fetal malformation, 6-mercaptopurine has not.
   b. **Alkylating agents** are less frequently associated with fetal malformation than are antimetabolites. A 14% overall occurrence rate has been reported in one series; cyclophosphamide was associated with congenital defects in three of seven exposed infants.
   c. **Vinca alkaloids.** Vinblastine resulted in malformation in 1 of 14 exposed infants. No data are available for vincristine.
   d. **Others.** Procarbazine is associated with fetal malformation. DES has been linked to clear cell vaginal cancer in offspring.
   e. **Combination chemotherapy regimens** are associated with a 25% rate of fetal malformation. MOPP was linked to congenital defects in four of seven exposed infants.
3. **Second- and third-trimester exposure.** Forty percent of fetuses exposed to a variety of antineoplastic agents in the second and third trimesters have exhibited low birthweight, with its attendant risk for developmental delay. Other potential adverse effects include prematurity, spontaneous abortion, and major organ toxicity.

G. **Recommendations concerning TAB**
1. **TAB not recommended**
   a. Treatment does not jeopardize the pregnancy (e.g., surgery for breast cancer).
   b. Refractory malignancies for which treatment has no significant impact
2. **TAB considered, but not strongly recommended**
   a. Treatment may be delayed with reasonable safety until fetal maturity allows delivery.
   b. Treatment may be delayed into the second or third trimester, when the fetus is relatively resistant to the effects of chemotherapy (e.g., acute leukemia) or RT.
3. **TAB strongly recommended**
   a. Cancers in which curative therapy cannot be delayed or accomplished during pregnancy (e.g., most gynecologic malignancies).
   b. Treatment that is likely to cause abortion or fetal malformation is required in the first trimester (e.g., MOPP, methotrexate, pelvic RT).

V. Management of specific cancers and pregnancy

A. **Cervical cancer**
1. **Screening.** Papanicolaou's (Pap) smears should be done on all prenatal patients.
2. **Evaluation of cervical dysplasia.** Colposcopy can be done. Endocervical curettage biopsy is contraindicated. In the absence of invasive disease, there is no urgency to treat cervical dysplasia during pregnancy. Cervical conization should be avoided, but it may need to be done to exclude invasive disease. In pregnancy, conization is associated with cervical hemorrhage and a high incidence of incomplete resection.
3. **Staging and treatment.** The extent of invasive disease is often underestimated because of limitations of physical examination and diagnostic procedures. Treatment of invasive cervical cancer, using either surgery or RT, is incompatible with fetal survival. Consideration may be given to expectant management of early-stage cervical cancer (stage IA with less than 3 mm invasion) until delivery.

B. **Breast cancer**
1. **Screening.** A delay in diagnosis of 5 months or more has been observed in gravid patients with breast cancer, resulting in node-positive disease in 74% of patients, as compared with 37% in nonpregnant patients. Physiologic changes in the breasts during pregnancy hamper adequate physical examination. Serial breast examinations should be done throughout pregnancy, and masses should be investigated promptly. Clinicians have tended to observe breast masses 2 months longer in pregnant than in nonpregnant patients.
2. **Diagnosis.** Mammograms are not helpful during pregnancy. Fine-needle aspiration may be inaccurate, and excisional biopsy is the procedure of choice. Estrogen and progesterone receptor studies may be falsely negative or difficult to interpret.
3. **Treatment.** Modified radical mastectomy is the procedure of choice. Lumpectomy with radiation results in unacceptable radiation exposure to the fetus. Tamoxifen is contraindicated during gestation. Adjuvant chemotherapy should be delayed until at least the second or third trimester, or, if possible, until after delivery.

C. **Hodgkin lymphoma**
1. Limit staging procedures that may expose the fetus to radiation. When lymphangiography would affect treatment, it may be performed after the first trimester; the important modification is that only one abdominal film is taken 24 hours after injection of dye (fetal dose is less than 1 cGy).
2. If the disease is diagnosed during the first trimester, either perform a TAB and proceed as usual or delay chemotherapy or RT until later in the pregnancy.
3. If the disease is diagnosed during the second or third trimester:
   a. Try to delay therapy until delivery if the mother's outcome will not be adversely affected.
   b. If therapy is necessary, proceed with proper counseling regarding possible growth and developmental abnormalities.
   c. Very-limited-field RT has been largely successful. Internal scatter from standard mantle field RT can result in fetal exposure of 50 to 250 cGy.

D. **Non-Hodgkin lymphoma** is generally a more virulent disease and poses a greater risk to the mother and secondarily to the fetus than does HL. Therapeutic recommendations parallel HL, except for the possibility of protracted delay of treatment with indolent lymphomas.

E. **Genetic counseling.** Retrospective studies and case reports of patients who were treated for malignancy in childhood or adolescence and bore children later show a 4% rate of major malformations in offspring. This rate is similar to the risk borne by the general population. The late effects of cancer treatment on infants exposed *in utero* are unknown. Female survivors of cancer who later become pregnant, particularly those who have had abdominal radiation, have an increased

rate of preterm delivery and low-birthweight infants.

Suggested Reading

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Chapter 27 Metabolic Complications

Harold E. Carlson

I. Hypercalcemia

A. **Mechanisms.** Cancer is the most common cause of hypercalcemia in hospitalized patients. Hypercalcemia usually results from excessive bone resorption relative to bone formation.
   1. **Bone metastases.** Most tumors capable of bone metastasis (see Chapter 33, section I) can also produce hypercalcemia. Some tumors, such as breast cancer (*de novo* or with "flare" after hormonal therapy), produce hypercalcemia only in the presence of bone involvement. Local production of various substances by tumor cells may stimulate osteoclastic bone resorption.
   2. **Ectopic parathyroid hormone** (PTH) appears to be rare.
   3. **Humoral hypercalcemia of malignancy** is caused by production of a PTH-like substance called PTH-related peptide (PTH-RP) by a variety of carcinomas (squamous tumors of many organs, hypernephroma, parotid gland tumors). PTH-RP has bone-resorbing activity and interacts with the renal PTH receptor to stimulate renal calcium resorption. PTH-RP is not measured in serum PTH assays.
   4. **Vitamin D metabolites** (e.g., 1,25-dihydroxyvitamin D) may be produced by some lymphomas; these metabolites promote intestinal calcium absorption.
   5. **Prostaglandins and interleukin-1** (IL-1) produced by various tumors may occasionally cause hypercalcemia, perhaps by enhancing bone resorption.
   6. **Tumors** rarely or never associated with hypercalcemia despite high frequencies of bone metastases.
      a. Small cell lung cancer
      b. Prostate cancer
      c. Colorectal cancer
B. **Diagnosis**
   1. **Symptoms of hypercalcemia** depend on both the serum level of ionized calcium and how fast the level rises. Rapidly rising serum calcium levels tend to produce obtundation and coma with only moderate elevated serum calcium levels (e.g., 13 mg/dL). Slowly rising serum calcium levels may produce only mild symptoms even with serum levels exceeding 15 mg/dL.
      a. **Early symptoms**
         1. Polyuria, nocturia, polydipsia
         2. Anorexia
         3. Easy fatigability
         4. Weakness
      b. **Late symptoms**
         1. Apathy, irritability, depression, decreased ability to concentrate, mental obtundation, coma
         2. Profound muscle weakness
         3. Nausea, vomiting, vague abdominal pain, constipation, obstipation, increased gastric acid secretion, acute pancreatitis
         4. Pruritus
         5. Abnormalities of vision
   2. **Differential diagnosis of hypercalcemia.** Idiopathic hypercalcemia is not a tenable diagnosis in adult patients. More and more often, benign causes of hypercalcemia are recognized to occur in patients with cancer. The possible etiologies of hypercalcemia include the following:
      a. Malignancy
         1. Metastases to bone
         2. Secretion of PTH-like or other humoral factors
         3. Production of vitamin D metabolites
      b. Primary hyperparathyroidism
      c. Thiazide diuretic therapy
      d. Vitamin D or vitamin A intoxication
      e. Milk-alkali syndrome
      f. Familial benign hypocalciuric hypercalcemia
      g. Others
         1. Immobilization of patients with accelerated bone turnover (e.g., Paget's disease or myeloma)
         2. Sarcoidosis, tuberculosis, and other granulomatous diseases
         3. Hyperthyroidism
         4. Lithium administration
         5. Adrenal insufficiency
         6. Diuretic phase of acute renal failure
         7. Severe liver disease
         8. Theophylline intoxication
   3. **Laboratory studies.** All patients with cancer and polyuria, mental status changes, or gastrointestinal symptoms should be evaluated for hypercalcemia.
      a. **Routine studies**
         1. **Serum calcium, phosphate, and albumin levels**
            a. Ionized calcium constitutes about 47% of the serum calcium and is in equilibrium with calcium bound to proteins, especially to albumin. Roughly 0.8 mg of calcium is bound by 1 g of serum albumin. An alkaline pH (e.g., resulting from repeated vomiting because of hypercalcemia) tends to decrease the fraction of ionized calcium. When serum albumin is low, the measured serum calcium can be corrected (to a "normal" albumin concentration of 4 g/dL) using the following formula:

            Corrected serum calcium (mg/dL) = measured calcium + 0.8(4.0 − measured albumin)

            b. Long-standing hypercalcemia with hypophosphatemia suggests primary hyperparathyroidism.
         2. **Serum alkaline phosphatase.** Elevated levels may be due to either hyperparathyroidism or metastatic disease to the bone or liver. Normal levels are typical in cases of hypercalcemia produced by myeloma.
         3. **Serum electrolytes.** Serum chloride concentrations are frequently elevated in primary hyperparathyroidism. Renal tubular acidosis may complicate chronic hypercalcemia.
         4. **Blood urea nitrogen** (BUN) **and serum creatinine.** The direct effect of hypercalcemia on the kidneys can result in azotemia and defective renal tubular water conservation (i.e., symptoms of polyuria).
         5. **Electrocardiogram** (ECG). Hypercalcemia results in relative shortening of the Q-T interval and prolongation of the P-R interval. The T wave widens at blood levels above 16 mg/dL, paradoxically lengthening the Q-T interval.
         6. **Radiographs of the abdomen and bones**

      a. **Nephrolithiasis** is rare in hypercalcemia caused by malignancy and suggests hyperparathyroidism.
      b. **Nephrocalcinosis** and other ectopic calcifications are common in long-standing hypercalcemia.
      c. **Subperiosteal reabsorption** is pathognomonic of hyperparathyroidism, but osteopenia is the most common radiologic finding.
  b. **Further studies.** Results from preliminary evaluation may indicate the need for measuring serum PTH levels or for performing other tests.
    1. **Evidence for concomitant primary hyperparathyroidism**
      a. Documented long history of hypercalcemia or renal stones
      b. Radiographic evidence of hyperparathyroid bone disease (subperiosteal reabsorption, osteitis fibrosa cystica, or salt- and-pepper skull)
      c. Hyperchloremic acidosis, particularly with a serum chloride-to-phosphate ratio equal to or greater than 34
      d. Elevated serum PTH level in the presence of hypercalcemia
      e. Absence of hypocalciuria; if the ratio of calcium clearance to creatinine clearance in a 24-hour urine specimen is less than 0.01, the patient probably has familial hypocalciuric hypercalcemia, which can otherwise mimic primary hyperparathyroidism.
    2. **Evidence for humoral hypercalcemia of malignancy**
      a. Low or low-normal serum PTH levels in the presence of hypercalcemia
      b. Elevated level of PTH-RP
      c. Metabolic alkalosis
      d. Low serum level of 1,25-dihydroxyvitamin D
  4. **When should neck exploration be considered?** Both primary hyperparathyroidism and humoral hypercalcemia of malignancy are characterized by hypercalcemia and, with many cancers, elevated urinary excretion of cyclic adenosine monophospate (cAMP). Neck exploration is justified *if all of the following apply*:
    a. Clinical and laboratory findings (see earlier) suggest hyperparathyroidism.
    b. The malignancy is under control and the patient's expected survival is reasonably long.
    c. The general condition of the patient makes the surgical risk surgery acceptable.
    d. The hypercalcemia is severe enough to warrant treatment. Mild hypercalcemia (e.g., 11.5 mg/dL or less) caused by primary hyperparathyroidism may remain stable and asymptomatic for many years and may never produce clinically significant complications during the patient's remaining life span.
C. **Management**
  1. **Acute, symptomatic hypercalcemia** should be treated as an emergency.
    a. **Hydration and saline diuresis.** Achieving and maintaining intravascular volume and hydration are the cornerstones of promoting calcium excretion. Normal saline containing KCl (10 mEq/L) is given at a dosage of 2 to 3 liters per day IV. Calciuresis may be enhanced by administering furosemide, 40 to 80 mg IV given twice daily, after fluid and volume deficits have been corrected.
      1. **Fluid intake and output and body weight** are carefully monitored. Patients are evaluated for evidence of congestive heart failure two or three times daily. Patients with a history of congestive heart failure or renal insufficiency should be monitored with central venous pressure measurements.
      2. **Blood levels of calcium, potassium, and magnesium** are measured every 8 to 12 hours, and concentrations of cations in the intravenous solutions are adjusted.
      3. **Treatment is continued until** the blood calcium concentration is below 12 mg/dL. Central nervous system manifestations in elderly or comatose patients may not improve until normal blood calcium levels are maintained for several days.
      4. **More vigorous administration of fluids** (e.g., 12 to 14 liters over 24 hours) and diuretics (e.g., every 1 to 2 hours) requires excellent cardiac and renal function and necessitates close monitoring in an intensive care unit. Treatment at this intensity is rarely necessary for patients with malignancies.
    b. **Bisphosphonates** are potent inhibitors of osteoclast activity and are effective in the treatment of hypercalcemia of malignancy. These drugs are relatively free of significant adverse effects. Pamidronate (Aredia) is the most effective of the available drugs; it is given as a single IV infusion of 60 to 90 mg in 1000 mL of normal saline over 24 hours. Shorter infusions (3 to 6 hours) of the same doses are equally safe and effective. Significant reductions in serum calcium occur in 1 to 2 days and generally persist for several weeks. About 20% of patients develop transient fever after receiving the drug.

      Etidronate (Didronel), which is also available, is given intravenously in 500 mL of normal saline over three hours at a dose of 7.5 mg/kg daily for 5 days. Three liters of normal saline is also infused daily. Significant reduction of serum calcium levels is usually achieved by the third day of treatment. Oral maintenance therapy with etidronate is investigational, but a dose of 20 mg/kg per day or more may be helpful.

    c. **Gallium nitrate** (Ganite), a potent inhibitor of bone resorption, is given intravenously in a dose of 200 mg/m^2 daily for 5 days. Serum calcium levels fall within a few days and remain normal for about 1 week. Renal function may worsen during gallium nitrate therapy, and the drug should not be given if the serum creatinine level is higher than 2.5 mg/dL.
    d. **Mithramycin.** Patients who have congestive heart failure, fluid overload, or unresponding calcium levels during saline diuresis can be treated with mithramycin. The drug inhibits bone resorption by reversibly poisoning osteoclasts. Mithramycin, 25 µg/kg, is given by rapid infusion into a well-established intravenous line; serum calcium levels are lowered in 24 to 48 hours. The dose may be repeated every 3 to 4 days. Hypocalcemia is averted by measuring blood calcium levels every 1 or 2 days or when mental status changes or tetany develops. Other important toxicities of mithramycin are discussed in Chapter 4, section III.I. The drug is contraindicated in the presence of severe thrombocytopenia or severe hepatocellular dysfunction. In patients with renal failure, mithramycin may be given in lower doses (10 µg/kg), but calcitonin is preferred in these cases.
    e. **Calcitonin** is useful for rapid reduction of blood calcium levels. Calcitonin can be given when mithramycin or saline diuresis is contraindicated or ineffective (e.g., in severe thrombocytopenia, renal failure, congestive heart failure). The drug inhibits bone resorption and increases renal calcium clearance. Blood calcium levels are decreased within 2 to 3 hours of administration. The effect is transient but may be prolonged to 4 or more days by concurrent administration of prednisone, 10 to 20 mg given three times daily. Allergy is the only important complication of therapy. Synthetic salmon calcitonin is given in a dose of 3 U/kg (Medical Research Council) as a 24-hour infusion, or 100 to 400 U given SC every 8 to 12 hours.
    f. **Dialysis.** Peritoneal dialysis and hemodialysis rapidly lower blood calcium levels but are rarely used.
    g. **Dangerous therapies** that have little clinical usefulness and are not recommended
      1. Intravenous phosphates (extraosseous calcification)
      2. Intravenous sodium sulfate (hypernatremia, heart failure)
      3. Calcium chelating agents (severe renal damage)
  2. **Chronic hypercalcemia.** Ambulation is encouraged to minimize bone resorption that accompanies immobilization. Liberal fluid intake (2 to 3 L/day) is prescribed. Foods containing large amounts of calcium, such as milk products, are avoided. Thiazide diuretics aggravate hypercalcemia and should not be taken.
    a. **Glucocorticoids.** Prednisone, 20 to 40 mg PO daily, or hydrocortisone, 100 to 150 mg IV every 12 hours, may be used for patients with tumors that are sensitive to glucocorticoids (e.g., lymphoma, multiple myeloma).
    b. **Phosphates** given orally lower blood levels by binding calcium in the gut. Because this may compromise renal function, effects of therapy should be monitored. Diarrhea nearly always accompanies phosphate therapy and is treated with diphenoxylate (Lomotil), 2 to 5 mg PO, with each dose of phosphate. Diarrhea may also be reduced by diluting the liquid or powder forms. The daily dose is 1 to 6 g of phosphate. *One gram of inorganic phosphate* is supplied by the following preparations:
      1. Fleet Phospho-Soda, liquid, 6.7 mL
      2. Neutra-Phos, 4 capsules or 1 teaspoon of powder (Neutra-Phos-K contains no sodium)
      3. K-Phos Original Formula, 6 tablets (contains no sodium)
    c. **Prostaglandin inhibitors,** such as aspirin and indomethacin, produce variable and inconsistent lowering of calcium levels but may be tried in patients with refractory hypercalcemia.
    d. **Mithramycin,** 10 µg/kg IV every 3 to 7 days, may be given until drug toxicity develops.

II. Hypocalcemia

A. **Mechanisms**
  1. **Paraneoplasia.** Hypocalcemia is an extremely rare paraneoplastic syndrome.
    a. **Rapid uptake of calcium.** Patients with bone metastases from prostate or breast cancer who are treated with hormonal agents may develop hypocalcemia, supposedly because of rapid bone healing. Calcifying chondrosarcoma is a rare tumor, which has been associated with hypocalcemia.
    b. **Oncogenic osteomalacia** appears to be caused by tumor products that interfere with the production of 1,25-dihydroxycholecalciferol and promote phosphaturia. This entity has been associated with mesenchymal neoplasms and prostate cancer.
    c. **Calcitonin** production by medullary carcinoma of the thyroid rarely causes hypocalcemia.
  2. **Magnesium deficiency.** Magnesium is necessary for both the release of PTH and its peripheral action. Hypomagnesemia results in hypocalcemia that does not respond to calcium replacement therapy. Magnesium deficiency occurs in the following circumstances:

a. Patients who have prolonged nasogastric drainage
b. Patients who receive parenteral hyperalimentation without magnesium replacement
c. Cisplatin therapy
d. Chronic diuretic therapy or diuresis due to glycosuria
e. Chronic alcoholism (alcohol interferes with renal conservation of magnesium)
f. Chronic diarrhea
3. **Other causes of hypocalcemia**
   a. Therapy for hypercalcemia, especially if with mithramycin or intravenous phosphates
   b. Hypoalbuminemia
   c. Hyperphosphatemia (see section III)
   d. Pancreatitis
   e. Renal disease
   f. Hypoparathyroidism
   g. Pseudohypoparathyroidism
   h. Rickets and osteomalacia
   i. Sepsis
B. **Diagnosis**
1. **Symptoms and signs** are aggravated by hyperventilation or other causes of alkalosis.
   a. Tetany is the most prominent symptom of hypocalcemia and is manifested by paresthesias (especially numbness and tingling of the face, hands, and feet), muscle cramps, laryngospasm, or seizures. Other problems include diarrhea, headache, lethargy, irritability, and loss of recent memory. Chronic hypocalcemia may be well-tolerated, however, with few symptoms.
   b. Dry skin, abnormal nails, cataracts, and papilledema may develop in long-standing cases.
   c. Chvostek's sign: twitching of muscles around the mouth, nose, or eyes after tapping the facial nerve.
   d. Trousseau's sign: Spasm of the hand during 3 to 4 minutes of exercise while a blood pressure cuff on the arm is inflated midway between systolic and diastolic pressures.
2. **Routine laboratory studies.** Serum levels of calcium, phosphate, magnesium, electrolytes, BUN, creatinine, and albumin should be obtained. The ECG may show a prolonged Q-T interval; the ECG is monitored during therapy.
3. **Differential diagnosis of hypocalcemia**
   a. Severe alkalosis resulting from prolonged nasogastric suction, vomiting, or hyperventilation
   b. Severe muscle cramps resulting from vincristine or procarbazine therapy
C. **Management**
1. **Severe hypocalcemia** (blood calcium 6 mg/dL or less) must be managed in an intensive care setting.
   a. **Calcium gluconate or calcium chloride.** 1 g by rapid IV injection, is given every 15 to 20 minutes as long as tetany persists.
   b. **Magnesium sulfate,** 1 g IV or IM every 8 to 12 hours is also administered if the blood magnesium level is unknown or less than 1.5 mg/dL until the calcium or magnesium blood levels have normalized.
   c. **Hyperventilating** patients should breathe into a paper bag to decrease respiratory alkalosis.
   d. **Serum calcium levels** are obtained every 1 to 2 hours until the serum calcium level exceeds 7 mg/dL.
2. **Moderate hypocalcemia** (blood calcium between 7 and 8 mg/dL)
   a. **Calcium gluconate,** 2 g IV in 500 mL of 5% dextrose in water is given every 8 hours. Blood levels should be measured twice daily until they exceed 8.5 mg/dL for 48 hours.
   b. **Hypomagnesemia** (less than 1.5 mg/dL) is treated with magnesium sulfate, 1 g IM or IV once or twice daily, until the blood level is normal.
   c. **Patients recovering from hypercalcemia** who were treated with mithramycin are in jeopardy of recurrent life-threatening hypocalcemia for as long as 4 days after treatment is stopped.
   d. **Patients with oncogenic osteomalacia** can be treated with oral calcium lactate, 2 g given four times daily PO. Control of the underlying tumor resolves the problem.
   e. **Patients with postthyroidectomy hypoparathyroidism** are discussed in Chapter 15, section III.F.1.A.

III. Hyperphosphatemia

A. **Mechanisms.** Hyperphosphatemia (more than 4.5 mg/dL) is a rare complication of treatment of certain tumors, notably leukemia and lymphoma (especially Burkitt lymphoma). Rapid tumor lysis releases large amounts of uric acid, potassium, and phosphate. Elevated blood phosphate levels may not be observed until 2 days after beginning tumor therapy; elevations may persist for 4 to 5 days and can exceed 20 mg/dL.
B. **Diagnosis.** The serum phosphate level itself does not cause symptoms. Renal damage or acute renal failure results from precipitation of calcium phosphate in the kidneys. Tetany may develop if ionized calcium concentration becomes inordinately reduced (e.g., with alkalosis from bicarbonate administration or vomiting).
1. **Laboratory studies.** Serum phosphate, calcium, and other electrolyte levels should be measured regularly in susceptible patients during the initial course of antitumor therapy.
2. **Differential diagnosis**
   a. Hypoparathyroidism
   b. Renal failure
   c. Rapid tissue breakdown after muscle trauma or burn
   d. Tumor lysis syndrome (see section XIII)
   e. Large oral doses of phosphates
C. **Management.** High phosphate levels must be lowered rapidly to avoid or reverse renal damage. Serum chemistries are monitored every 4 to 6 hours. The following methods are used *simultaneously* until the phosphate concentration reaches 5 mg/dL:
1. An intravenous infusion of 20% dextrose containing 10 U/L regular insulin is administered at a rate of 50 to 100 mL/hour until the blood phosphate level falls below 7 mg/dL. The extracellular volume is expanded by infusing half-normal saline at 100 to 200 mL/hour. Potassium is added to the solution if the serum level is less than 4 mg/dL.
2. An aluminum hydroxide gel preparation (e.g., Amphojel), 30 to 60 mL PO, every 2 to 6 hours, is given to bind phosphate in the intestine.
3. **Oral fluids** are given at a rate of 2 to 4 liters every 24 hours.
4. **Dialysis** may be necessary for patients with renal failure.

IV. Hypophosphatemia

A. **Mechanism.** Hypophosphatemia (less than 3 mg/dL) is occasionally associated with rapidly growing tumors (such as acute leukemia), presumably because tumor cells consume phosphate. Severe hypophosphatemia (less than 1 mg/dL) may result in rhabdomyolysis or hemolysis. Hypokalemia may be associated with hypophosphatemia, the reasons for which are unclear. In patients with cancer, hypophosphatemia more commonly accompanies marked nutritional deprivation or cachexia.
B. **Diagnosis**
1. **Laboratory studies.** Hypophosphatemia is usually recognized by routine serum electrolyte studies in patients with nutritional disturbances.
2. **Differential diagnosis of hypophosphatemia**
   a. Renal phosphate wasting accompanies certain syndromes associated with malignancies, including myeloma (Fanconi's syndrome), multiple endocrine neoplasia (hyperparathyroidism), and oncogenic osteomalacia (hypocalcemia, see section II)
   b. Therapy with phosphate-binding antacid gels
   c. Starvation or malabsorption (decreased phosphate intake)
   d. Cachexia
   e. Alcoholism
   f. Nutritional recovery (e.g., during hyperalimentation) without adequate phosphate supplementation
   g. Massive, rapid tumor growth
   h. Alkalosis
   i. Diabetic ketoacidosis
C. **Management**
1. Patients with phosphate levels less than 1 mg/dL are given 30 to 40 mmol/L of neutral sodium phosphate or sodium potassium phosphate administered IV at

a rate of 50 to 150 mL/hour. Doses and precautions are about the same as for intravenous potassium preparations.

2. Patients with blood phosphorus levels of 1 to 2 mg/dL may be given oral inorganic phosphate supplements (see <u>section I.C.2.b</u>). One bottle of Neutra-Phos (64 g of phosphorus) is dissolved in 4 L of water, and 2 to 3 ounces of the solution is given four times daily PO.

3. Patients with *simultaneous hypokalemia* are treated with 20 mEq of KCl in 10% solution three times daily, or with potassium-containing phosphate preparations. Neutra-Phos-K and Phos-Tabs both contain 50 to 57 mEq of potassium per gram of phosphate.

V. Hypernatremia

A. **Mechanisms.** Hypernatremia nearly always is due to a loss of water from the body fluids. Any hypotonic fluid loss (e.g., sweating, hyperventilation, fever, vomiting, nasogastric suction) causes mild hypernatremia if not treated. *Extreme elevations* of plasma sodium concentrations (more than 160 mEq/L) are usually encountered in only three clinical situations:

1. **Decreased or absent fluid intake** is the most common cause of hypernatremia, especially in patients who have disabilities that impair normal fluid intake.

2. **Diabetes insipidus** (insufficient production of antidiuretic hormone [ADH]) is usually caused by head trauma (accidental or neurosurgical) or pituitary or hypothalamic neoplasms (primary or metastatic). Breast and lung cancers appear to have a special propensity for metastasizing to the hypothalamus. Although there are other rare causes of diabetes insipidus, nearly half of cases are idiopathic. Diabetes insipidus is an exceptionally rare paraneoplastic syndrome. Nephrogenic diabetes insipidus occurs when the kidney is unable to respond to normal circulating levels of ADH.

3. **Osmotic diuresis** and often osmotic diarrhea are encountered in obtunded patients who receive a massive urea load from high-protein nasogastric tube feedings. Progressive dehydration develops, and the osmotic diuresis produces an apparently normal urine output. Daily weighing and twice-weekly measuring of serum electrolytes and urea nitrogen are necessary to detect or prevent this problem.

B. **Diagnosis**

1. **Signs and symptoms.** Most patients with severe hypernatremia are already seriously ill. The specific contribution of hypertonicity is frequently difficult to distinguish from the underlying disease. Polyuria draws attention to the problem in most cases. If the solute intake is low, however, urine output may not exceed 2 to 3 L/day.

2. **Laboratory studies.** To make a diagnosis of diabetes insipidus, a water deprivation test is performed. Baseline body weight, serum sodium concentration, serum osmolality, urine specific gravity, and urine osmolality are measured. Water intake is completely restricted; however, these patients should *never* be deprived of water without continuous observation. Beginning in the morning, urine volume and the baseline studies are determined hourly. The test must be *terminated* if the patient's weight decreases by more than 3% or serum osmolality exceeds 310 mOsm/kg. Pending results of direct measurement, the serum osmolality can be rapidly and accurately estimated from serum concentrations of sodium, urea nitrogen, and glucose by the following formula:

Serum osmolality = 2 (sodium) + BUN/2.8 + glucose/18

    a. **Criteria for diagnosing diabetes insipidus**
      1. Urine osmolality never exceeds 200 mOsm/kg unless there is severe dehydration.
      2. The initial serum osmolality determination exceeds 280 mOsm/kg.
      3. Serum osmolality rises above the initial determination.
      4. The urine flow rate consistently exceeds 1 mL/min.
    b. **Differentiating pituitary diabetes insipidus.** Significant diabetes insipidus is excluded if the urine osmolality is greater than 600 mOsm/kg after water deprivation in the absence of glycosuria or recently injected contrast media. Urine osmolality between 200 and 600 mOsm/kg suggests partial diabetes insipidus. It is necessary to distinguish pituitary (central) diabetes insipidus from nephrogenic diabetes insipidus. To do this, the kidney's response to ADH is assessed. Desmopressin, 0.5 µg, is given SC at the conclusion of the water deprivation test, and hourly urine specimens are collected for an additional 3 hours. Urine osmolality exceeds 400 mOsm/kg in patients with ADH deficiency and 800 mOsm/kg in normal subjects; values are lower in patients with nephrogenic diabetes insipidus.

C. **Management**

1. **Severe hypernatremia** is life-threatening and must be carefully managed. Correcting the water deficit too rapidly precipitates fatal cerebral edema. Therapy should not lower the serum sodium level by more than 2 to 4 mEq/hour. Emergency therapy for patients in shock consists of plasma volume expansion with normal saline solution (200 to 250 mL boluses IV over 10 minutes until the systolic blood pressure exceeds 90 mm Hg); volume expansion itself induces a saluresis and initiates reduction of the serum sodium level. When the patient is hemodynamically stable, **the total volume of 5% dextrose in water** (5% D/W) is given according to the following formula:

$$\frac{(\text{serum sodium concentration} - 140) \times (0.6 \times \text{body weight in kg})}{140}$$

2. **Therapy for chronic ADH deficiency**
    a. **Chlorpropamide,** 250 to 500 mg PO each morning, appears to be effective only in patients with incomplete pituitary diabetes insipidus. The drug is not approved for this purpose by the U.S. Food and Drug Administration. Serious and prolonged hypoglycemia or hyponatremia may complicate therapy with chlorpropamide.
    b. **Desmopressin** (desamino-d-arginine vasopressin; DDAVP), 5 to 10 µg intranasally or 0.5 to 1.0 µg by SC injection, produces 6 to 18 hours of antidiuresis. To avoid water intoxication, the next dose is not given until thirst and polyuria redevelop. Oral desmopressin is also available for chronic therapy; doses of 0.05 to 0.8 mg/day are employed.

VI. Hyponatremia: syndrome of inappropriate antidiuretic hormone (SIADH)

A. **Mechanisms**

1. **ADH** is normally released from the posterior pituitary gland in response to increased osmolality or decreased volume of plasma. The release of ADH is normally inhibited by decreased plasma osmolality and increased plasma volume. The hormone acts by increasing water resorption from the renal collecting tubules.

2. **SIADH.** Unregulated tumor production of ADH results in increased water retention by the kidney, increased total-body water, and moderate expansion of plasma volume. Plasma hypotonicity fails to suppress the tumor source of ADH. Hyponatremia, plasma hypoosmolality, and inability to excrete maximally diluted urine are the consequences of SIADH.

3. **Associated tumors.** Ectopic production of ADH may occur with any malignancy but is most frequently associated with bronchogenic carcinoma, especially the small cell type, and mesothelioma.
    a. About half of patients with small cell lung cancer are unable to excrete an exogenous free water load normally; however, only a small portion of these develop severe hyponatremia (less than 120 mEq/L).
    b. Abnormalities of serum electrolytes, other than hyponatremia and (occasionally) hypouricemia, do not occur in SIADH. Some tumors, however, produce multiple ectopic hormones. Concomitant hypokalemia suggests a complicating ectopic adrenocorticotropic hormone (ACTH) syndrome. Concomitant hypercalcemia suggests the presence of a paraneoplastic disorder of calcium metabolism.

4. **Central nervous system disease** (e.g., mass lesions, hemorrhage, infection) and pulmonary infection (e.g., pneumonia, tuberculosis, abscess) may result in excessive ADH release from the posterior pituitary.

5. **Drugs associated with hyponatremia**
    a. **Diuretics** commonly produce hyponatremia, particularly in patients with unrestricted fluid intake.
    b. **Vincristine** may produce SIADH and profound hyponatremia. Manifestations develop 1 to 2 weeks after treatment.
    c. **Cyclophosphamide,** when given intravenously, may produce SIADH. Mild hyponatremia develops 4 to 12 hours after a dose, persists for about 20 hours, and is usually asymptomatic.
    d. **Chlorpropamide** occasionally causes SIADH; other oral hypoglycemics rarely do so.
    e. **Carbamazepine** induces ADH secretion.
    f. **Intravenous narcotics** have been associated with SIADH.
    g. **Psychotropic agents,** amitriptyline (Elavil) and thioridazine (Mellaril), have been rarely associated with SIADH.

B. **Diagnosis**

1. **Symptoms and signs.** Lethargy, nausea, anorexia, and generalized weakness are common symptoms in patients with hyponatremia; however, the symptoms may be related more to comorbid conditions than to the serum sodium concentration. Confusion, convulsions, coma, and death may ensue if the hyponatremia is severe or rapid in onset.

2. **Laboratory studies.** Laboratory results in conditions associated with hyponatremia are shown in Table 27.1. Measurements that should be obtained in

patients with hyponatremia are as follows:

Table 27.1 Hyponatremia: differential diagnosis and laboratory results

    a. **In all patients with hyponatremia**
        1. Serum electrolytes, creatinine, urea nitrogen, calcium, phosphate, glucose, total protein, and triglycerides
        2. Urine sodium
    b. **In patients with hyponatremia and without an elevated BUN**
        1. Blood and urine osmolality
        2. Chest radiograph to look for evidence of lung cancer
        3. Patients who meet the diagnostic criteria for SIADH but in whom there is no obvious cause should have a bone marrow biopsy performed to look for metastases from small cell lung cancer (some patients have normal chest radiographs).
    c. **In patients with evidence of endocrine hypofunction**
        1. Thyroid function tests
        2. Adrenal function tests
        3. Pituitary gland function tests as necessary

3. **Diagnostic criteria for SIADH** include *all five* of the following:
    a. **Hyponatremia** with a disproportionately low BUN (often less than 10 mg/dL)
    b. **Absence of intravascular volume contraction**
        1. Volume contraction is a potent stimulus for ADH secretion and overrides the suppressive effect of hypotonicity.
        2. Persistent urinary excretion of sodium constitutes indirect evidence of volume expansion (urine sodium concentration more than 30 mEq/L; fractional excretion of sodium more than 1).
    c. **Absence of abnormal fluid retention,** such as peripheral edema or ascites
    d. **Normal renal function**
    e. **Serum hypotonicity along with urine that is not maximally dilute.** A normal adult should be able to dilute urine to an osmolality of 50 to 75 mOsm/kg in the presence of decreased plasma osmolality; higher values are presumptive evidence for ADH activity at the renal tubules. Urine must be less than maximally dilute but need not be hypertonic relative to serum. Urine osmolality greater than 75 to 100 mOsm/kg (or urine specific gravity more than 1.003) with plasma osmolality less than 260 mOsm/kg is usually diagnostic of SIADH.

C. **Management.** Control of the responsible cancer usually corrects the problems associated with ectopic SIADH.
    1. **Severe hyponatremia** (serum sodium less than 110 mEq/L). Comatose or seizing patients with severe hyponatremia must receive aggressive management. Lowering the plasma volume is essential to promote proximal tubular reabsorption of sodium. Administering saline solutions without diuresis to patients with SIADH does not correct the problem; saline increases plasma volume and results in further loss of sodium in the urine.
        a. An IV infusion of 3% NaCl at a rate of 1 L every 6 to 8 hours is started.
        b. Furosemide, 40 to 80 mg IV every 6 to 8 hours, is administered simultaneously.
        c. The central venous pressure (CVP) is monitored every 15 to 30 minutes; serum sodium and potassium concentrations are obtained hourly. Give additional doses of furosemide, 20 to 40 mg IV, or decrease the saline infusion rate if the CVP exceeds 18 cm of water or if congestive heart failure becomes evident on physical examination.
        d. Furosemide and saline are discontinued when the serum sodium concentration exceeds 110 mEq/L. More rapid treatment increases the risk for cerebral herniation. The hyponatremia should then be further corrected more slowly as described in section C.2; serum sodium should rise no more than 12 mEq/L in the first 24 hours to avoid myelinolysis. Correction to serum sodium values of 125 to 130 mEq/L is usually sufficient.
        e. The development of mental status changes or seizures after partial correction of severe hyponatremia is *prima facie* evidence of cerebral herniation; dexamethasone, 10 to 20 mg IV, and mannitol, 50 g IV, are given immediately.
    2. **Moderately severe hyponatremia** (serum sodium more than 110 mEq/L)
        a. **Fluid restriction** is of paramount importance in treatment of all patients with SIADH and should result in correction of hyponatremia within 3 to 5 days. Patients with serum sodium levels less than 125 mEq/L should be restricted to 500 to 700 mL/day. Patients with higher serum sodium levels can be restricted to 1000 mL/day.
        b. **Demeclocycline** (Declomycin), 150 to 300 mg PO given four times daily, induces renal resistance to ADH and facilitates free water excretion. The drug is useful in patients who cannot tolerate chronic fluid restriction or who have insufficient improvement of hyponatremia with fluid restriction. The only significant toxicity of the drug is azotemia, which may be a problem in patients who receive the higher doses or simultaneous nephrotoxic agents.
        c. **Lithium salts** are less reliable than demeclocycline.

VII. Hyperkalemia

A. **Mechanisms**
    1. Hyperkalemia in patients with or without cancer usually develops as a consequence of renal failure.
    2. Hyperkalemia may result from rapid tumor lysis after therapy, especially in patients with Burkitt lymphoma.
    3. Adrenal metastases are common in patients with many types of cancer, but clinical adrenal insufficiency from metastases is unusual.
    4. Pseudohyperkalemia occurs in patients with persistent thrombocytosis, especially in the myeloproliferative disorders (see Chapter 24, Comparative Aspects, section III.A.7.b).
B. **Diagnosis**
    1. **Symptoms** mostly consist of weakness and other neuromuscular complaints.
    2. **Laboratory studies**
        a. Serum potassium concentration
        b. The severity of the ECG abnormalities corresponds to the severity of hyperkalemia; as hyperkalemia gets worse, the ECG shows increased T-wave amplitude, decreased R-wave amplitude, and increased S-wave depth; prolongation of P-R intervals and widening of the QRS complex; and then a "sine wave" pattern, eventuating in asystole or ventricular tachyarrhythmias.
    3. **Differential diagnosis**
        a. Renal insufficiency
        b. Excessive potassium intake, especially with renal insufficiency
        c. Potassium-sparing diuretics
        d. Adrenal insufficiency
        e. Acidosis
        f. Cell destruction (e.g., tumor lysis, rhabdomyolysis)
        g. Angiotensin-converting enzyme inhibitors
C. **Management**
    1. Immediate lowering of the potassium is achieved by IV administration of 10 U of regular insulin plus 50 to 100 mL of 50% dextrose solution. If the patient is acidotic, 150 to 300 mEq (1 to 2 ampules) of sodium bicarbonate is given IV.
    2. Removal of potassium from the body can be achieved with cation exchange resins like Kayexalate, 15 to 30 g every 6 hours. Sorbitol, 20 mL of 70% solution PO four times daily, or 100 g in a water retention enema, is given to expel the resin from the bowel.
    3. Hemodialysis is necessary for management of chronic or refractory hyperkalemia.
    4. Hyperkalemia due to adrenal insufficiency may be corrected with the synthetic mineralocorticoid, fludrocortisone, 0.05 to 0.20 mg/day.

VIII. Hypokalemia: ectopic secretion of ACTH

A. **Mechanism.** A variety of tumors may ectopically synthesize ACTH and produce Cushing's syndrome. Biologically active ACTH is secreted in varying proportions with biologically inactive prohormone and pre-prohormone. All of these substances possess antigenic cavity for ACTH. Thus, assays based on ACTH antigenic activity do not prove the presence of Cushing's syndrome.
    1. **Tumors commonly producing ectopic ACTH syndrome**
        a. Small cell lung cancer

b. Malignant thymoma
c. Pancreatic cancer, especially islet cell tumors
d. Bronchial carcinoids
2. **Tumors uncommonly or rarely producing ectopic ACTH syndrome**
a. Ovarian cancer
b. Thyroid cancer
c. Pheochromocytoma
d. Prostate cancer
e. Renal cancer
f. Sarcomas
g. Hematologic malignancies
B. **Diagnosis**
1. **Symptoms and signs.** The most common malignant causes of ectopic ACTH syndrome are rapidly fatal. The typical features of adrenal or pituitary Cushing's syndrome are often absent. Presenting signs usually are cachexia, weakness, and hypertension. Slower-growing cancers and benign tumors give rise to the characteristic rounded facies, truncal obesity, purple striae in skin stretch areas, and overt diabetes mellitus.
2. **Laboratory studies**
a. Cancer patients who complain of weakness should have serum electrolytes measured. Hypokalemia and metabolic alkalosis may be severe (serum potassium as low as 1 mEq/L, bicarbonate more than 30 mEq/L) in patients with ectopic ACTH syndrome.
b. The diagnosis of ectopic ACTH syndrome may be quickly made by demonstrating the failure of dexamethasone to suppress ACTH levels in most cases (see Chapter 15, section V.C.2).
3. **Differential diagnosis**
a. Gastrointestinal losses associated with alkalosis (vomiting, prolonged nasogastric suctioning, colonic neoplasms [villous adenomal, chronic laxative abuse)
b. Gastrointestinal losses associated with acidosis (chronic diarrhea, ureterosigmoidostomy, Zollinger-Ellison syndrome)
c. Potassium-wasting drugs (e.g., diuretics, cisplatin, corticosteroids)
d. Hyperaldosteronism
e. Hypercortisolism
f. Licorice ingestion
g. Renal tubular acidosis
h. Hypercalcemia, hypomagnesemia
i. Hypophosphatemia in anabolic states (e.g., rapid tumor growth)
j. Respiratory therapy in patients with chronic carbon dioxide retention
k. Correction of nutritional anemias
C. **Management.** Control of the underlying tumor is the most effective method. Hypokalemia is often difficult to correct. Potassium replacement consists of PO or IV doses of 80 to 150 mEq/day. Severe symptoms may occasionally improve using adrenal suppressant medications, such as various combinations of mitotane, metyrapone, ketoconazole, and aminoglutethimide. The toxicity of these drugs may be worse than the symptoms from the underlying disease. Spironolactone, 100 to 400 mg daily, may be useful. Adrenalectomy is a consideration in the rare patient with an indolent, unresectable tumor that causes the ectopic ACTH syndrome.

IX. Hyperuricemia

A. **Mechanisms.** Hyperuricemia and hyperuricosuria pose a major problem for patients with myeloproliferative disorders, lymphomas, myeloma, or leukemias but usually not for patients with solid tumors.
1. **Hyperuricosuria.** Urinary uric acid excretion is increased in untreated patients who have myeloproliferative disorders, acute or chronic myelocytic leukemia, or acute lymphoblastic leukemia. Patients with lymphoma have normal or slightly increased uric acid excretion. During treatment with either cytotoxic agents or radiation, massive tumor lysis results in excess production of uric acid, especially in patients with lymphoma or leukemia.
2. **Uric acid nephropathy** results from the precipitation of uric acid crystals in the concentrated, acidic urine of the renal medulla, distal tubules, and collecting ducts. The resultant sludge leads to intrarenal obstructive nephropathy and distinct inflammatory interstitial changes. Hyperuricemic nephropathy comprises four types of renal disease.
a. **Acute hyperuricemic nephropathy** is seen in patients treated for hematologic malignancies. It is characterized by acute renal failure with a rapidly rising serum creatinine concentration. Blood uric acid levels of more than 20 mg/dL are consistently associated with acute renal functional impairment or failure. Lower levels may acutely compromise renal function if the patient is dehydrated or acidotic.
b. **Gouty nephropathy** is usually mild to moderate and is characterized by the deposition of uric acid crystals (tophi) in the medulla or pyramids and a surrounding giant cell reaction.
c. **Uric acid nephrolithiasis** develops in gouty and nongouty subjects with or without hyperuricemia. Symptomatic uric acid calculi are usually manifested by renal colic. Acute or chronic renal failure may develop secondary to obstructive uropathy.
d. **Interstitial nephritis** of hyperuricemia may lead to chronic renal failure after 20 to 30 years. This condition is almost always associated with hypertension and is questioned as an isolated cause of renal failure.
3. **Xanthine stones,** resulting from the inhibition of xanthine oxidase by allopurinol in the setting of purine hypermetabolism, rarely complicates malignancies.
4. **Oxypurinol stones** have rarely developed after therapy with massive doses of allopurinol.
B. **Diagnosis** is established by measurement of serum and urine uric acid concentrations. The normal excretory rate for uric acid is 300 to 500 mg/day.
C. **Management**
1. **Prevention** is the cornerstone of management.
a. **Vigorous hydration** is essential for increasing uric acid clearance and diluting the concentration of uric acid in the renal tubules. Urinary flow should be at least 100 mL/hour.
b. **Alkalinization of the urine.** The urine pH should be maintained between 7.0 and 7.5 (by dipstick). Sodium bicarbonate is given (1 to 3 tablets PO every 4 hours) while the patient is awake. Acetazolamide (Diamox), 250 to 500 mg PO, is given at bedtime to maintain urine alkalinization. Other preparations that contain sodium or potassium citrate are also available.
c. **Allopurinol** should be given continuously to patients with myeloproliferative disorders and at least 12 hours before starting antitumor therapy to patients with the other hematologic malignancies. The usual dose is 300 to 600 mg/day PO; larger doses may be required. Allopurinol can be discontinued when remission is obtained.
2. **Renal failure** because of uric acid nephropathy
a. **Ureteral lavage** through nephrostomies and **surgical removal of stones** may be necessary to relieve acute renal pelvis and ureteral obstructions.
b. **Hemodialysis** should be used if the measures in section 2.a fail to improve renal function because uric acid nephropathy is usually a complication of effective antitumor therapy. Hemodialysis is superior to peritoneal dialysis for clearing uric acid.

X. Hypouricemia

A. **Mechanisms.** Hypouricemia is usually caused by defects in proximal renal tubular reabsorption of uric acid. Hypouricemia has also been reported to be associated with a variety of tumors, especially Hodgkin lymphoma and myeloma.
B. **Diagnosis**
1. **Symptoms.** Patients do not have symptoms.
2. **Laboratory studies.** Blood uric acid levels identify the abnormality.
3. Differential diagnosis
a. Proximal renal tubular disease
1. Falconi's syndrome (myeloma is a common cause in adults)
2. Wilson's disease
3. Isolated defect in otherwise healthy patients
b. Uricosuric agents
1. Aspirin
2. Radiographic contrast agents
3. Glyceryl guaiacolate
c. Xanthine oxidase inhibitors (allopurinol)

      d. Hereditary xanthinuria
      e. Neoplastic diseases, especially Hodgkin lymphoma
      f. Liver disease
      g. SIADH
  C. **Management.** Treatment of hypouricemia is not necessary.

XI. Hyperglycemia

  A. **Mechanisms**
    1. **Diabetic glucose tolerance curves** with relative insulin deficiency are present in many patients with cancer. Paradoxical hypersecretion of growth hormone from the pituitary gland occurs in most of these patients. Nutritional replenishment appears to improve the abnormal glucose tolerance, hyperinsulinemia, and paradoxical growth hormone secretion.
    2. **Hyperglycemia** occurs in patients with glucagonoma, somatostatinoma, pheochromocytoma, and hypercortisolism.
    3. **Nonketotic hyperosmolar coma** can be a complication of treatment with cyclophosphamide, vincristine, l-asparaginase, or prednisone in patients with even mild diabetes mellitus. Hyperosmolar coma also occurs as a result of hyperalimentation therapy.
  B. **Diagnosis.** Random or 2-hour postprandial blood glucose determinations disclose the abnormality in most patients.
  C. **Management**
    1. **Nutritional status** should be improved in cancer patients with glucose intolerance, if feasible. Management of substantial hyperglycemia on account of tumor is effected by control of the neoplasm and by administration of insulin or oral hypoglycemics as needed.
    2. **Hyperosmolar coma** must be vigorously treated with fluid replacement of volume losses with intravenous saline until the blood pressure is stable. Insulin infusion (1 to 4 U/hour) usually controls the hyperglycemia.

XII. Hypoglycemia

  A. **Mechanisms.** Insulin-like substances may be produced by some tumors, especially large retroperitoneal sarcomas and occasionally other cancers. Hepatocellular carcinomas and extensive liver metastases from a variety of primary sites may deplete glycogen stores and impair gluconeogenesis. Insulinoma is discussed in Chapter 15, section VI.C.
    1. **Etiologies of hypoglycemia**
      a. **Malignant tumors**
        1. Insulinoma
        2. Large retroperitoneal tumor
        3. Hepatocellular carcinoma
        4. Extensive hepatic metastasis
      b. **Drugs**
        1. Surreptitious or therapeutic insulin administration
        2. Oral hypoglycemic agents
        3. Alcohol
        4. Salicylates
        5. Jamaican vomiting sickness (akee fruit)
        6. Quinine (in antimalarial doses)
      c. **Metabolic disorders**
        1. Starvation
        2. Chronic liver disease
        3. Hypoadrenalism
        4. Hypopituitarism
        5. Myxedema
        6. Glycogen storage diseases
        7. Reactive hypoglycemias (e.g., prediabetes, postgastrectomy)
    2. **Pseudohypoglycemia.** Falsely low glucose levels may occur in patients with marked granulocytosis, especially patients with myeloproliferative disorders, because of *in vitro* consumption of glucose.
  B. **Diagnosis**
    1. **Symptoms and signs.** Tumor-associated hypoglycemia produces mental status change, fatigue, convulsions, or coma. Some patients show features of fasting hypoglycemia, such as an altered morning personality that improves after breakfast. Tremors, sweating, tachycardia, and hunger pangs are suggestive of acute decrease in blood sugar level.
    2. **Laboratory studies.** A blood glucose concentration of less than 40 mg/dL establishes the presence of hypoglycemia. Further evaluation of fasting hypoglycemia is discussed in Chapter 15, section VI.C. Patients who surreptitiously abuse insulin should have C peptide and insulin serum levels measured. Absent C peptide with elevated insulin level suggests the diagnosis of exogenous insulin administration.
  C. **Management**
    1. **Intravenous glucose.** Any patient with suggestive signs, symptoms, or unexplained coma should have a blood sample drawn for glucose determination, followed immediately by rapid IV infusion of 50 mL of 50% dextrose solution. Serum glucose can remain low even while concentrated glucose solutions are being administered. All patients with glucose levels of less than 40 mg/dL and symptomatic patients with glucose levels of less than 60 mg/dL should be treated by continuous infusion of 20% glucose at 50 to 150 mL/hour; rates are adjusted to maintain glucose levels higher than 60 mg/dL. Blood glucose levels are measured every 3 to 4 hours until stabilization occurs.
    2. **Glucagon,** 1 mg IM, also raises blood glucose by promoting glycogenolysis and gluconeogenesis.
    3. **Octreotide,** a somatostatin analogue, can decrease insulin hypersecretion.
    4. **Other measures.** If the blood glucose cannot be increased to safe levels with infusions, prednisone or diazoxide should be administered (see Chapter 15, section VI.C.2.d).

XIII. Tumor lysis syndrome

  A. **Mechanisms.** Effective chemotherapy of several malignancies may result in the massive release into the blood of potassium, phosphate, uric acid, and other breakdown products of dying tumor cells. Hypocalcemia may occur with severe hyperphosphatemia. Tumor lysis syndrome develops within hours to a few days of treatment for the underlying neoplasm.
    1. **Associated tumors** most commonly are acute leukemia, Burkitt lymphoma, and occasionally other lymphoreticular malignancies. The syndrome rarely occurs after the treatment of solid tumors.
    2. **Life-threatening complications** include renal failure from hyperuricemia and cardiac arrhythmias from hyperkalemia or hypocalcemia.
  B. **Diagnosis**
    1. **Physical examination.** Oliguria may call attention to the metabolic disorders. Tetany may be a presenting feature. Cardiac arrhythmias or cardiopulmonary arrest develop if the process is not controlled.
    2. **Laboratory studies.** Patients treated for acute leukemia or Burkitt lymphoma should have measurements of serum levels of potassium, calcium, phosphate, uric acid, and creatinine performed daily for 1 week and every few hours if the syndrome develops.
  C. **Management.** Vigorous intravenous hydration with half-normal saline is initiated. Severe metabolic problems are treated as follows:
    1. Hypocalcemia. See section II.C.
    2. Hyperphosphatemia. See section III.C.
    3. Hyperkalemia. See section VII.C.
    4. Hyperuricemia. See section IX.C.
    5. Hemodialysis may be necessary on an emergency basis for patients who do not respond to treatment or who develop renal insufficiency.

Suggested Reading

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Chapter 28 Cutaneous Complications

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I. Metastases to the skin

A. **Incidence and pathology.** Skin metastases occur in 25% of patients with breast carcinoma, 7% of patients with lung cancer, 5% of patients with renal cancer, 3% of patients with colon cancer, and 1% to 2% of patients with other solid tumors. Tumor extension or metastasis to the skin also commonly occurs with oral cavity carcinoma or malignant melanoma. Iatrogenic metastases as a result of invasive procedures are exceedingly rare. T-cell lymphoma characteristically involves the skin.

B. **Natural history.** Metastases to the skin may be delayed 10 to 15 years after the initial surgical treatment of primary melanoma, breast carcinoma, and renal cancer or may be the first indication of an internal malignancy. Draining fistulas may connect the skin to serosal surfaces. Large, bulky, malodorous masses may form.

   1. **Distribution.** Skin involvement most often occurs in a region near the primary tumor but may occur anywhere.
      a. **Breast cancer** that metastasizes to the skin typically involves the chest wall and scalp.
      b. **Lung cancer.** Cutaneous metastases most commonly appear on the chest wall or scalp. The small cell type of lung cancer tends to metastasize to the skin of the back. Lung cancer also has a rare but peculiar tendency to metastasize to the anal area, finger tips, or toes.
      c. **Gastrointestinal tract cancers** most commonly metastasize to the skin of the abdominal wall, often as closely grouped nodules around the umbilicus (see section 1.f). Anal cancer metastases to skin involve unusual sites, such as the scalp, eyelid, nose, or legs.
      d. **Urinary tract cancers.** Renal and bladder cancers most commonly metastasize to the skin of the lower abdominal wall, genitalia, or scalp, often in closely grouped clusters. Renal cancer may metastasize to unusual areas, such as the nose, eyelids, or finger tips. Prostate cancer may produce a zoster-like distribution of lesions over the flank because of lymphatic spread.
      e. **Melanoma** typically produces multiple skin metastases with some sparing only of anal areas. The face, scalp, torso, and proximal extremities may be diffusely involved with multiple nodular tumors. Placental and fetal metastases are known to occur.
      f. **Umbilical metastases** ("sister Mary Joseph's nodules") are nearly always adenocarcinomas. The primary site is most likely to be the gastrointestinal tract, but it may be the ovary or endometrium. Umbilical masses must be considered malignant until proved otherwise.
   2. **Prognosis.** The prognosis of patients with skin metastases depends on the type of tumor and what other areas are involved. The average survival time from the recognition of skin metastases is 3 months but can be years for lymphomas, melanoma, and breast cancer.

C. **Diagnosis**
   1. **History and physical examination**
      a. **Nodular lesions** begin as subepidermal mobile masses. The nodules enlarge gradually or rapidly, invade the overlying epidermis, become fixed, and occasionally ulcerate. Nodular masses in the dermis are firm, rubbery, or stony-hard. The lesions are usually painless but may be painful and tender if they evolve rapidly. Early lesions usually are flesh-tone to pink. Invasion of the overlying epidermis is associated with purplish discoloration and progressive induration that expands radially. Melanoma lesions may be jet-black. In some patients, ecchymoses or hair loss develops over subepidermal tumor masses.
      b. **Diffuse lesions** are most liable to develop in T-cell lymphomas and are characterized as diffusely indurated and erythematous skin. Diffuse infiltration of subcutaneous tissues by solid tumors is frequently manifested by tender swellings without nodularity or discoloration.
      c. **Inflammatory metastatic carcinoma** (carcinoma erysipelatoides) is associated most frequently with breast cancer but also occurs with cancers of the lung, ovary, uterus, vulva, pancreas, stomach, rectum, and melanoma.
   2. **Biopsy.** In patients with known solid malignancy, biopsy may be necessary to exclude treatable diseases with a similar morphology, such as opportunistic infection. If visceral malignancy was not known, cutaneous metastasis initiate further evaluation.
      a. **Small nodules** can be readily excised *in toto*.
      b. **Diffuse skin masses** can be evaluated by punch biopsy.
      c. **Subcutaneous spreading solid tumors** may be incised deeply without locating an identifiable mass; histologic examination demonstrates cancer in grossly normal tissue.

D. **Management**
   1. **Tumors involving large areas of skin** may be treated with cytotoxic or hormonal agents; the regimen is determined by the kind of primary tumor.
   2. **Localized skin metastases** are treated with RT, local excision, or cryotherapy.
   3. **Intralesional thiotepa** may be used *if only a few nodules exist* and other therapy is unavailable, is contraindicated, or fails to cause tumor regression. Thiotepa is absorbed and should not be used if other myelosuppressive therapy is being administered. Injection of thiotepa is done as follows:
      a. Thiotepa, 30 mg (two vials), is dissolved in 5 to 10 mL of normal saline in a Luer-Lok syringe equipped with a 21-gauge needle.
      b. The skin is anesthetized with a generous spray of ethylene chloride.
      c. The thiotepa is forcibly injected into the tumor nodule until it appears white and uniformly infiltrated. Injections may be repeated weekly.
      d. Eventually the tumor becomes blackened and necrotic and sloughs. Healing with normal skin usually occurs after about 6 to 8 weeks.

II. Paraneoplastic cutaneous diseases
The etiology of paraneoplastic cutaneous disease is unknown. Some syndromes may be mediated by immune mechanisms.

A. **Bowen's disease** is intraepithelial (*in situ*) squamous cell carcinoma. The lesions typically appear as eczematous, scaly, red-brown plaques. Studies have questioned earlier work that linked Bowen's disease to internal malignancy.
   1. **Associated tumors** include cancer of the hypopharynx, larynx, lung, prostate, breast, ovary, esophagus, stomach, kidney, and bladder.
   2. **Diagnosis.** Biopsy of the scaling lesion must be done, and if it proves to be Bowen's disease arising on sun-protected skin, a search for a possible underlying malignancy should be considered.
   3. **Therapy.** Local therapy is the same as for other squamous skin cancers (Chapter 16, Basal Cell and Squamous Cell Carcinoma, section VI).

B. **Paget's disease** presents as an erythematous patch on the breast areola, vulva, or other skin area. Patients with unilateral nipple eczema are suspected of having Paget's disease if topical therapy fails to resolve the patch.
   1. **Associated tumors**
      a. **Mammary Paget's disease** is almost invariably associated with *an underlying ductal cancer of the breast*.
      b. **Extrmammary Paget's disease** is associated with *genital or visceral cancer* in about 50% of cases.
   2. **Diagnosis**
      a. Bilateral nipple eczema is usually benign and should be treated with topical steroid creams and avoidance of possible allergens in clothing. If the rash persists, a biopsy is indicated. All patients with suspected Paget's disease should have a biopsy. If Paget's disease is proved, it is necessary to evaluate both breasts for underlying malignancy.
      b. Biopsy proof of extramammary Paget's disease mandates search for a primary tumor.
   3. **Therapy.** Excision of extramammary Paget's disease is done whenever possible. Mammary Paget's disease with underlying cancer is managed the same way as is primary breast cancer.

C. **Acanthosis nigricans** is a black-to-brown warty eruption occurring in intertriginous areas (the axillae, groins, under the breast) as well as on the palms and soles. The lesions resemble dirty skin during the early phases.
   1. **Associated tumors.** Acanthosis nigricans resulting from a malignancy is associated with abdominal cancer in 80% of patients; primary gastric cancer constitutes 60% of these patients. Other tumors include cancers of the pancreas, liver, colon, ovary, lung, and breast. The dermatosis precedes evidence of the malignancy in 20% of cases. Malignant causes of acanthosis nigricans are associated with rapid progression of the skin lesions and an 80% mortality rate in the first year after diagnosis.
   2. **Benign causes of acanthosis nigricans**

      a. Acromegaly, gigantism

      b. Adrenal insufficiency

      c. Hyperthyroidism, hypothyroidism

      d. Lipodystrophy

      e. Diabetes mellitus

      f. Syndrome of hirsutism, obesity, amenorrhea, and acanthosis nigricans

      g. Inherited abnormality in humans (and Swedish dachshunds)

   3. **Diagnosis** is established by inspection of the lesions. Biopsy is not essential.

   4. **Therapy** must control the underlying tumor. The dermatosis may regress or temporarily disappear when the cancer is removed.

D. **Erythema gyratum repens** is a rare condition manifested by undulating bands of urticarial eruptions over the entire body. Alternating bands of red and white streaks give the appearance of tiger stripes or knotty pine.

   1. **Associated tumors.** Erythema gyratum repens is nearly always associated with malignancy, usually rectal, esophageal, head and neck, lung, breast, or uterine cervical cancers.

   2. **Therapy** is directed at control of the underlying disease and treatment of pruritus.

E. **Dermatomyositis** (DMS) presents with symmetric proximal muscle weakness and a violaceous rash that is most prominent in sun-exposed areas. In the beginning, periorbital changes develop, such as edema, erythema, and bluish-red discoloration ("heliotrope ring"). Later, purplish plaquelike lesions appear over the knuckles (Gottron's papules), elbows, and other stretch areas of the skin. Some patients have muscle weakness without the skin rash (polymyositis) or the rash without myositis.

   1. **Associated tumors.** About 25% of patients with DMS have, had, or will develop underlying cancer. Breast cancer is the tumor most commonly associated with DMS. Lymphoma, melanoma, and cancers of the nasopharynx, lung, stomach, bowel, urinary bladder, and ovary are also associated with DMS. The cancer is diagnosed before DMS occurs in one third of patients, concurrently in one third, and months to years afterward in one third.

   2. **Diagnosis.** The characteristic skin rash or progressive proximal muscle weakness suggests the diagnosis of DMS. Diagnostic features of myositis include elevated serum creatine phosphokinase and aldolase, an inflammatory pathology on muscle biopsy, and myopathic features on electromyogram studies.

   3. **Therapy.** The myopathy tends to be progressive unless the underlying tumor is controlled. Cyclophosphamide, 50 mg PO twice daily, with prednisone, 40 mg/m^2 PO daily, may retard symptoms in some patients.

F. **Circinate erythemas.** Erythema figuratum perstans is a circular elevation of the skin that remains stable for weeks to months. Initially, erythema annulare centrifugum is a small erythematous area that slowly enlarges, leaving a central circle of normal-appearing skin. Lesions may be pruritic.

   1. **Associated tumors** include lymphoma and, occasionally, visceral cancer. Circinate erythemas are associated less commonly with tumors than with nonmalignant diseases (especially collagen vascular syndromes, angiitides, and infections). Many cases are idiopathic.

   2. **Diagnosis** is made by inspection.

   3. **Therapy** is directed at control of the underlying illness.

G. **Hyperkeratosis,** particularly of the palms and soles, occurs as a result of tylosis palmaris et plantaris, chronic arsenic exposure, or an idiopathic paraneoplastic syndrome.

   1. **Associated tumors**

      a. Tylosis is a hereditary syndrome associated with esophageal cancer.

      b. Arsenical keratoses and idiopathic hyperkeratoses are associated with squamous skin cancer and a large variety of visceral tumors, including cancers of the lung, stomach, ovary, and genitourinary tract.

   2. **Diagnosis.** Hyperkeratosis is usually obvious on inspection.

   3. **Therapy.** Propylene glycol and salicylic acid (Keralyt gel) may help to remove excess skin.

H. **Acquired ichthyosis** is a condition of the skin appearing as fish-scale– like patches. Lesions appear over the body surface, particularly on the extremities; palms and soles are relatively spared.

   1. **Associated tumors.** Hodgkin lymphoma is the malignancy most frequently associated with acquired ichthyosis. It also occurs with breast cancer, non-Hodgkin lymphoma, and multiple myeloma.

   2. **Diagnosis.** Ichthyosis in childhood is not rare. The onset of ichthyosis in a previously normal adult, however, suggests a possible underlying cancer. Acquired ichthyosis is not a specific sign of cancer because it may be seen in a variety of other conditions such as leprosy and sarcoidosis.

   3. **Therapy.** Effective antitumor therapy often eliminates the ichthyosis. A urea cream is applied liberally to the affected areas and wiped off while showering. Patients are advised to keep their environment humidified and to use skin emollients.

I. **Pachydermoperiostosis** exhibits thickening of skin and creation of new skin folds (leonine facies). The scalp, forehead, lids, ears, and lips are the typical sites. The tongue, thenar and hypothenar eminences, elbows, and knees may be enlarged. The fingers are clubbed.

   1. **Associated tumors.** The familial form of pachydermoperiostosis is not usually associated with malignant tumors. The acquired variety occurs almost exclusively in patients with undifferentiated lung cancer. Clubbing and hypertrophic osteoarthropathy are also associated with a variety of nonmalignant disorders.

   2. **Diagnosis** is made by inspection. Biopsy shows thickening of the horny layer and hypertrophy of the sweat and sebaceous glands.

   3. **Therapy.** No specific management is available other than control of the underlying cancer.

J. **Vitiligo** is the hypopigmentation of skin due to the loss of melanocytes.

   1. **Associated tumors.** Melanoma is most common; patients with metastatic melanoma and vitiligo tend to survive longer than patients with metastatic melanoma without vitiligo.

   2. **Diagnosis** is made by inspection. Vitiligo or a halo nevus may rarely be a sign of an occult melanoma.

   3. **Therapy.** No specific therapy can be recommended except control of the malignancy. Vitadye lotion can be used to provide cosmetic camouflage.

K. **Sweet's syndrome** (acute febrile neutrophilic dermatosis) manifests as suddenly appearing, painful, erythematous plaques or nodules, or both, typically on the upper extremities, head, and neck. Fever and elevated peripheral neutrophils are usually present. About 15% of cases have an associated neoplasm.

   1. **Associated tumors.** Acute myelogenous leukemia (most common malignant association); lymphoma, myelodysplastic syndromes, myeloproliferative disorders; genitourinary, breast, and gastrointestinal cancers.

   2. **Diagnosis.** Skin biopsy shows a neutrophilic dermatosis without vasculitis, often with karyorrhexis and endothelial swelling.

   3. **Therapy.** Systemic corticosteroids dramatically resolve manifestations.

L. **Glucagonoma syndrome** (necrolytic migratory erythema) is caused by tumors of the pancreatic a cells. The skin disease, initially localized to the groin, waxes and wanes. Glucagonomas are discussed in Chapter 15, section VI.D.

M. **Cutaneous flushing** is associated with carcinoid syndrome (see Chapter 15, section II) and mastocytosis (see Chapter 19, section IV).

N. **Miscellaneous skin diseases associated with visceral cancers**

   1. **Alopecia mucinosa** may develop during the course of lymphoreticular neoplasms as a consequence of mucinous degeneration of collagen around hair follicles and sebaceous glands. The resultant alopecia is unrelated to therapy.

   2. **Bazex's syndrome** (acrokeratosis paraneoplastica) is the psoriasiform changes of the face and extremities associated with malignancy of the upper respiratory or GI tracts.

   3. **Erythema multiforme** is rarely associated with cancer and is usually caused by medications or infectious processes such as herpes simplex. The typical "bull's eye" lesions may appear anywhere, but they are most noticeable on the palms, extremities, and torso.

   4. **Erythromelalgia** presents as painful, warm extremities that appear erythematous. Myeloproliferative diseases are the most common associated malignancies. Aspirin provides relief.

   5. **Florid cutaneous papillomatosis** is a rare warty eruption of the extremities and trunk. All reported instances have been linked to internal malignancy, predominantly gastric adenocarcinoma.

   6. **Gardner's syndrome** is familial intestinal polyposis with various anomalies and cystic lesions, mostly on the face and extremities. Epidermal inclusion cysts are more common than sebaceous cysts (see Table 9.2 in Chapter 9).

   7. **Leser-Trélat sign** is defined by the sudden appearance and rapid increase in the number and size of seborrheic keratoses on previously normal skin. It is usually a rare manifestation of gastrointestinal cancer.

   8. **Malignant down** (acquired hypertrichosis lanuginosa). Extensive, sudden growth of lanugo-like hair, at first over the face but later over the entire body, has been most frequently observed in association with cancer of the lung, colon, and rectum. Hair may grow to be 10 to 15 cm in 2 months.

   9. **Multicentric histiocytosis** appears as cutaneous papules and nodules associated with arthritis. It is associated with a variety of solid and nonsolid tumors in 28% of presentations.

   10. **Paraneoplastic pemphigus,** which is most commonly associated with lymphoid tumors, is a bullous disease that usually presents with painful oral erosions and flaccid cutaneous blisters. In contrast to other forms of pemphigus, immunoglobulin G (IgG) antibodies bind to columnar and transitional epithelia during indirect immunofluorescence. Other immunoprecipitants are also unique. The skin disease is usually resistant to treatment and fatal.

   11. **Peutz-Jeghers syndrome** is familial intestinal polyposis associated with cutaneous manifestations. Within the first year of life, brown-to-black pigmented spots appear on the vermilion border of the lip; in the oral cavity; around the eyes, nose, and mouth; and on the fingers and toes. The spots usually disappear between puberty and 20 years of age (see Table 9.2 in Chapter 9).

12. **Pityriasis rosea–like eruptions, erythroderma, and exfoliative dermatitis** may complicate a variety of tumors, mostly lymphoma. Prednisone, 40 mg/m^2 PO daily, usually controls life-threatening exfoliation until the underlying cause is managed. In erythroderma and exfoliative dermatitis, a skin biopsy should be considered to exclude cutaneous T-cell lymphoma.
13. **Pityriasis rotunda** is a circular scaly patch appearing on the buttocks, trunk, and thighs. It is associated with hepatocellular carcinoma, gastric cancer, and other malignancies.
14. **Porphyria cutanea tarda** (PCT) is a blistering disease that appears in skin exposed to sunlight. Hepatocellular carcinoma and metastatic liver tumors are occasionally associated with paraneoplastic PCT.
15. **Pruritus.** Generalized pruritus is most frequently associated with Hodgkin lymphoma, lymphocytic leukemia, mycosis fungoides, and polycythemia rubra vera. Localized pruritus has been associated with brain tumors (nostrils) and squamous cell carcinoma (vulva).
16. **Pyoderma gangrenosum** appears as painful skin ulcers with a necrotic base and a purplish border. Of all malignant associations, it is most commonly found with acute myelogenous leukemia. It is also associated with myeloma, lymphoma, myeloproliferative diseases, and solid tumors.
17. **Scleroderma** is associated with bronchoalveolar carcinoma of the lung.
18. **Tripe palms** resembles bovine foregut and appears as thickened palmar skin with exaggerated dermatoglyphics. More than 90% of patients with tripe palms have associated malignancy, most frequently of the lung, stomach, and genitourinary tract.
19. **Urticaria pigmentosa** usually presents with reddish brown papules that produce urtication when rubbed (Darier's sign). This condition is due to increased mast cells in the skin. It is rarely associated with systemic mastocytosis and mast cell proliferation in the bone marrow and viscera.
20. **Vasculitis,** mainly leukocytoclastic angiitis or polyarteritis nodosa, is associated with hematologic malignancy.

III. Adverse effects of radiation to the skin

Modern equipment has greatly decreased both acute and late skin damage. The severity of skin changes is dependent on treatment site, dose, dose rate, beam energy, beam quality, and beam direction. Beams passing through the skin tangentially or through skin folds result in focal areas of more severe reaction.

A. **Early side effects**
   1. **Types of skin reactions**
      a. **Erythema** is a transient early response to RT.
      b. **Pigmentation** is rarely permanent and gradually disappears within 3 to 4 months.
      c. **Dry desquamation** (peeling) heals within 2 to 4 weeks.
      d. **Moist desquamation** (weeping) is often a desirable end point for treatment, particularly with primary skin tumors or dermal involvement by others tumors. Moist desquamation most commonly occurs around intertriginous areas and usually heals in 4 to 8 weeks.
      e. **Skin necrosis.** Focal epidermal and dermal loss can result from moist desquamation or from chronic compromise of connective tissue or blood vessels.
   2. **Management of skin reactions.** Severe erythema and moist desquamation are managed with cool water compresses for 10 minutes and are air-dried. Dry desquamation is treated with unscented lubricating ointments.
   3. **Precautions to prevent skin damage**
      a. Avoid local irritants, such as antiperspirants and alcohol.
      b. Do not apply tape within the current radiation portal because the epidermis may be removed with the tape.
      c. Be sure that no physical irritants (such as straps, belts, or collars) are rubbing against the irradiated skin.
      d. Avoid direct sun on the treatment field, both during irradiation and even years afterward. Hats, protective clothing, and sunscreen lotions are advised.
      e. Skin lubricants and moisteners may help.
B. **Late skin changes**
   1. **Mild late (benign) changes.** Even minimal, transient radiation therapy (RT)–induced changes result in some late, often clinically inapparent, skin damage. Biologically and histologically, the skin never completely recovers. The skin may always show altered pigmentation, decreased natural oils, or woody subcutaneous fibrosis (less than 5% of patients).
   2. **Severe late (benign) changes** (marked atrophy, hyperkeratosis, fissures, telangiectasis, ulceration, and fragility) are rare with modern equipment and techniques. Atrophy is best treated by the avoidance of trauma and the use of ointments. Late irradiation skin ulcers may have to be treated by surgical excision and repair.
   3. **Radiation-induced skin cancer** is a problem that arose in the early years of RT development, especially among patients who were occupationally exposed or treated for benign skin conditions. The likelihood of a new skin cancer arising in an RT portal is greater than normal, but less than 0.1% of all skin cancer has occurred in these patients. Squamous cell carcinoma, basal cell carcinoma, and melanoma are all reported.

IV. Adverse cutaneous effects of chemotherapy

A. **Skin and nail changes associated with cytotoxic agents**
   1. **Acne.** Actinomycin D, methotrexate (uncommon), steroids
   2. **Bullous pemphigoid.** Fluorouracil (rare)
   3. **Dermatitis, nonspecific** (uncommon). Methotrexate, mercaptopurine, thioguanine, fluorouracil, chlorambucil, nitrogen mustard, actinomycin D, mithramycin, mitomycin C; mitotane, hydroxyurea, procarbazine
   4. **Erythroderma.** Bleomycin
   5. **Hyperpigmentation.** Busulfan, fluorouracil, bleomycin ("flagellate"); rarely, doxorubicin (Adriamycin), cyclophosphamide
   6. **Local irritation after drug infiltration** ("irritant" drugs). Carmustine, cisplatin, dacarbazine, etoposide, fluorouracil, liposomal doxorubicin, mithramycin, mitoxantrone, paclitaxel, streptozocin, vinorelbine
   7. **Local necrosis after drug infiltration** ("vesicant" drugs). Dactinomycin, daunorubicin, doxorubicin, epirubicin; idarubicin, mechlorethamine (nitrogen mustard), mitomycin C, vinblastine, vincristine, vindesine
   8. **Nails** (dark bands or loss). Bleomycin, fluorouracil, busulfan; rarely, doxorubicin, cyclophosphamide
   9. **Photosensitivity.** Fluorouracil, methotrexate, vinblastine
   10. **Pressure area vesiculation or ulceration.** Fluorouracil, methotrexate
   11. **Radiation recall** (erythema or moist desquamation over a previous radiation port). Doxorubicin, daunorubicin, bleomycin, actinomycin D, methotrexate, procarbazine
   12. **Sclerodermoid changes.** Bleomycin, docetaxel
   13. **Telangiectasis.** Topical nitrogen mustard, topical nitrosoureas, topical fluorouracil, l-asparaginase
   14. **Ulceration near malleoli.** Hydroxyurea
   15. **Urticaria, angioedema.** Doxorubicin, daunorubicin, l-asparaginase, chlorambucil, cyclophosphamide, melphalan, methotrexate, nitrogen mustard, procarbazine
B. **Extravasation of antitumor agents.** "Flare" during an infusion occurs in about 3% of cytotoxic agent infusions, involves pruritus and patchy erythema along the course of the vein, disappears within 30 minutes without sequelae, and does not indicate extravasation. Subcutaneous infiltration of irritant drugs (see section A.6) can cause a burning pain and sometimes erythema at the injection site, but without necrosis. Application of cold or heat and elevation of the affected extremity usually relieve symptoms without the need for further therapy.

Subcutaneous infiltration of vesicant cytotoxic agents (see section A.7), on the other hand, usually causes immediate and intense pain. Edema and painful erythema develop within a few hours, and marked induration within a few days. Necrosis with ulceration usually develops within 1 to 4 weeks, if it is to occur (about 30% of infiltrations) and almost never heals spontaneously. The necrosis may involve fascia, paratenon, and periosteum. A reasonable approach to the subcutaneous infiltration of vesicant drugs is as follows:

   1. **Stop the drug administration** with any questionable pain or swelling at the intravenous site. Using the original indwelling needle or catheter, try to aspirate drug from the infiltrated site.
   2. **Apply cold compresses for all drugs except vinca alkaloids** for 30 to 60 minutes and then 15 minutes off and on for 1 day. Vinca alkaloid extravasations require dry warm compresses. Avoid pressure on the affected area.
   3. **Elevate the affected extremity** for 24 to 48 hours. Physical therapy is prescribed as needed.
   4. **Administer an antidote,** when applicable (most attempted antidotes have failed)
      a. **Infiltration of vinca alkaloids.** Infiltrate the affected area with 150 U (1 mL) of hyaluronidase within 1 hour of extravasation.
      b. **Infiltration of mechlorethamine** (and cisplatin possibly). Immediately inject 0.17 M sodium thiosulfate (1.6 mL of 25% solution diluted in 8.4 mL of sterile water). Inject 2 mL of solution for each 1 mg of mechlorethamine infiltrated. Sodium thiosulfate acts as an alternative substrate for alkylation by mechlorethamine to form nontoxic compounds.

  c. **Infiltration of doxorubicin and other vesicant drugs.** Apply dimethyl sulfoxide (DMSO, 1.5 mL of a 50% solution) to the site every 6 to 8 hours for 7 to 14 days, and allow it to air dry (do not cover). DMSO has potent free-radical scavenging properties. DMSO is anecdotally reported to be helpful for infiltrations of doxorubicin, mitomycin C, and some other cytotoxic agents. Local injection of any medication has not been proved beneficial.

 5. **Surgical débridement.** Early referral to a plastic surgeon may prevent subsequent tissue damage, particularly for lesions that are large or on the hand or wrist. Once painful necrosis appears, surgical débridement and skin grafting are indicated. The best clinical indicators for subsequent surgery are significant worsening of the condition after 48 hours or pain at the extravasation site 1 to 2 weeks after the event. Physical therapy is resumed 1 week after surgery.

V. Other cutaneous complications

 A. **Skin pigmentation**
  1. **Gray discoloration** of the skin because melanosis may develop in patients with extensive malignant melanoma
  2. **Periorbital purplish discoloration** can develop in patients who have amyloid deposition in the eyelids from infiltration and purpura. The syndrome of postproctoscopic palpebral purpura is well described in these patients.
 B. **Skin infections** may be caused by bacteria, fungi, or viruses in cancer patients. Nonspecific rashes may be the only clue for infection and thus a skin biopsy may be necessary.
 C. **Pruritus** is discussed in Chapter 5, section VII.A.
 D. **Preventive skin care in the dying patient** is discussed in Chapter 5, section VII.B.
 E. **Alopecia** is discussed in Chapter 5, section VII.C.
 F. **Necrotic, malodorous tumor masses** are discussed in Chapter 5, section VIII.

Suggested Reading

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Chapter 29 Thoracic Complications

Donna L. Walker and Dennis A. Casciato

I. Superior vena cava (SVC) obstruction

A. **Epidemiology and etiology**
   1. **Malignant etiologies** (85% to 95% of cases)
      a. **Lung cancer** (about half of the small cell type) accounts for 80% of cases of SVC obstruction. SVC syndrome develops in about 5% of patients with lung cancer.
      b. **Malignant lymphoma** accounts for 15% of cases of SVC obstruction. Nearly all cases have high-grade histology. Hodgkin lymphoma or low-grade nodular lymphomas rarely cause SVC obstruction.
      c. **Other etiologies.** Metastatic disease (most commonly the result of breast adenocarcinoma or testicular seminoma), sarcomas, and other malignancies account for the small remainder of cases.
   2. **Benign etiologies** (less than 15% of cases)
      a. **Mediastinal fibrosis**
         1. Idiopathic fibrosing mediastinitis
         2. Histoplasmosis (in endemic regions), actinomycosis
         3. Tuberculosis and pyogenic infections
         4. Associated with Riedel's thyroiditis, retroperitoneal fibrosis, sclerosing cholangitis, and Peyronie's disease
         5. After radiation therapy (RT) to the mediastinum
      b. **Thrombosis of vena cava**
         1. Long-term central venous catheterization, transvenous pacemakers, balloon-tipped pulmonary artery catheters, peritoneal venous shunting
         2. Polycythemia vera, paroxysmal nocturnal hemoglobinuria
         3. Behçet's syndrome
         4. Idiopathic
      c. **Benign mediastinal tumors**
         1. Aneurysm of aorta or right subclavian artery
         2. Dermoid tumors, teratomas, thymoma
         3. Goiter, sarcoidosis
B. **Pathogenesis**
   1. **Obstruction and thrombosis.** Tumors growing in the mediastinum compress the thin-walled vena cava, leading to its collapse. Venous thrombosis because of stasis or vascular tumor invasion often appears to be responsible for acute-onset SVC syndrome.
   2. **Collateral circulation.** Vena cava obstruction caused by malignancy often progresses too rapidly to develop sufficient collateral circulation, which might alleviate the syndrome. If the obstruction occurs above the azygous vein, the obstructed SVC could then drain into the azygous system. The azygous vein, however, is frequently obstructed by malignancy below its origin.
   3. **Incompetent internal jugular vein valves,** a rare occurrence, is a dire emergency that is manifested by filling of these veins. Patients who present with this finding die within hours or days of massive cerebral edema unless treatment is immediately instituted.
C. **Diagnosis.** The diagnosis is usually based on the clinical findings and the presence of a mediastinal mass. *SVC syndrome rarely has to be treated before a histologic diagnosis is made.*
   1. **Symptoms** of SVC syndrome are present for less than 2 weeks before diagnosis in 20% of patients and for more than 8 weeks in 20%.
      a. The most common presenting symptoms are shortness of breath (50% of patients), neck and facial swelling (40%), and swelling of trunk and upper extremities (40%). Sensations of choking, fullness in the head, and headache are also frequent complaints. Chest pain, cough, lacrimation, dysphagia, hallucinations, and convulsions are less frequent.
      b. SVC obstruction may occasionally be accompanied by spinal cord compression, usually involving the lower cervical and upper thoracic vertebrae. The SVC syndrome consistently precedes spinal cord compression in these cases. The coexistence of these two complications should be seriously suspected in patients with upper back pain.
   2. **Physical findings.** The most common physical findings are thoracic vein distention (65%), neck vein distention and edema of face (55%), tachypnea (40%), plethora of the face and cyanosis (15%), edema of upper extremities (10%), and paralysis of vocal cords and Horner's syndrome (3%). Veins in the antecubital fossae are distended and do not collapse when elevated above the level of the heart. Retinal veins may be dilated on funduscopic examination. Dullness to percussion over the sternum may be present. Laryngeal stridor and coma are grave signs.
   3. **Radiographs**
      a. **Chest radiographs** demonstrates a mass in more than 90% of patients. The mass is located in the right superior mediastinum in 75% of cases and is combined with a pulmonary lesion or hilar adenopathy in 50%. Pleural effusions are present in 25% of cases, nearly always on the right side.
      b. **Chest computed tomography** (CT) **scan.** Contrast-enhanced CT can pinpoint the area of obstruction, the degree of occlusion, and the presence of collateral veins. Although not needed if RT is planned, CT scans may be helpful in determining candidacy for percutaneous stenting procedures.
      c. **Superior venocavogram.** Digital subtraction angiography demonstrates the exact site of obstruction and is the procedure of choice in planning stenting procedures. This information is rarely needed for localization of RT ports.
      d. **Magnetic resonance imaging** (MRI) **scans** of the cervical and upper thoracic vertebrae should be planned in patients with SVC syndrome and back pain, particularly in the presence of Horner's syndrome or vertebral destruction on plain films.
   4. **Histologic diagnosis** is important for identifying malignancies that must be treated with cytotoxic agents to improve survival (e.g., lymphoma, small cell lung cancer). After RT is started, tissue diagnosis becomes exceptionally difficult, if not impossible; biopsies of masses within radiation portals usually demonstrate nondescript necrosis shortly after irradiation is begun. Invasive biopsy procedures can be performed safely if there is no tracheal obstruction.
      a. **Cytology** of sputum is positive in 67% of patients and of pleural effusion fluid in nearly all patients with SVC syndrome.
      b. **Bronchoscopy** and bronchial brushings are positive in 60% of patients. Bronchoscopy and bronchial biopsy are rarely associated with serious complications when performed by experienced endoscopists.
      c. **Lymph node biopsy** of palpable nodes below the level of obstruction is desirable; biopsy of supraclavicular lymph nodes is associated with a substantial risk for bleeding. Biopsy of *palpable* scalene nodes in patients with SVC syndrome reveals tumor in 85% of cases; biopsy of nonpalpable, scalene nodes reveals tumors in only 30% to 40% of cases.
      d. **Transthoracic fine-needle aspiration** can be attempted for peripheral lesions that cannot easily be approached by bronchoscopy or in whom bronchoscopy results are nondiagnostic. The risk for pneumothorax is a small but real.
      e. **Minithoracotomy** nearly always results in a definitive histologic diagnosis. Bleeding points are usually visualized and can be controlled. Limited anterior thoracotomy should be considered in patients with early SVC syndrome and without productive cough, diagnostic bone marrow evaluation, pleural effusion, or palpable lymphadenopathy.
      f. **Mediastinoscopy** with biopsy is not recommended and may be contraindicated because of the high incidence of severe hemorrhage, neck edema, and failure of wound healing. When mediastinoscopy is performed on a highly selected group of patients, positive results are obtained in 80% of cases.
      g. **Bone marrow biopsy** is helpful in patients suspected of having small cell lung cancer or lymphoma, especially in patients with cytopenia or leukoerythroblastic blood smear.
D. **Management.** There is little clinical or experimental evidence that unrelieved SVC syndrome is life-threatening. Emergency treatment is indicated only in the presence of cerebral dysfunction, decreased cardiac output, or upper airway obstruction.
   1. **Supportive therapy.** Airway obstruction should be corrected and hypoxia treated by oxygen administration. Corticosteroids reduce brain edema and improve the obstruction by decreasing the inflammatory reaction associated with the tumor and early RT. Diuretics may be helpful.

2. **Stenting.** Percutaneous placement of self-expanding metal endoprostheses gives rapid symptomatic relief in 90% to 100% of patients. When available, stenting is the procedure of choice, especially in the setting of recurrent SVC obstruction after RT. Complications are infrequent, but interventional radiologists experienced in stent placement are not universally available.
3. **RT.** The total dose of RT varies between 3000 and 5000 cGy, depending on the general condition of the patient, severity of the symptoms, anatomic site, and histologic type of underlying malignant tumor. Symptoms may resolve dramatically even without establishment of patency of the SVC.
   a. **Response.** Improvement is evident within 3 to 7 days for most patients. Complete response is observed in about 75% of patients with lymphoma and in 25% with lung cancer. Virtually all patients with lymphoma have at least a partial response, whereas about 15% of patients with lung cancer experience no real benefit from treatment.
   b. **Median survival** is about 10 months for small cell lung cancer, and 3 to 5 months for other types of lung cancer.
   c. **Local relapse** and recurrent SVC syndrome occur in 15% to 20% of patients but rarely after RT for lymphoma.
4. **Chemotherapy** is indicated in patients with malignant lymphoma or with small cell lung cancer. Chemotherapy is used in combination with RT in these conditions.
5. **Anticoagulants** and antifibrinolytic agents rarely result in disappearance of caval thrombosis but may be used in conjunction with stent placement.
6. **Surgical decompression** of acute SVC obstruction and incompetence of jugulosubclavian valves consists of reconstructing or bypassing the SVC using a spiral saphenous vein graft or left saphenoaxillary vein bypass, which can be done under local anesthesia.

II. Pulmonary metastases

A. **Epidemiology and etiology**
1. **Incidence.** The lungs are the most frequent site of distant metastases for nearly all malignant tumors except those arising in the gastrointestinal tract.
2. **Dissemination.** Malignant melanoma, bone and soft tissue sarcomas, trophoblastic tumors, and renal cell, colonic, and thyroid carcinomas tend to spread to vascular routes and usually produce discrete metastatic lung nodules. Malignant tumors of the breast, pancreas, stomach, and liver may spread directly through lymphatic channels, involve mediastinal lymph nodes, and produce diffuse interstitial or lymphangitic infiltration, focal or segmental atelectasis, and pleural metastasis or effusion. Germ cell tumors and sarcomas may also involve the mediastinum.
3. **Metastatic sites**
   a. **Endobronchial metastasis** is not uncommon in Hodgkin lymphoma, hypernephroma, and breast adenocarcinoma.
   b. **Solitary pulmonary metastasis** is relatively uncommon but can occur in patients with carcinoma of the breast, uterus, testis, kidney, or urinary bladder or malignant melanoma.
   c. **Isolated pulmonary metastasis.** Osteogenic sarcoma, soft tissue sarcoma, and testicular carcinoma are the tumors that are most likely to have lung metastases without involvement of other organs. Renal and uterine carcinomas may also produce isolated lung metastases. Colonic adenocarcinoma and malignant melanoma rarely have pulmonary metastases without other organ involvement as well.
B. **Natural history and prognostic factors**
1. **Nodular lung metastases** have a highly variable course ranging from slow-growing cystic adenoid carcinoma to rapidly growing teratocarcinoma and osteogenic sarcoma.
   a. **Symptoms.** Most patients with solitary or multiple pulmonary metastases do not have symptoms; the presence of symptoms portends a poor prognosis.
   b. **Histology.** Well-differentiated tumors have a better prognosis than undifferentiated tumors. Melanoma has a worse prognosis than breast, colonic, or renal cell carcinoma.
   c. **Hilar lymphadenopathy** worsens the prognosis.
   d. **Tumor doubling time** (TDT) is calculated by plotting tumor volumes against time on semilogarithmic graph paper. Pulmonary metastases with a TDT of less than 40 days are associated with a distinctly poorer prognosis than those with a TDT of more than 60 days.
   e. **Disease-free interval** (DFI) is the time that elapses from resection of the primary tumor to detection of metastases. Patients with long DFIs have a better prognosis than patients with short DFIs.
   f. **Multiple metastases.** Multiple or bilateral pulmonary nodules usually, but not invariably, have a worse prognosis than single or unilateral metastases.
   g. **Amenability to chemotherapy.** Responsive tumors (e.g., trophoblastic and testicular tumors) obviously have a better prognosis.
2. **Lymphangitic pulmonary metastases** are rapidly lethal. Median survival is less than 2 to 3 months for patients without effective treatment.
3. **Central pulmonary metastases.** Malignant tumors that invade hilar or mediastinal structures may result in SVC obstruction, major airways obstruction, postobstructive pneumonia, and invasion of the pericardium, myocardium, or esophagus. Consequently, this type of pulmonary metastases is associated with a poorer prognosis than nodular metastases.
C. **Diagnosis**
1. **Symptoms and signs.** Most patients with solitary pulmonary metastasis do not have symptoms. Patients with multiple pulmonary metastases; central, hilar, or mediastinal metastatic involvement; or lymphangitic metastasis are more often symptomatic cough, chest pain, hemoptysis, or progressive dyspnea. Physical examination may be absolutely negative.
2. **Radiographic studies.** No current imaging modality can distinguish a benign tumor from a malignant tumor or a primary tumor from a metastasis. Plain films do not detect lesions smaller than 1 cm in diameter. CT scans can detect nodules as small as 0.5 mm in diameter, however. About half of patients with lymphangitic lung metastases have normal chest radiographs; the remainder of patients have interstitial changes that are indistinguishable from radiation fibrosis, chemotherapy-induced lung disease, or a variety of infectious processes.
3. **Sputum cytologies** are positive in only 5% to 20% of patients with nodular metastases.
4. **Pulmonary function studies.** *Lymphangitic* pulmonary metastases characteristically produce a restrictive defect with hypocapnia but without hypoxemia. Restrictive lung disease can be confirmed by finding impaired diffusing capacity for carbon monoxide Dlco and low residual and total-lung volumes.
5. **Bronchoscopy.** Bronchoscopy with biopsy or brushings of the lesion identified on chest radiograph may be necessary to establish the diagnosis in patients with a history of malignancy (especially with tumors that do not typically metastasize to the lung), pulmonary lesions appearing 4 to 5 years after the original tumor was resected, or lesions that are likely to be a new primary lung carcinoma.
D. **Management**
1. **Nodular lung metastases**
   a. **Surgery.** About 5% to 15% of patients with solid tumors become candidates for resection of pulmonary metastases at some time during the course of their disease. The type of histology, number of lesions, and whether they are bilateral do not appear to contraindicate resection or adversely influence the survival if the selection criteria discussed here are adhered to. Bilateral pulmonary nodules can be resected in one operation using a median sternotomy. The 5-year survival rate of patients who undergo successful resection is as high as 30%. Resection (preferably wedge resection) is the recommended treatment of pulmonary metastases in patients who meet all of the following criteria:
      1. The patient's general medical condition and pulmonary function status are suitable for surgery.
      2. The primary tumor is under control (no evidence of local recurrence).
      3. Metastases are limited to the lung and appear more than 1 year after definitive treatment of the primary lesion.
      4. Pulmonary metastases are encompassable and resectable.
      5. TDT is prolonged (more than 41 to 60 days).
      6. There is no other effective treatment.
   b. **RT** is useful for palliation of local complications of metastatic tumors, such as bronchial obstruction, vena cava obstruction, hemoptysis, or pain caused by tumor invasion of the chest wall.
   c. **Chemotherapy** or hormonal therapy has proved useful in responsive tumors and is curative in trophoblastic and nonseminomatous testicular tumors.
2. **Lymphangitic lung metastases** represent an emergent problem in diagnosis and management. Symptomatic relief of dyspnea can often be rapidly achieved with prednisone, 60 mg PO daily. Chemotherapy is effective in responsive tumors. Hormonal manipulation is usually ineffective or achieves a response too slowly to be helpful. Symptoms from refractory lymphangitic lung metastases may be palliated by low- dose lung irradiation.
3. **Terminal problems in patients with lung cancer** such as hemoptysis and air hunger are discussed in Chapter 5, section VI.C.

III. Malignant pleural effusions

A. **Pathogenesis**
1. **Etiology.** Malignant tumors causing pleural effusions are as follows (in order of decreasing frequency): lung cancer (especially adenocarcinoma), breast carcinoma, lymphoma, unknown primary, gastric carcinoma, ovarian carcinoma, melanoma, and sarcoma.
2. **Types of malignant effusions.** Pleural effusions are usually caused by direct involvement of the pleura by tumor or by lymphatic or venous obstruction or both. Central effusions, particularly those caused by lymphoma or nerve tissue tumors, may be chylous, and have high triglyceride and low cholesterol concentrations. Atelectasis, pneumonia, and severe hypoalbuminemia that complicates malignancy may also cause pleural effusion.
B. **Natural history.** Malignant pleural effusion is a sign of advanced disease. The pleural space is progressively obliterated by fibrosis and serosal tumor. Patients with carcinomatous pleural effusions have a mean survival of 3 months from the time of diagnosis, but this varies with the underlying tumor type.

C. **Differential diagnosis.** The differentiation of pleural fluid from pleural fibrosis or pulmonary consolidation may not be possible by physical examination or chest radiographs. Aspiration of fluid may be difficult because of loculation. Ultrasonography is helpful for identifying and sampling small pockets of effusion.

1. **Symptoms and signs.** Cough and dyspnea are the most common symptoms of pleural effusion. Dullness to percussion, decreased breath and voice sounds, decreased vocal fremitus, and egophony are the classic physical findings. The trachea may be shifted to the side opposite the effusion. Thickened pleura from fibrosis or neoplastic involvement also produce dullness and decreased vibration.

2. **Thoracentesis** should be performed in any patient with a suspected malignant, infectious, or empyematous pleural effusion. Pleural fluid should be assayed for protein, lactate dehydrogenase level, specific gravity, pH, glucose, cell count, cytology, and stained and cultured for bacteria (especially mycobacteria) and fungi. If the effusion appears chylous, triglyceride and cholesterol concentrations should be measured. Malignant effusions are usually exudative but may be transudative. Results of fluid examination frequently are nonspecific.

   a. **Discrimination.** The following findings characterize effusions as *exudates* rather than transudates:
      1. Total protein more than 3 g/dL or a pleural-to-serum protein ratio of more than 0.5
      2. Specific gravity higher than 1.018
      3. Pleural-to-serum LDH ratio of more than 0.6
      4. White blood cell count more than 2500/μL (counts less than 2500/μL are not definitive)
   b. **Cytology** is positive in half of malignant pleural effusions.
   c. **Leukocyte counts** in malignant pleural fluid may be low or high; the predominant cells may be either neutrophils or lymphocytes. Eosinophilia is nonspecific in pleural effusions and can be associated with cancer, infection, trauma, pulmonary embolism, and even prior thoracentesis.
   d. **pH.** In patients with bronchopneumonia, a pH less than 7.2 at the initial thoracentesis may be predictive for the development of an empyema that has to be drained by tube. Values of less than 7.2, however, may also be found in patients with malignancy or collagen vascular disease.
   e. **Tumor markers** or combination of markers have not been definitive in proving malignancy.

3. **Pleural biopsy.** Pleural needle (Cope) biopsy is a blind procedure and is less sensitive than cytology. Fiberoptic pleuroscopy may be particularly useful; the entire costal pleura and a good portion of the diaphragmatic and mediastinal pleura can be visualized, thus allowing direct biopsy of any pleural lesion.

D. **Management.** Respiratory insufficiency caused by malignant effusion may be relieved by removing up to 1500 mL of fluid by needle aspiration. The effusion should be later tapped dry if possible. In a few percentage of patients, no recurrence of the effusion develops after a single evacuation. In most cases, the effusion recurs, and more definitive methods of therapy are required.

1. **Chemotherapy.** Pleural effusion secondary to metastatic tumors that are sensitive to chemotherapy (lymphoma, breast or ovarian carcinoma) should be treated with appropriate combinations of agents. The results may be dramatic if the effusion presents early in the disease before resistance to the chemotherapeutic drugs develops. Pleural effusions that occur in the late or terminal stage are usually resistant to chemotherapy.

2. **RT.** Pleural effusions caused by mediastinal lymphadenopathy are best treated with RT.

3. **Pleurodesis** (visceroparietal pleural symphysis) is accomplished with tube thoracostomy.

   a. **Patient selection.** Pleurodesis should be performed in patients who meet the following conditions:
      1. The patient's symptoms (shortness of breath) are caused by the pleural effusion and not by lymphangitic or intrapulmonary metastasis (i.e., symptoms improve after aspiration of fluid).
      2. The pleural effusion recurs after repeated needle aspirations (two times) or rapidly reaccumulates (within a few days).
      3. The patient's life expectancy is estimated to be longer than 1 month (pleurodesis should not be done in terminally ill patients).
   b. **Drainage procedure**
      1. The chest tube is inserted in the most dependent location, preferably at the anterior axillary line. The pleural fluid is first allowed to drain through a water-seal gravity drainage system. Negative suction may be later applied to ensure completeness of drainage.
      2. When less than 100 mL drains in 24 hours, a chest radiograph is obtained to assess the amount of residual fluid and the extent of reexpansion of the underlying lung.
      3. The evacuation of pleural fluid may take 1 to 3 days. The expansion of the underlying lung is necessary to bring the visceral and parietal pleural surfaces in close proximity in preparation for symphysis. Injecting sclerosing agents without apposition of the pleural surfaces is ineffective and may result in loculation.
   c. **Instilling sclerosing agents**
      1. The chest tube is first cross-clamped and is cleaned with antiseptic solution. A narcotic is given to prevent pain.
      2. The sclerosing agent in 30 mL of normal saline is injected into the chest tube, which is then flushed with 50 mL of saline. Changing the patient's position to distribute the agent throughout the pleural space usually is not necessary.
      3. The chest tube should remain clamped for 6 hours for all other drugs. The pleural fluid is then allowed to drain, preferably with negative suction, until less than 100 mL drains in 24 hours.
      4. After a drug has been instilled, there may be a great deal of drainage because of pleural weeping from drug irritation. A nonfunctioning or blocked tube may produce complications (pain, atelectasis, and infection) and should be removed.
   d. **Choice of sclerosing agents.** Drugs and doses used for the treatment of malignant effusions are shown in Table 29.1. These agents are successful in 70% to 85% of cases.

Table 29.1 Drugs used for pleural and pericardial instillation

1. **Talc.** Asbestos-free sterilized talc may be used as a powder at thoracotomy (poudrage) or thoracoscopy (insufflation) or as a slurry through a chest tube. The last example is associated with efficacy rates of 90% to 100% in control of malignant pleural effusions.
2. **Doxycycline.** Replacement of parenteral tetracycline (no longer available) for pleurodesis with doxycycline has been suggested. Studies reveal that doxycycline may require repeat installations to achieve response rates of 60% to 85% with a relatively low cost.
3. **Antineoplastic agents.** Bleomycin is the most commonly used of the antineoplastic agents for control of malignant pleural effusion. It is associated with 60% to 85% response rates. This agent is nearly 50% systemically absorbed but rarely causes systemic effects. The antineoplastic agents are generally more costly than the alternatives.

   e. **Complications of pleural sclerosis**
      1. **Pneumothorax.** Suction may be applied to the chest bottles to reexpand the lung if the chest tube is not blocked. If the chest tube is obliterated (no fluid oscillation), insertion of a new chest tube is indicated.
      2. **Cough** may result from re-expansion of an atelectatic lung after the compressing pleural fluid is removed. This symptom is self-limited and may be advantageous because it further clears atelectasis.
      3. **Chest pain** may be secondary to the chest tube insertion or the instillation of drugs. Pain usually dissipates within 5 days but may require narcotics.
      4. **Fever** may be caused by atelectasis or pneumonitis or by the sclerosing agent.
      5. **Loculation of fluid** may be caused by inadequate drainage or the instillation of sclerosing agents before the lung has completely reexpanded. Injection of radiopaque material (Hypaque) into the pleural space followed by upright and lateral decubitus chest radiographs may confirm this problem. Trying to break the loculation by tube manipulation is not recommended.
      6. **Empyema and pleurocutaneous draining sinus** may occur when tumor seeds the chest tube site. Empyema may be the result of either contamination or bronchopleural communication.

4. **Pleurectomy** carries high morbidity and mortality and is indicated only for otherwise healthy patients in whom all more conservative measures have failed.

IV. Other pulmonary complications

A. **Chemotherapy lung**
   1. **Etiology**
      a. **Associated drugs.** Carmustine (BCNU), bleomycin, mitomycin C, methotrexate, cyclophosphamide, busulfan, melphalan, and cytarabine have been associated with pulmonary toxicity (Table 29.2). The pathogenesis of these reactions is unknown.

Table 29.2 Chemotherapy lung

  b. **Association with RT.** Cytotoxic drugs and thoracic RT, administered concomitantly or sequentially, may produce pulmonary toxicity. The interaction of RT with bleomycin has been particularly well documented in patients with testicular carcinoma. Severe pulmonary irradiation reactions have been associated with concurrent doxorubicin (Adriamycin) therapy, prior busulfan therapy, and concurrent or prior actinomycin D therapy; doxorubicin and actinomycin D have not been associated with pulmonary disease in the absence of RT.

 2. **Differential diagnosis.** Chemotherapy lung has no characteristic radiographic pattern, may be associated with a normal chest radiograph, or diffuse infiltrates. Hilar or mediastinal lymphadenopathy or a purely segmental or lobar pattern should make other diagnostic possibilities more likely. Establishing the diagnosis of drug pulmonary toxicity is often difficult because cancer patients may also have pulmonary abnormalities caused by the following:

  a. Chronic lung disease
  b. Opportunistic pulmonary infection
  c. Lymphangitic lung metastases
  d. RT of the thorax
  e. Pulmonary hemorrhage, collagen disease, vasculitis, or granulomatous angitis
  f. Pulmonary toxicity from oxygen therapy
  g. Pulmonary toxicity from blood component therapy
  h. Graft-versus-host disease

 3. **Diagnosis.** Drug-induced pulmonary toxicity may be insidious or acute in onset, and it rarely develops after the drugs have been discontinued. Clinical features are similar regardless of the specific drug involved.

  a. **Symptoms.** Dry cough and dyspnea are prominent.
  b. **Signs.** Fever, tachypnea, and rales are common. Incomplete or asymmetric chest expansion (respiratory lag) may be an early finding. Skin eruptions are common with methotrexate pulmonary toxicity.
  c. **Eosinophilia** is often an associated finding, especially if methotrexate or procarbazine have been used.
  d. **Chest radiographs** may be normal. The most typical abnormalities are bibasilar linear densities. Nodular, interstitial, alveolar, and mixed patterns also occur. Pleural effusions are distinctly uncommon.
  e. **Pulmonary function tests** usually show hypoxemia, a decreased Dlco, and a restrictive ventilatory defect (decreased vital and total-lung capacities).
  f. **Lung biopsy** may be necessary. Histology reveals acute and organizing interstitial pneumonia with hyaline membranes, atypical epithelial desquamation, and nodular inflammation or fibrosis. Busulfan lung toxicity may result in atypical, malignant-appearing cells on sputum cytology.

 4. **Management.** Prospective measurement of pulmonary function has not clearly decreased the incidence or severity of drug toxicity problems. The drugs should be discontinued in any patient who develops symptoms, signs, or abnormalities in pulmonary function tests or chest radiographs that suggest drug toxicity. Pulmonary toxicity may progress even after the drug is stopped. Treatment is mostly for control of symptoms. Administration of a pulse of high-dose glucocorticoids is suggested but not always helpful.

B. Radiation pneumonitis

 1. **Acute radiation pneumonitis.** An acute alveolar infiltrate can develop 3 to 10 weeks after the completion of RT. Withdrawal of corticosteroids while the lungs are being irradiated or soon thereafter may precipitate this process. Pneumonitis is more frequent the higher the radiation dose and the greater the portal size.

  a. **Manifestations.** The patient usually does not have symptoms, although a dry cough, dyspnea, fever, and leukocytosis may be present. Symptoms usually subside within 2 weeks. On radiograph, the infiltrate is the shape of the RT portal, which is usually sharply outlined. Pneumonitis may progress to interstitial fibrosis.
  b. **Management** is symptomatic, particularly with nonsteroidal antiinflammatory agents. Prednisone, 60 to 80 mg/day PO, may be effective. Antibiotics are used for superimposed infections.

 2. **Pulmonary interstitial fibrosis** may appear as early as 4 months after RT. Patients may develop restrictive lung disease, alveolarcapillary block, or cor pulmonale. Corticosteroids have an uncertain role in preventing progression of fibrosis.

C. Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension is characterized by fibrocellular intimal proliferation of small pulmonary arteries and arterioles in patients with metastatic carcinoma, particularly adenocarcinoma. This condition develops when microscopic tumor cell embolism induces both local activation of coagulation and fibrocellular proliferation of intima, but does not occlude the affected vessels. The increased vascular resistance results in pulmonary hypertension. This complication should be considered in the differential diagnosis in patients with known carcinoma who develop acute or subacute cor pulmonale.

D. Pulmonary infections are discussed in Chapter 35, section II.A.

V. Pericardial and myocardial metastases

A. Epidemiology and etiology

 1. Malignant pericardial effusion is usually a preterminal event. About 10% to 20% of patients who die from carcinoma have metastases in the heart or pericardium at autopsy. The epicardium is involved in 75% of metastatic lesions, and pericardial effusions are associated with 35% of epicardial metastases.

 2. Carcinomas of the lung and breast constitute about 75% of all cases of malignant pericardial effusion. Melanoma, leukemia, and lymphoma also commonly affect the heart. Pericardial effusion, which is usually insignificant, occurs in 20% of patients with non-Hodgkin lymphoma at the time of presentation.

B. Natural history

 1. Most myocardial and pericardial metastases are clinically silent; about two thirds are not diagnosed antemortem. Prognosis appears to be related to tumor type.

 2. Pericardial metastases produce symptoms by causing pericardial effusion with tamponade, constrictive pericarditis, or arrhythmias.

 3. Myocardial metastases produce symptoms by causing conduction blocks and arrhythmias. Metastases infrequently cause myocardial rupture, valvular disease, or emboli to other organs.

C. Diagnosis of pericardial effusion. Clinical manifestations arise from decreased cardiac output and venous congestion.

 1. **Symptoms.** Frequently, pericardial tamponade develops slowly, and symptoms resemble those of congestive heart failure.

 2. **Signs of pericardial tamponade**

  a. Neck vein distention that increases on inspiration (Kussmaul's sign)
  b. A fall in systolic pressure of more than 10 mm Hg at the end of inspiration (pulsus paradoxus)
  c. Distant heart sounds with decreased cardiac impulse; possible pericardial friction rub
  d. Pulmonary rales, hepatosplenomegaly, or ascites may be seen.

 3. **Differential diagnosis.** The differential diagnosis of malignant pericardial effusion includes SVC syndrome, radiation pericarditis, and a variety of nonmalignant causes of pericarditis, including myocardial infarction, connective tissue disorders, acute and chronic infections, uremia, myxedema, trauma, and drugs (hydralazine, procainamide).

 4. **Diagnostic studies**

  a. **Chest radiographs** may show enlargement of the cardiac silhouette or a "water-bottle" configuration.
  b. **Electrocardiogram** (ECG) **abnormalities** are generally not specific. Total electrical alternans involving both the P wave and QRS complex is almost pathognomonic of pericardial tamponade. Alternans of only the QRS complex is suggestive of but not specific for cardiac tamponade.
  c. **Echocardiography** is the most effective method of making the diagnosis. False-positive echocardiograms may be secondary to tumor infiltration or encasement of the heart rather than fluid accumulation.
  d. **Cardiac catheterization** is the gold standard for diagnosis and monitoring. Equalization of pressures across the chambers defines tamponade.
  e. **Pericardiocentesis.** A small catheter should be introduced through the needle into the pericardial sac and attached to water-seal gravity drainage to prevent the recurrence of effusion until the final diagnosis is made.
  f. **Fluid analysis.** Malignant pericardial fluids are usually exudative and often hemorrhagic. Fluid analysis and interpretation are the same as for pleural effusions (see section III.C.2). Cytologic findings may be difficult to interpret in patients who have received RT. Negative cytologic results do not exclude the diagnosis of malignant effusion.

D. Management

 1. **Pericardiocentesis and catheter drainage.** Conservative treatment of malignant pericardial effusion using pericardiocentesis or short-term catheter drainage as needed (with or without instillation of intrapericardial chemotherapeutic drugs) may be effective treatment for some patients. Serious complications of pericardial aspiration through a left parasternal or xiphosternal approach are rare, but they include laceration of the heart or coronary arteries, other vessels, liver, or stomach, and (very rarely) a dramatic shocklike reaction. Pneumothorax and arrhythmia occur rarely. Emergency subxiphoid pericardial decompression under local anesthesia, however, is reported to be associated with no operative mortality.

 2. **RT** may be used in radiosensitive tumor types. Overall response rates are reported to be 60% with a dose of 3500 cGy given for 3 to 4 weeks.

 3. **Sclerosing agents.** Chemotherapeutic drugs or doxycycline may be instilled intrapericardially to induce pericardial sclerosis and obliterate the pericardial space. Pericardial sclerosis results in decreased pericardial fluid reaccumulation in 50% to 75% of patients. The dose and method of administration of intrapericardial drugs are similar to those for malignant pleural effusion (Table 29.1). Drug instillation should be performed with ECG monitoring and an

intravenous line in place in case arrhythmia develops. The development of constrictive pericarditis and refractory heart failure has been reported.

4. **Pericardiectomy.** The length of hospital stay for any surgical procedure represents a major portion of the life expectancy of these patients. Surgery should be reserved for patients with (1) rapidly accumulating pericardial effusions that cannot be controlled conservatively and (2) radiation-induced constrictive pericarditis.
   a. **Subtotal pericardiectomy** (resection of entire pericardium anterior to the phrenic nerves) is the surgical procedure of choice in patients whose expected survival is reasonably long. Subtotal pericardiectomy is superior to the pericardiopleural window, which may seal off shortly after surgery. Surgery may be performed by means of thoracotomy or with video-assisted thoracostomy. Success rates range from 90% to 95%.
   b. **Alternative surgical interventions for pericardial tamponade**
      1. **Percutaneous balloon pericardiotomy** proved successful in relieving the cardiac tamponade in more than 90% of cases with few complications.
      2. **Subxiphoid pericardiotomy** was safe and efficacious in 85% of patients at 6 months.
5. **Myocardial metastases.** Patients with disseminated malignancy and new, unexplained cardiac arrhythmias that are refractory to treatment should be considered for cardiac irradiation, particularly if there is known mediastinal or pericardial involvement.

VI. Other cardiac complications

A. **Nonbacterial thrombotic endocarditis** is most common in patients with mucinous adenocarcinoma of the lung, stomach, or ovary, but it can complicate any systemic cancer. Fibrin vegetations appear on heart valves that are otherwise normal. Heart murmurs and other stigmata of bacterial endocarditis usually are not present. Endocarditis is manifested by embolic peripheral or cerebral vascular occlusions that may become clinically apparent as acute peripheral arterial insufficiency, progressive encephalopathy, acute focal neurologic defects suggesting a stroke, or acute multifocal neurologic disease. Treatment with anticoagulants or antiplatelet drugs may be reasonable in some cases, but the results of such treatment are not encouraging.

B. **Bacterial endocarditis** is not more frequent in cancer patients than in the general population.

C. **Radiation pericarditis and pancarditis**
1. **Acute pancarditis or pericarditis** is dependent on the volume of heart irradiated and the radiation dose. This complication develops in about 3% of patients who have received more than 4000 cGy to the internal mammary chain for breast carcinoma or to the mantle for Hodgkin lymphoma. Pancarditis or pericarditis can occur weeks, or even years, after treatment is completed.
   a. **Manifestations.** Symptoms and signs resemble acute or chronic pericarditis of other etiologies: pleuritic chest pain, pericardial friction rub, ECG abnormalities, and enlargement of the cardiac silhouette on radiographs. Most patients, however, do not have symptoms. Cytologic findings from irradiated mesothelium may suggest malignancy and obfuscate the cause of the effusion.
   b. **Management.** Treatment in the acute phase includes giving corticosteroids and antipyretics and doing pericardiocentesis. The disease is usually self-limiting but may become chronic. In the chronic phase, a pericardial window for symptomatic effusions or pericardiectomy for constrictive pericarditis may become necessary.
2. **Myocardiopathy** is a rare sequela of large doses of irradiation to the heart, particularly with concomitant or prior use of doxorubicin. Refractory heart failure may result.

D. **Anthracycline-induced cardiomyopathy.** A major dose-limiting toxicity of the anthracyclines (doxorubicin, liposomal doxorubicin, daunorubicin, and idarubicin) is cardiomyopathy. Proposed mechanisms of cardiac toxicity involve the generation of free radicals, which damages cell membranes through peroxidation of membrane lipids, the binding of drug to a variety of membrane sites (including cardiolipin and spectrum), which can cause alterations in membrane structure and ion transport, and the selective inhibition of cardiac muscle gene expression.
1. **Types of cardiac toxicity**
   a. **Acute myocardiopathy** is not related to total dose. Manifestations include the following:
      1. Arrhythmias, especially sinus tachycardia, which do not correlate with subsequent development of chronic cardiomyopathy
      2. Nonspecific ST-T–wave changes
      3. Pericardial and pleural effusions (after 1 to 2 days)
      4. Clinically inapparent decrease in left ventricular ejection fraction. Reversible congestive heart failure may develop after the first dose.
      5. "Myocarditis-pericarditis syndrome." Decreased myocardial function can be persistent in these patients.
      6. Rarely, sudden death or myocardial infarction
   b. **Chronic myocardiopathy** is related to the total dose and method of administration. The overall incidence of congestive heart failure related to doxorubicin use is about 3% to 4%. The incidence is 1% to 2% for total doses of 300 mg/m^2, 3% to 5% for 400 mg/m^2, 5% to 8% for 450 mg/m^2, and 6% to 20% for 500 mg/m^2. The heart becomes dilated and may contain mural thrombi. Microscopy is nonspecific and reveals interstitial edema, cytoplasmic vacuolization, muscle fiber degeneration, and deformed mitochondria. Manifestations include the following:
      1. Subclinical left ventricular dysfunction
      2. Overt congestive heart failure, which usually develops within 2 months of the last dose but can occur 6 months to many years later
2. **Evaluation of cardiac injury.** Symptoms, physical findings, and ECG abnormalities (reduction of QRS voltage by 30%) occur too late to be helpful.
   a. **Endomyocardial biopsy** is the most specific method for determining anthracycline cardiotoxicity (short of waiting for overt heart failure). Semiquantitative scoring systems reveal a linear correlation of abnormalities with cumulative dose. This technique can be safely performed in an outpatient setting. Only specially trained personnel, however, can perform the biopsies and interpret the results.
   b. **Echocardiogram** and multigated radionuclide angiography are noninvasive methods for determining left ventricular ejection fraction (LVEF); they should be obtained at baseline, especially in patients with risk factors, and should be repeated as the cumulative dose approaches 400 mg/m^2.
3. **Prevention.**
   a. **Infusion rates.** The development of cardiac toxicity is related to peak serum levels of doxorubicin. Weekly administration (20 mg/m^2) is associated with a lower incidence of cardiotoxicity when compared with monthly administration (60 mg/m^2). Continuous infusion over 24 to 96 hours through a central venous catheter also is less cardiotoxic than bolus administration; cumulative dosages much greater than 500 mg/m^2 have been administered by this technique without significant cardiac toxicity.
   b. **Dexrazoxane** (Zinecard) is a cardioprotectant that can decrease the incidence and severity of cardiomyopathy associated with doxorubicin when more than 300 mg/m^2 is given. It is indicated for women with metastatic breast cancer to whom more than 300 mg/m^2 of doxorubicin has been given and who are believed will benefit from further doxorubicin.
4. **Recommendations**
   a. Recognize patients who are at high risk for developing cardiac toxicity; risk factors are the following:
      1. Age older than 70 years
      2. Preexisting heart disease or hypertension
      3. Prior chest or mediastinal RT (especially if more than 4000 cGy)
      4. Concurrent treatment with cyclophosphamide or mitomycin C
   b. Limit the total cumulative dose of doxorubicin to 450 to 500 mg/m^2.
   c. Consider altering the schedule of administration (weekly or infusion).
   d. If one or more risk factors (see section 4.a) are present, measure LVEF before starting treatment and after every 100 mg of doxorubicin. Discontinue the drug if the LVEF is less than 45% of predicted value or if the LVEF decreases by 10% on subsequent measurements.
   e. If expertise in endomyocardial biopsy and interpretation are available, interpret abnormal LVEFs in the light of biopsy results.
   f. Discontinue the drug at the first sign of an unexplained tachycardia, cough, dyspnea, or S3 gallop. Manifestations of congestive heart failure often do respond to therapy, but there are still a large number of patients with refractory symptoms.

E. **Other chemotherapy-induced cardiotoxicity**
1. **5-Fluorouracil** can cause cardiac ischemia with angina, hypotension, or congestive heart failure. The incidence of such toxicity is uncertain but has been reported to occur in 2% to 8% of patients, particularly when the drug is given by continuous intravenous infusion in patients with a prior history of cardiac disease. These manifestations are reversible when the drug is stopped; patients respond well to conventional cardiac treatments.
2. **Cyclophosphamide** can potentiate doxorubicin-induced cardiotoxicity. When given in high doses, cyclophosphamide can cause myocardial necrosis and hemorrhagic myocarditis.
3. **Mitoxantrone** can cause a decrease in ejection fraction in 3% to 6% of patients with overt congestive heart failure in 1% to 3%. This toxicity is related to cumulative dose and occurs in more than 10% of patients receiving more than 120 mg/m^2 who have received prior doxorubicin.
4. **Paclitaxel** (Taxol) commonly results in asymptomatic bradycardia but can also occasionally cause conduction defects, cardiac ischemia, and ventricular tachycardia.
5. **Interferon-**a has been associated with reversible cardiac dysfunction.
6. **Interleukin-2** is associated with arrhythmias.

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Chapter 30 Abdominal Complications

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I. Gastrointestinal (GI) bleeding

A. **Etiology**
1. **Benign causes.** GI bleeding in patients with active cancer is usually caused by erosive gastritis, peptic ulcer disease, esophageal or gastric varices, or other benign diseases; only 20% is caused by direct tumor bleeding. Hemorrhage is often related to the use of aspirin or glucocorticoids.
2. **Malignant causes.** Most primary GI cancers produce slow blood loss; massive hemorrhage is not common. Melanomas and leiomyosarcomas involving the GI tract, on the other hand, are likely to result in extensive hemorrhage. Blood or clots from ostomies or mucous fistulas usually signify recurrent cancer.

B. **Management**
1. **Benign conditions causing GI bleeding** in patients with advanced cancer should be managed in the same way as in patients without cancer, with the following exceptions:
   a. Surgery should not be undertaken in patients who have a life expectancy of less than 2 months even if the bleeding is correctable.
   b. Nonsurgical therapy to control benign causes of bleeding is preferred for patients who have advanced cancer and a prognosis of more than 2 months, even if surgery is usually indicated. Surgery should generally be considered, however, for large gastric peptic ulcers or recurrent peptic ulcer bleeding.
2. **Patients with persistent GI bleeding from unresectable tumors** may be managed with RT. Resection of local tumor recurrence may be used if permitted by the patient's general condition.

II. Bowel obstruction

A. **Etiology.** Bowel obstruction in patients with a history of cancer is due to the original tumor or its metastases in 60% to 70% of cases. About 20% to 30% of patients have a benign cause of obstruction, and 10% to 20% have a new, and often resectable, primary lesion. Bowel obstruction caused by malignancy occurs most often as a complication of ovarian carcinoma or GI tumors.
1. **Mechanisms** of bowel obstruction in malignancy
   a. External pressure on the intestine
   b. Obstructing masses in the bowel lumen
   c. Invasion of the intestine's neural plexus, causing localized or diffuse ileus clinically indistinguishable from mechanical obstruction
   d. Intussusception with certain tumors, notably melanoma
   e. Pseudo-obstruction as a paraneoplastic syndrome (see section VIII.B)
2. **Differential diagnosis.** Diagnostic considerations in cancer patients include the following:
   a. **Vinca alkaloid neurotoxicity** may produce constipation. Particularly in elderly patients, paralytic ileus or decreased bowel tone may lead to high fecal impaction with bowel obstruction. Impaction is better prevented than treated (see Chapter 5, section IV.A).
   b. **Radiation injury of small bowel** (see section VI.C) may be seen on small bowel radiographs or computed tomography (CT) scan as mucosal effacement, ulcers, rigidity, narrowing, adhesions, bowel wall thickening, and bowel dilation.
   c. **Diverticulitis** may produce tightly narrowed areas in the distal colon that are often radiologically indistinguishable from constricting carcinoma. In the absence of metastatic disease elsewhere, these lesions must be resected regardless of coexistent tumor.
   d. **Other nonmalignant causes of ileus and obstruction** include adhesions, hernia, inflammatory bowel disease, volvulus, spontaneous intussusception, acute pancreatitis, and bowel infarction.

B. **Management of bowel obstruction caused by cancer**
1. **Decompression.** Patients with evidence of intestinal obstruction should have decompression by placement of a nasogastric tube and intermittent suction. The eventual outcome does not depend on whether a gastric or long (Miller-Abbott) tube is used.
2. **Stents.** Expandable metallic stents have been used to treat obstruction in nearly all portions of the GI tract, including the esophagus, gastric outlet, duodenum, proximal jejunum, terminal ileum, colon, and rectum. Although stent placement requires a trained endoscopist or interventional radiologist, this procedure palliates obstruction in more than 80% of patients and may obviate the need for surgery in patients who cannot be cured. Complication rates are low but include bleeding, stent migration, and tumor growth into stent.
3. **Operative intervention**
   a. A history of cancer or even the presence of active tumor is not necessarily a contraindication to surgery. About 75% of patients with a bowel obstruction resume normal bowel function after surgery. Function is maintained until death in 45% of patients. About 25% of these patients do not experience improvement of symptoms with surgery.
   b. Surgical intervention should be considered if the obstruction does not improve after 4 to 5 days of decompression and if the following conditions are met:
      1. The patient's medical condition makes the operative risk low.
      2. The patient does not have malignant ascites.
      3. The patient's life expectancy would be greater than 2 months if the bowel obstruction were relieved.
      4. The patient underwent no more than one surgical intervention for obstruction during the previous year and was significantly palliated by that operation for more than 4 months.
      5. The most recent operative intervention did not disclose multiple or widespread tumor sites causing obstruction.
4. **Other modalities of management**
   a. **Chemotherapy** may be tried in patients with obstruction caused by carcinomatosis. Specific regimens depend on the type of primary tumor.
   b. **RT** to relieve bowel obstruction may be beneficial in patients who have peritoneal carcinomatosis from ovarian carcinoma or extensive abdominal lymphoma that is resistant to chemotherapy. Abdominal irradiation produces severe side effects and is not recommended for other types of malignant bowel obstruction.
   c. **Treatment of preterminal patients with refractory obstruction caused by cancer**
      1. Nasogastric suction is used to alleviate abdominal pain. Intravenous fluids are given to maintain hydration.
      2. In some situations, the abdominal pain is treated with appropriate analgesics, and the patient is allowed to eat whatever he or she wants and then vomits as necessary. The risk for intestinal rupture is not a consideration in terminal situations.
      3. Parenteral hyperalimentation is generally not indicated.

III. Metastases to the liver and biliary tract

A. **Incidence and pathology**
1. **Liver.** The liver is a common site of metastases. Liver metastases account for more than half of the deaths in certain malignancies, such as colorectal cancer.
   a. **The relative risks** of tumor metastasizing to the liver during the course of advanced disease are as follows:
      1. **Liver commonly involved:** GI tract cancers (including carcinoids, pancreatic adenocarcinoma, and islet cell tumors), lung cancer (especially small cell), breast cancer, choriocarcinoma, melanoma, lymphomas, and leukemias
      2. **Liver occasionally involved:** carcinoma of the distal esophagus, kidney, prostate, endometrium, adrenal gland, and thyroid; testicular cancers, thymoma; angiosarcoma

3. **Liver rarely involved:** carcinoma of the proximal esophagus, ovary, and skin; plasma cell myeloma; most sarcomas
   b. **Types of metastases**
      1. **Nodular metastases** are the most common type and occur with all tumors capable of metastasizing to the liver, including lymphoma.
      2. **Diffuse metastases** most frequently occur with lymphomas. Breast cancer, small cell lung cancer, poorly differentiated GI tumors, and rarely, other types of tumors can also produce diffuse metastases.
   2. **Extrahepatic biliary obstruction** can occur from lymph node metastases in the porta hepatis, particularly from GI cancers and lung cancers (especially small cell type).

B. **Natural history.** The clinical course of liver metastases depends on the tumor's behavior and responsiveness to chemotherapy. In patients with solid tumors, death commonly occurs within 6 months with nodular metastases and more rapidly with diffuse metastases. A liver that appreciably increases in size in less than 8 weeks is typical in small cell lung cancer and high-grade lymphoma; both of these tumors respond well to treatment. Rapid liver enlargement in patients with other tumor types is less common.

C. **Diagnosis**
   1. **Symptoms and signs.** Any combination of pain or discomfort in the right upper quadrant, weight loss, fatigue, anorexia, jaundice, or fever should raise the possibility of liver metastases, particularly in patients with a history of cancer. Symptoms are present in 65% of patients and hepatomegaly in 50% when liver metastases are discovered.
   2. **Laboratory studies**
      a. **LFTs** should be obtained in all patients suspected of having liver metastases. An elevation of the alkaline phosphatase level out of proportion to that of the transaminases suggests either a mass lesion or biliary obstruction.
      b. **Liver imaging** is obtained in all patients with history, physical findings, or laboratory values suggestive of hepatic metastases. Hepatic CT or magnetic resonance imaging (MRI) scans are the most sensitive techniques. Ultrasonography and ^{99m}Tc colloid liver scans have lower diagnostic accuracy. Ultrasound may be useful in determining whether a lesion is solid or fluid. The evaluation of a single focal lesion in the liver is discussed in Chapter 9, Liver Cancer.
   3. **Selective hepatic angiography** is the most predictive diagnostic test to assess the presence, number, and distribution of hepatic metastases but is usually unnecessary unless an embolization procedure is planned.
   4. **Liver biopsy** should be performed to confirm the presence and type of tumor in the following circumstances:
      a. There is no *primary history of cancer* and the liver is the only obvious site of disease.
      b. There has been a *long disease-free interval* (more than 2 years) since the removal of the primary tumor.
      c. The liver abnormality is *not typical* of the natural history of the primary cancer. Suggestive evidence for hepatic metastases in patients with primary tumor type that does not usually metastasize to the liver (see section A.1.a.[3]) indicates biopsy *if the results are likely to affect therapeutic decisions.*
      d. **Relative contraindications** for liver biopsy include the following:
         1. Coagulation protein or platelet abnormalities
         2. Evidence of a vascular tumor (e.g., angiosarcoma)
   5. **Extrahepatic biliary obstruction.** These patients must have special studies to exclude benign causes of obstruction, such as gallstones or bile duct strictures.
      a. **CT scan** or Disida scan of the liver is performed to look for parenchymal or porta hepatis masses and obstruction of the biliary tree.
      b. **Percutaneous transhepatic cholangiogram** or retrograde contrast study of the biliary tree is performed, depending on the availability of experienced radiologists and gastroenterologists.
      c. **Laparotomy** is indicated for both definitive diagnosis and treatment if the other studies suggest extrahepatic obstruction and if other sites of tumor are well controlled or not evident.

D. **Management**
   1. **Surgery**
      a. **Resection of hepatic metastases** has been used in highly selected patients. Modern anatomic techniques have decreased surgical mortality to less than 6%. Overall, in properly selected patients (those with four or fewer metastases, no presence of disease outside the liver, and good performance status), 20% to 40% of patients survive 5 years. Success is greater in patients with slow-growing tumors and with a disease-free interval of greater than 1 year.
      b. **Extrahepatic biliary tract obstruction** may be decompressed surgically if pruritus is severe. Jaundice *per se* is generally not an indication for surgery unless the patient must have a laparotomy for diagnosis. Biliary cirrhosis occurs only after 6 to 8 months of total obstruction, a period that exceeds the life expectancy of most patients with malignant obstructive jaundice.
         1. **Percutaneous drainage** through internal or external catheter placement offers reasonable palliation. Drainage is achieved in 60% to 85% of cases. This procedure has a 25% to 40% morbidity rate and a 2.5% to 5% mortality rate. The most frequent complication is cholangitis, which appears to relate to multiple sites of obstruction or inadequate drainage. Further intervention with tube manipulation, tube replacement, or surgery is required in 20% to 75% of patients. The success rate for palliation is about 80%, similar to that achieved with cholecystojejunostomy.
         2. **Endoscopic placement of prostheses** is another option that is successful in about 80% of patients. The difficulties of cholangitis from inadequate drainage result in a 2% to 5% mortality rate. Morbidity rates are similar to those associated with percutaneous procedures. Drainage is internal and more convenient for patients.
      c. **Hepatic artery ligation or hepatic dearterialization** alone or in combination with perfusion produces no significant benefit.
   2. **RT** in low doses (less than 2400 cGy) is useful to palliate refractory pain from liver metastases. RT to portal masses may relieve biliary tract obstruction.
   3. **Chemotherapy**
      a. **Oral and intravenous chemotherapy** is useful for treating responsive tumors such as lymphomas, breast cancer, and small cell lung cancer. The primary tumor determines the selection of drugs. Prednisone, 60 mg PO daily, may be helpful to control pain from liver metastases that do not respond to chemotherapy.
      b. **Direct perfusion of chemotherapy** into the liver through hepatic artery cannulation is used by some physicians to treat isolated liver metastases when no other organs are involved. The most extensively used drugs are fluorouracil, floxuridine, and doxorubicin (Adriamycin). Compared with systemic chemotherapy (including continuous peripheral venous infusion), hepatic artery infusion is associated with more responses, less systemic drug toxicity, significantly greater development of extrahepatic metastases, and no difference in survival. Complications of hepatic artery infusion include hospitalization for catheter placement and perfusion (if a portable pump is not used), hemorrhage, thrombosis of the perfused vessels, embolization, catheter displacement or breakage, catheter sepsis, GI bleeding, chemical hepatitis, acalculous cholecystitis, and biliary sclerosis.
   4. **Other options** under investigation for hepatic metastases include selective chemoembolization, alcohol instillation, cryoablation, and radiofrequency ablation. Large randomized studies have not yet been conducted to determine whether these modalities affect survival.

IV. Malignant ascites

A. **Pathogenesis**
   1. **Peritoneal carcinomatosis** with malignant ascites is most often caused by ovarian, unknown primary, colon, gastric, and biliary tract carcinomas. The most common extraabdominal malignancies to produce peritoneal carcinomatosis include breast and lung carcinomas. Mesothelioma is a rare cause.
   2. **Hepatic venous obstruction** from hepatocellular carcinoma or extensive hepatic metastases from other tumors may result in ascites. Hyperviscosity states, particularly polycythemia vera, may result in the Budd-Chiari syndrome. Patients with hepatic venous obstruction have large, tender livers and rapidly evolving ascites.
   3. **Chylous ascites** may result from obstruction or rupture of the major abdominal lymphatic passages. More than 80% of cases in adults are caused by abdominal neoplasms, usually lymphoma.
   4. **Peritonitis** caused by *Streptococcus bovis* may be a presenting feature for right-sided colon carcinoma. Ascites from any cause may become infected.

B. **Diagnosis**
   1. **Differential diagnosis of ascites.** Neoplastic diseases that cause ascites include liver metastases, peritoneal metastases, pseudomyxoma peritonei, and primary mesothelioma. The etiologies of ascites can be best classified by the *serum–ascites albumin gradient,* which is the difference between serum and ascitic fluid albumin concentration. This gradient predicts the presence or absence of portal hypertension and, in parallel, the responsiveness to treatment with diuretics.

High albumin gradient ($\geq$1.1 g/dl) (portal hypertension likely)	Low albumin gradient (<1.1 g/dl) (portal hypertension unlikely)
Massive hepatic metastases	Peritoneal carcinoma
Chronic liver disease	Peritoneal inflammation (fungal, tuberculous, vasculitic)

Hepatic vein obstruction (Budd-Chiari syndrome)	Oncotic (hypoalbuminemia): nephrotic syndrome, protein-losing enteropathy, chronic disease
Hepatic veno-occlusive disease	
Cardiac failure	Hollow organ leak: pancreatic, biliary, ureteric, chylous
Hemodialysis with fluid overload	
Myxedema (?)	Idiopathic

2. **Paracentesis** should be done in all patients with presumed malignant ascites for diagnosis and to rule out complicating infections. Ascites from carcinomatosis is usually exudative and often bloody. Ascitic fluid should be studied for the following:
   a. **Culture** for bacteria (including acid-fast bacilli) and fungi
   b. **Albumin** should be measured to calculate the gradient.
   c. **Exudates** are associated with total protein values more than 2.5 g/dL, white blood cell count more than 250/µL (lymphocytosis suggests tuberculous peritonitis), and lactate dehydrogenase level more than 50% of serum values.
   d. Values in ascitic fluid significantly greater than in serum of **amylase or triglyceride** indicate a pancreatic etiology or chylous content, respectively.
   e. **Glucose** level is often less than 60 mg/dL in carcinomatosis.
   f. **Fibronectin** levels greater than 75 µg/mL in the absence of infection or pancreatic disease or carcinoembryonic antigen (CEA) levels greater than 12 ng/mL are rarely caused by benign disease.
   g. **Cytology** is positive in more than half of cases of peritoneal carcinomatosis.

C. **Management.** With the exception of ovarian cancer–associated malignant ascites, which is treated with cytoreductive surgery and chemotherapy, management of malignant ascites is principally directed toward the palliation of symptoms.
   1. **Diuretics,** such as furosemide and spironolactone, may be tried but are unlikely to be effective for ascites from peritoneal carcinomatosis.
   2. **Large-volume paracentesis.** A 14- to 16-gauge plastic catheter or a peritoneal dialysis catheter can be used; the latter is preferred for removing a large volume of fluid. A single suture should hold the catheter in place.
      a. Removal of large volumes of peritoneal fluid should not be done if a hepatic cause, such as cirrhosis or Budd-Chiari syndrome, is suspected.
      b. If cancer is suspected, as much fluid as possible should be removed; nonpalpable abdominal masses may later become evident. Removal of large volumes of ascites fluid that is a result of peritoneal carcinomatosis does not usually cause dangerous fluid shifts.
   3. **Systemic chemotherapy** is the treatment of choice for responsive tumors.
   4. **Intraperitoneal chemotherapy.** Instillation of chemotherapy directly into the abdomen may control some malignant effusions. The abdomen is drained to be as dry as possible, preferably using a peritoneal dialysis catheter. The chosen drug is dissolved in 100 mL of normal saline, injected into the catheter, and followed by another 100 mL of normal saline for flushing. The patient's position is shifted every few minutes for an hour to disperse the drug. If treatment is effective, the dose may be repeated at intervals. Fever or abdominal pain or tenderness may develop after the procedure, may persist for up to 1 week, and may require paracentesis to confirm that the peritonitis is sterile.
      a. **Effective agents** include bleomycin (15 U), 5-fluorouracil (1000 mg), thiotepa (45 mg), doxorubicin (30 mg), cisplatin, and mitoxantrone (10 mg).
      b. **Radioactive phosphorus** may be tried, but leakage of the radioisotope through the needle tract is a major problem. Radioactive gold and vesicant drugs, such as nitrogen mustard, are extremely hazardous and can cause bowel necrosis, especially if the fluid is loculated.
   5. **Peritoneovenous shunts** (LeVeen and Denver) may be used to treat refractory cases if the patient has a life expectancy of greater than 1 month and does not have significant cardiac or renal disease or disseminated intravascular coagulation (DIC). The ascitic fluid should not be hemorrhagic, infected, or loculated, and it should not contain large numbers of malignant cells. Complications of these shunts include primary fibrinolysis or clinically silent DIC (virtually 100%), sepsis (20%), pulmonary edema (15%), pulmonary emboli (10%), upper GI bleeding, fever without sepsis, superior vena cava thrombosis, pneumonia, shunt displacement, seromas around the catheter (10%), and neoplastic seeding to the superior vena cava on adjacent subcutaneous tissues. Thrombocytopenia is caused by both DIC and hemodilution.
   6. **Pseudomyxoma peritonei.** Mucinous adenocarcinomas, "benign" mucin-producing tumors, and appendiceal mucoceles can produce abundant gelatinous material that is impossible to remove by paracentesis. Recurrent bowel obstruction and progressive ascites develop. Laparotomy with removal of as much of the jelly-like substance as possible is indicated. The procedure may be repeated if there is recurrence, depending on the changing anatomy and formation of adhesions.

V. Pancreatitis and metastases to the pancreas

A. **Etiology.** Pancreatitis rarely complicates primary or metastatic cancer of the pancreas. When abdominal carcinomatosis with secondary pancreatic involvement is excluded, metastases to the pancreas is rare. Small cell lung cancer metastasizes to the pancreas most commonly, but lymphoma and carcinomas of the breast, colon, and kidney do also.

B. **Diagnosis** of pancreatitis depends on signs and laboratory findings. CT scan of the abdomen is the best technique to demonstrate a mass in the pancreas. Differential diagnosis includes the following:
   1. Pancreatitis associated with hypercalcemia
   2. Drug-induced pancreatitis from the following:
      a. Alcohol
      b. Glucocorticoids, indomethacin, salicylates
      c. l-Asparaginase, mercaptopurine, azathioprine
      d. Isoniazid, thiazides, oral contraceptives, certain antibiotics

C. **Management.** Pancreatitis complicating metastatic cancer should be treated with analgesics. Intravenous fluids should be administered to replace losses.

VI. Adverse effects of radiation to the liver and alimentary canal

A. **Radiation hepatitis.** Clinical hepatitis is uncommon at doses of less than 2500 cGy to the liver. This dose is usually not exceeded except in the treatment of Wilms' tumor. Acute hepatitis from radiation can be mild to severe and may result in cirrhosis.
   1. **Manifestations.** Signs and symptoms become evident 2 to 6 weeks after irradiation. Hepatomegaly and ascites develop. Enzyme abnormalities are indistinguishable from those in viral hepatitis. Decreased uptake of ^{99m}Tc in the treatment portal is observed on liver scan. Liver biopsy demonstrates endophlebitis with thickening and obstruction of central veins and mild cellular necrosis or atrophy, findings similar to those seen with veno-occlusive disease induced by chemotherapy.
   2. **Management** is symptomatic. Corticosteroids may help.

B. **Radiation esophagitis**
   1. **Acute esophagitis.** Transient esophageal dysphagia and odynophagia may occur toward the end of a course of RT to the mediastinum. Analgesics or viscous lidocaine solution may be helpful. Occasionally, nutritional supplementation may be required through a gastrostomy tube.
   2. **Esophageal stricture** is a rare late complication that is more common when chemotherapy, particularly doxorubicin or methotrexate, is given concomitantly. Dilation is performed in patients with symptoms.

C. **Radiation enteritis**
   1. **Acute radiation enteritis**
      a. **Manifestations** are usually related to the volume of the bowel irradiated and to the daily dose. Most injuries involve the terminal ileum.
         1. Nausea, vomiting, and anorexia usually do not persist more than 3 days after RT is stopped.
         2. Diarrhea is more severe in patients who have had laparotomies and have developed adhesions. Symptoms can occur after the second week of RT and usually disappear within 2 weeks after its completion.
      b. **Management**
         1. **Antiemetics** are given regularly throughout the day for patients with persistent vomiting. If symptoms are severe, parenteral hyperalimentation and reduction of the daily dose of radiation may be necessary.
         2. **Diarrhea** is managed by eliminating alcoholic beverages, roughage, and milk products from the diet. Paregoric (tincture of opium), cholestyramine, or diphenoxylate-atropine (Lomotil) may be useful.
   2. **Chronic radiation enteritis.** Abdominal pain syndromes, malabsorption, bowel strictures, hemorrhage, perforations, and fistulas usually occur with doses to the abdomen of more than 4500 cGy and are more frequent in the presence of postsurgical adhesions. Symptoms may develop months to many years after completion of therapy. Parenteral hyperalimentation may be necessary while the bowel abnormality is being corrected.
      a. **Abdominal pain syndromes** are treated with analgesics, bulk laxatives, and dietary modifications.
      b. **Perforations and fistulas** indicate a poorer prognosis than strictures and hemorrhage; malignancy recurs in 70% of these patients.
      c. **Bowel obstruction.** Tube decompression may lead to resolution. Laparotomy should be avoided if possible. If the obstruction progresses, intestinal bypass (10% mortality rate) rather than bowel resection should be performed in the absence of gangrenous bowel (75% mortality rate).
      d. **Chronic diarrhea** with malabsorption is rare and is treated symptomatically. Anorexia, nausea, and vomiting may occur. Medium-chain triglycerides may

be of help to decrease stool fat loss and to relieve radiation-induced intestinal lymphangiectasia with protein loss. Steatorrhea may result from bacterial overgrowth; tetracycline, 250 mg given four times daily, may be tried for 10 to 14 days on an empiric basis. Prednisone and sulfasalazine may also be used.

    D. **Radiation proctitis**

        1. **Acute transient proctitis**

            a. **Manifestations.** Tenesmus, diarrhea, and occasionally, minor bleeding develop. Symptoms usually resolve soon after RT is completed.

            b. **Management** is usually not indicated. If symptoms are prolonged or severe, steroid enemas and suppositories, stool softeners, mineral oil, low-residue diet, or paregoric or diphenoxylate-atropine may be helpful.

        2. **Late radiation proctitis** occurs 6 months to 2 years after RT.

            a. **Manifestations.** Symptoms include tenesmus, diarrhea, and hematochezia. Proctoscopic examination reveals hemorrhagic, edematous mucosa with decreased pliability and, occasionally, ulcers.

            b. **Management**

                1. **For severe inflammation,** treat as described for acute proctitis.

                2. **For rectal ulcers** refractory to conservative management (see section 1.b), surgery is advised.

                3. **For late rectal narrowing,** treat with dilation and stool softeners.

VII. Hepatic veno-occlusive disease
Hepatic veno-occlusive disease is a nonthrombotic obliterative process of the central or sublobular hepatic veins characterized by ascites, hepatomegaly, and varied clinical outcome.

    A. **Causes**

        1. The hepatotoxic pyrrolizidine alkaloids that occur naturally in plants (other implicated dietary contaminants include aflatoxin and nitrosamines) are the most common cause worldwide. Chemotherapy and irradiation, especially in patients who have had bone marrow or kidney transplantation and graft-versus-host disease, are important causes in the Western world.

        2. Virtually any high-dose chemotherapeutic regimen can cause hepatic veno-occlusive disease. Azathioprine, 6-mercaptopurine (a metabolite of azathioprine), 6-thioguanine (a compound related to 6-mercaptopurine), and dacarbazine have been implicated as causes of hepatic vascular damage.

        3. Other causes include postnecrotic cirrhosis, metastatic or primary hepatic malignancy, myeloproliferative disorders (particularly polycythemia vera), and a variety of other hypercoagulable states.

    B. **Diagnosis.** The diagnosis of hepatic veno-occlusive disease is suggested by reversal of flow in the portal vein by Doppler ultrasound. The diagnosis is established by liver biopsy, which should be done early when hepatic dysfunction is evident because alteration of therapy may improve subsequent clinical outcome.

    C. **Management.** Optimal treatment is still unclear, but defibrotide, tissue plasminogen activator (tPA), and transjugular intrahepatic portosystemic shunt procedures have all been reported to have benefit in selected cases.

VIII. Paraneoplastic GI tract syndromes
The cause of paraneoplastic gastrointestinal tract syndromes is not known.

    A. **Esophageal achalasia** may accompany gastric cancer and is reversible when the cancer is resected. Patients present with dysphagia for all foods and liquids.

        1. **Diagnosis.** The barium esophagogram reveals a large, aperistaltic esophagus. Esophageal manometry shows weak contractions with a "hypertensive" lower esophageal sphincter.

        2. **Therapy.** Patients with achalasia and unresectable cancer must have gastrostomy, an esophageal tube (e.g., Celestin tube), or forced pneumatic dilation.

    B. **Intestinal pseudo-obstruction** occurs in patients with peritoneal carcinomatosis in the absence of mechanical obstruction. Signs of obstruction are crampy abdominal pain, absence of stools, nausea, vomiting, hyperactive bowel sounds, and nonlocalized air-fluid levels on abdominal plain films.

        1. **Diagnosis.** Pseudo-obstruction and mechanical obstruction are clinically indistinguishable. Pseudo-obstruction, however, often remits spontaneously. Hypokalemia, hypomagnesemia, fecal impaction, history of vincristine use, and other causes of ileus should be sought.

        2. **Therapy** is the same as for suspected bowel obstruction (see section II).

IX. Symptom care for alimentary canal problems
is discussed in Chapter 5.

    A. **Oral problems,** including stomatitis, xerostomia, abnormal taste, halitosis, caked material in the mouth, and dysphagia. See Chapter 5, section II.

    B. **Nausea and vomiting.** See Chapter 5, section III.

    C. **Colorectal symptoms,** including constipation and rectal discharge. See Chapter 5, section IV.

    D. **Anorexia,** including hyperalimentation. See Chapter 5, section XII.

Suggested Reading

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Chapter 31 Renal Complications

David W. Knutson

I. Prerenal failure

A. **Pathogenesis.** In all patients with prerenal failure, a decrease in effective circulating volume (ECV) leads to a decrease in renal blood flow with a consequent reversible decrease in glomerular filtration rate (GFR). Decreased ECV provides a baroreceptor-mediated stimulus for the secretion of antidiuretic hormone (ADH). The simultaneous decrease in renal blood flow stimulates the production of renin with consequent increases in circulating levels of angiotensin II (AII) and aldosterone. The combined effects of decreased renal blood flow and increased levels of ADH, AII, and aldosterone result in excretion of urine that is low in volume, is highly concentrated, and contains little sodium but relatively large amounts of potassium. (Table 31.1 shows laboratory values that distinguish prerenal failure from renal failure.)

Table 31.1 Distinguishing prerenal from renal causes of azotemia

1. **Decreased GFR** leads to a retention of urea and creatinine. Reabsorption of filtered urea is increased in the distal nephron because of slow tubular flow, a high concentration of urea in tubular fluid, and elevated ADH. Thus, more urea than creatinine is retained, leading to a characteristic elevated blood urea nitrogen (BUN) to serum creatinine ratio.
2. **Creatinine production** is proportional to muscle mass, and urea production is dependent on protein intake, among other things. Thus, these values may be lower than normal in the wasted patient with cancer who often has poor nutritional intake. In such patients, normal or borderline high values of BUN and serum creatinine may suggest significant impairment of renal function.

B. **Causes of prerenal failure.** Table 31.2 shows general causes of prerenal failure with specific factors that may predispose patients with malignancies to prerenal failure.

Table 31.2 Cause of decreased effective circulating volume and prerenal failure in patients with malignancies

C. **Diagnosis and management.** The history often reveals likely causes of increased fluid loss (e.g., diarrhea, vomiting) or sequestration (e.g., congestive heart failure [CHF], edema). Decreased intake may be more difficult to elicit. The physical examination is of paramount importance in assessing volume status and finding clues to the pathogenesis of aberrations, as follows.
1. **Supine systolic blood pressure** of less than 90 mm Hg, orthostatic decreases of greater than 10 mm Hg diastolic, or orthostatic increases in pulse rate of more than 10 beats/min suggest intravascular volume depletion.
2. **Flat neck veins** (in patients whose neck veins can be demonstrated by gentle occlusion) suggest volume depletion.
3. **In patients without findings of volume depletion,** careful palpation and percussion of the bladder, rectal examination of the prostate of male patients and pelvic examination in female patients may divert attention to an obstructive cause.
4. **Occult prerenal failure** may be present that escapes detection by any of the above measures. Thus, many clinical scenarios require the careful administration of a fluid challenge. In the absence of clear physical findings of fluid overload, 1 L of normal saline can be safely administered to most normal-sized adults without untoward effect. Often, a gratifying increase in urinary output results, and BUN and serum creatinine values subsequently return to normal.
5. **Loop diuretics** given as an intravenous challenge are often used in acutely oliguric patients. An increased urinary output suggests that obstruction is not present and that the renal tubules are functioning. Such response, however, does not clarify or correct the underlying abnormality causing the initial decrease in urine production, and except for overload states such as CHF, the diuretic may make the prerenal failure worse.
6. **Overall management** of prerenal failure is to correct the underlying cause and, when possible, restore ECV to normal. In hypovolemic patients, this usually requires large volumes of salt-containing solutions. Although albumin solutions specifically increase intravascular volume, they are expensive and the effect is often transient. Obstruction to urinary outflow should be considered in all patients who do not respond to a fluid challenge. In such patients (especially men), insertion of a Foley catheter should be performed. If the problem is still not corrected, all such patients should undergo an imaging procedure to visualize the kidneys and collecting system. Ultrasonography is often the safest and most convenient choice.

II. Obstructive uropathy causing renal failure

A. **Pathogenesis**
1. **Ureteral obstruction.** Uremia may be caused by bilateral obstruction (or unilateral obstruction in the case of a single functioning kidney) as a result of the following:
    a. Bladder tumors and tumors of the collecting systems
    b. Uterine tumors, especially carcinoma of the cervix
    c. Retroperitoneal tumors (rare), including lymphoma, sarcomas, and metastatic tumors
    d. Intrinsic renal tumors (rare)
    e. Retroperitoneal fibrosis, including that induced by irradiation, drugs (busulfan), carcinoid tumors (especially rectal), Gardner's syndrome (intestinal polyposis), or desmoplastic reactions to metastases
    f. Nephrolithiasis
    g. Blood clots
2. **Outlet obstruction of the urethra.** Causes include primary cancer of the prostate, urethra, cervix, ovary, bladder, or endometrium. Metastases from the lung, gastrointestinal tract, breast, and melanoma to the pelvic organs, prostate, or urethra are rare causes of this complication.
B. **Diagnosis**
1. **Symptoms** are often absent or insidious in onset. Anuria is highly suggestive, but partial high-grade obstruction of ureters can occasionally cause renal failure with a normal urine volume. A variable urine output or overflow incontinence causing dribbling (and the strong smell of urine during physical examination) suggest bladder outlet obstruction.
2. **Physical findings** are those of the underlying disease. Dullness to percussion in the suprapubic region suggests a mass or distended bladder.
3. **Postvoid residual urine** determination is often useful in evaluating for outlet obstruction.
4. **Ultrasonography** may show hydronephrosis. However, acute obstruction or chronic obstruction wherein the collecting system is encased in tumor may show minimal abnormalities. A normal-appearing but full collecting system in an oliguric patient suggests obstruction.
5. **Cystoscopy** demonstrates bladder outlet obstruction, shows the extent of bladder tumors, and permits retrograde ureterography.
C. **Management**
1. **Lymphomas** are usually successfully managed with chemotherapy, with or without focal RT.
2. **Solid tumors** usually require percutaneous catheter placement under combined ultrasound and fluoroscopic guidance. Stents placed from below are less commonly used. Systemic chemotherapy may be considered for responsive tumors. High-dose pelvic irradiation may be considered as an alternative, as may diverting urethral surgery. Most patients with pelvic tumors causing obstruction, however, are at an advanced stage of disease; therapy, including

percutaneous drainage of the renal pelvis, must be carefully considered in light of the potential for palliation, the extent of disease, and the overall prognosis.

III. Intrinsic renal disease causing renal failure

A. **Acute renal failure** may have an abrupt onset immediately after renal insult (e.g., radiocontrast administration). Acute renal failure may also arise more insidiously over days to weeks as an indirect consequence of malignancy (e.g., hypercalcemia, myeloma kidney resulting from deposits of Bence Jones proteins) or therapy (e.g., hyperuricemia after tumor lysis, nephrotoxicity, interstitial nephritis after administration of certain therapeutic agents). Although acute renal failure is often transient and reversible, certain causes can result in permanent renal failure (e.g., cisplatin toxicity, mitomycin-induced hemolytic-uremic syndrome). Oliguria is often present in more dramatic episodes of acute renal failure; in this case, laboratory parameters in Table 31.1 may be useful in distinguishing it from prerenal failure. Most causes of acute renal failure and many patients with acute renal failure, however, present with normal or nearly normal urine volumes.

B. **Acute tubular necrosis** (ATN) usually has an abrupt onset and is often oliguric. Urine specific gravity is usually near isosthenuria, and mild proteinuria is typical. ATN can often be suspected by the presence of many "dirty-brown" granular casts in the urine. Usually only small numbers of white and red blood cells and tubular epithelial cells are present. Early on, the sediment may be remarkably bland. Red blood cell casts are rare.

   1. **Several pathogenetic mechanisms** are recognized, and multiple mechanisms may be responsible in a given patient. Direct tubular toxicity is likely the mechanism for ATN as a result of aminoglycosides. Intratubular obstruction with cellular debris, protein casts, or (in the case of hyperuricemia) uric acid crystals may play a role. Ischemic injury due to sepsis or shock contributes in ATN.
   2. **The major histologic findings** are death and sloughing of tubular epithelial cells with preservation of tubular basement membranes and evidence of epithelial regeneration (mitotic figures). Proteinaceous casts and inflammatory cells may be present. Glomeruli are generally preserved. The lesion may be spotty with some nephrons appearing nearly normal. Disruption of tubular basement membranes (tubulorrhexis) and disrupted glomeruli suggest cortical necrosis, which carries a poor renal prognosis. Management includes avoidance of fluid imbalance and other supportive measures until function returns. Dialysis may be needed in some cases.
   3. **Radiocontrast** is a particularly important cause of acute renal failure in patients with malignancies because of the frequency with which these patients undergo radiocontrast studies.
      a. **Predisposing factors** include age older than 60 years, diabetes mellitus, volume depletion, other recent radiocontrast studies, high dose of contrast, concomitant nephrotoxic drug therapy, and, possibly, hyperuricemia.
      b. **Prevention** is the best management by hydrating patients and avoiding serial studies in a short period of time. Our routine in high-risk patients is 1 L of normal saline IV over 12 hours preceding the study, 12.5 to 25 g of mannitol IV "on call" to radiology suite, 40 to 80 mg furosemide at the end of the procedure, and, importantly, replacement of urinary losses for 8 to 12 hours with half normal saline. We have not encountered a single case of acute renal failure in which either the serum creatinine doubled or the patient required dialysis using this approach in high-risk patients.

C. **Tubulointerstitial nephritis** occurs acutely after the administration of a growing list of drugs but can occur more insidiously after 6 to 12 months of therapy with nonsteroidal antiinflammatory drugs (NSAIDs; see section D). The acute presentation is that of nonoliguric acute renal failure with variable systemic findings of allergic skin rash, fever, or arthralgias. Leukocytosis with eosinophilia may be seen, but pyuria with eosinophiluria is probably more common. Microscopic hematuria is a remarkably frequent finding in acute allergic tubulointerstitial nephritis.

   1. **Histologically,** there is a diffuse inflammatory reaction in the interstitium, sometimes with invasion of tubules by white blood cells. Eosinophils may dominate or may be only minimally present.
   2. **The renal prognosis** is good if the offending agent is discontinued. Anecdotal evidence favors the use of a short course of corticosteroids (40 to 60 mg/day of prednisone) if renal failure is severe or persists. Dialysis is only rarely required.

D. **Drugs that affect the kidneys of cancer patients**
   1. **Acute tubular necrosis**
      a. **Antibiotics.** Aminoglycosides, amphotericin, pentamidine, cephalosporin (rare), vancomycin (rare, but especially with aminoglycosides)
      b. **Chemotherapeutics.** Methotrexate, cisplatin (often irreversible damage), carboplatin (especially in high doses), streptozocin (and other nitrosoureas), cyclosporine (acute, hydrodynamic changes; chronic, interstitial fibrosis), FK-506, ifosfamide (especially when combined with cyclophosphamide), interferon-a, and suramin.
   2. **Acute interstitial nephritis.** Penicillins, cephalosporins, sulfa drugs, thiazide, furosemide, bumetanide (but not ethacrynic acid), antituberculous drugs, NSAIDs (usually after 3 to 6 months of use)
   3. **Chronic irreversible renal failure**
      a. **Acute hemolytic-uremic syndrome.** Mitomycin (most often reported cytotoxic agent; potentiated by tamoxifen), cisplatin, and rarely with cyclosporine, gemcitabine, and deoxycoformycin
      b. **Tubular interstitial fibrosis.** Cisplatin, cyclosporine, FK-506, ifosfamide
   4. **Fanconi's syndrome** (with or without rickets). Ifosfamide

E. **Tumor invasion**
   1. **Primary renal tumors** commonly invade renal parenchyma, of course, but renal failure requires extensive bilateral renal involvement and is a rare event. The more common cause of renal failure in patients with primary renal tumors is surgical ablation of renal tissue, the consequence of attempts to extirpate the tumor. Because renal cell carcinomas occur bilaterally in at least 5% of patients, preservation of renal tissue by segmental or heminephrectomy is an option to consider; it is a necessity in the patient with only one kidney if dialysis is to be avoided. Such selective ablative surgery may be impossible if tumor has invaded the renal vein (as it tends to do). Patients with renal vein involvement extending into the inferior vena cava often have degrees of renal thrombosis and occasionally consequent renal failure.
   2. **Solid tumor metastasis** to kidneys occurs frequently late in the course of many tumors but is a rare cause of renal failure or death.
   3. **Lymphoid tumors.** Renal involvement is common in acute lymphoblastic leukemia (about half of cases) and lymphoma. Renal failure is less common but does occur. Urinary findings include mild proteinuria, hematuria, and often tumor cells that, when present, are highly suggestive of renal invasion. Imaging studies show large, poorly functioning kidneys without hydronephrosis. Treatment with local irradiation or chemotherapy is associated with resolution of renal failure and diminution of renal size to or toward normal; both abnormalities may recur.
   4. **Retinoic acid syndrome.** Leukocytes may infiltrate the kidney and cause ARF as part of the retinoic acid syndrome, which is caused by the treatment of acute promyelocytic leukemia with all-*trans*-retinoic acid (see Chapter 25, section V.A.2.c). The syndrome responds to corticosteroids.

F. **Acute glomerulonephritis** causing renal failure is as rare in patients with underlying malignancies as it is in the general population. Certain lymphoproliferative disorders may result in mixed cryoglobulinemia that can cause rapidly progressive (crescentic) glomerulonephritis. Occasionally, tumor antigens can cause membranoproliferative glomerulonephritis, a presumably immune complex–mediated process that can result in renal failure (see section IV).

G. **Radiation nephritis** can occur 6 to 12 months after doses to the kidneys exceeding 2000 cGy as a function of dose and proportion of kidney tissue irradiated. Earlier-onset cases may manifest as severe or malignant hypertension, proteinuria of less than 2 g/day, and an active urinary sediment with microscopic hematuria and granular casts. Later-occurring cases mimic chronic interstitial nephritis with a bland urinary sediment, possible salt wasting, or hyporeninemic hypoaldosteronism. Treatment of either presentation involves controlling the blood pressure when elevated.

IV. Immunologic glomerular injury: the nephrotic syndrome

The nephrotic syndrome is an unusual but recognized complication of neoplasms. The syndrome may be caused by glomerular deposits of amyloid, by the deposition of immune complexes, or by less well-defined immunologic mechanisms.

A. **Incidence.** The incidence of nephrotic syndrome as a consequence of malignancies is unknown. From 6% to 10% of patients with nephrotic syndrome eventually manifest a malignancy, but the duration before clinical onset of the malignancy, the large number of patients with a wide variety of malignancies, and the number of isolated (single) case reports make some associations questionable. Accordingly, the clinical maxim that "patients older than 50 years of age with nephrotic syndrome should have a diligent search for cancer" probably overstates the case. Our approach in such patients is to perform a careful history and physical examination with attention to the lymphatic system, coupled with a complete blood count, chest radiograph, and stool for occult blood unless symptoms or findings suggest the need for further workup. Women should undergo mammography and pelvic examination with Papanicolaou's smear as part of their routine examination.

B. **Associations** exist with Hodgkin lymphoma (most common); other lymphoproliferative disorders; squamous cell carcinoma; and adenocarcinomas of the lung, kidney, thyroid, colon, cervix, and gastrointestinal tract (including esophagus, stomach, pancreas, and colon). The nephrotic syndrome may occur simultaneously with the clinical manifestation of malignancy. More often, what appear to be true associations of nephrotic syndrome occur months before or after the tumor manifestations, and such associations may occasionally exceed a year. Recurrence of previously treated tumor may be heralded by the return of the nephrotic syndrome by weeks or months.

C. **Pathology** is correlated with the most common tumors, as shown in Table 31.3.

Table 31.3 Renal pathology in the Nephrotic Syndrome associated with malignancy

D. **Pathogenesis.** Because of the similarity between the minimal change lesion seen in lipoid nephrosis and the lesion sometimes seen with Hodgkin lymphoma, a defect in T-lymphocyte function causing the generation of an aberrant T-cell factor (yet to be defined) has been postulated for both of these lesions. Glomerular deposition of immune complexes containing specific tumor antigens, viral antigens, and normal autoantigens has been described in single case reports regarding a number of tumors.

E. **Management.** Remission of nephrotic syndrome may occur with partial or complete elimination of the tumor, especially in Hodgkin lymphoma. Corticosteroid therapy for tumor-associated nephrotic syndrome is usually ineffective if the tumor cannot be controlled.

Suggested Reading

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Chapter 32 Neuromuscular Complications

Ellen E. Mack

I. Metastases to the brain

A. **Pathogenesis**
1. **Incidence.** Autopsy series show that 25% of patients who die of cancer have brain metastases.
2. **Tumor of origin.** The tumor that most commonly metastasizes to the brain is lung cancer, which is responsible for 30% of brain metastases. Brain metastases from pulmonary tumors tend to occur early in the course of malignancy, and their diagnosis is synchronous (i.e., before or at the same time as the primary tumor) in about one third of cases. Other types of tumors that commonly metastasize to the brain include renal cancer, breast cancer, and melanoma (each 10% of cases), along with metastases from tumors of unknown primary sites (15%). Carcinomas of the ovary, uterus, and prostate rarely produce intracerebral metastases.
3. **Mechanism.** Tumor dissemination to the central nervous system (CNS) is usually by the hematogenous route, and the distribution of lesions parallels the distribution of arterial blood flow. Eighty percent of brain metastases are supratentorial, 15% are cerebellar, and 5% are in the brain stem. About half of metastases are solitary, especially those from breast, renal, and colon cancers; metastases from melanoma and lung cancer are more likely to be multiple. Metastases can be solid, cystic, or hemorrhagic (especially choriocarcinoma, melanoma, and testicular carcinoma).
B. **Natural history.** Left untreated, metastatic brain tumors cause progressive neurologic deterioration leading to coma and death; the median survival time is only 1 month. About half of patients with brain metastases die of their neurologic disease, and the remainder die of systemic causes. Among treated patients, the median survival time is 3 to 8 months; patients with breast cancer and those with limited systemic disease who undergo surgical treatment survive longer.
C. **Clinical presentation.** The symptoms of brain metastases usually develop insidiously and progress to disability over a few weeks. The onset may be sudden, however, resembling a stroke, and occasionally symptoms may improve spontaneously (particularly in patients with hemorrhagic metastases). Single metastases usually cause focal cerebral dysfunction at presentation; multiple metastases often cause headache and mental status changes and, less commonly, focal deficits.
1. **Nonfocal signs and symptoms.** The classic morning headache is seen in only 40% of patients. Other nonlocalizing findings include papilledema, nausea and vomiting, mental status changes, and in some instances, diplopia. Calvarial metastases over the sagittal sinus may produce headache and papilledema without other neurologic signs.
2. **Focal signs and symptoms,** including hemiparesis, hemisensory loss, and aphasia, depend on the site of metastasis.
3. **Differential diagnosis.** Conditions that should be considered in the differential diagnosis of brain metastasis include the following:
   a. **Metabolic encephalopathy,** including hyponatremia, hypercalcemia, hypoxemia, uremia, hepatic encephalopathy, and hypothyroidism
   b. **Drug-induced encephalopathy** from analgesics, sedatives, steroids, chemotherapeutic agents, and other drugs
   c. **CNS infections,** including bacterial and fungal meningitis, herpes encephalitis, progressive multifocal leukoencephalopathy, cerebral abscess. (See Chapter 35, section II.B.)
   d. **Nutritional deficiency** (e.g., Wernicke's encephalopathy)
   e. **Cerebrovascular disease,** including stroke, hemorrhage, and venous obstruction due to thrombotic disorders and disseminated intravascular coagulation (DIC)
   f. **Paraneoplastic disorders,** especially subacute paraneoplastic cerebellar degeneration (see section V.A)
D. **Evaluation.** Brain metastases are readily detectable by computed tomography (CT) or magnetic resonance imaging (MRI). Most metastatic tumors enhance after administration of contrast material, but a noncontrast study should also be performed to evaluate for hemorrhage. MRI is more sensitive than CT, especially for lesions of the posterior fossa. CT scans, however, particularly if bone windows are used, are more sensitive in detecting bone metastases, especially at the base of the skull. Lesions detectable by CT or MRI that may resemble brain metastases include cerebral abscesses, parasitic disease, and occasionally stroke. Lumbar puncture is not useful in diagnosing brain metastases and is often contraindicated.
E. **Management.** The aims of therapy for patients with brain metastases are to relieve neurologic symptoms and to prolong survival. Exact treatment recommendations depend on the histology of the tumor, the degree of systemic dissemination of the tumor, and the patient's clinical condition.
1. **Dexamethasone,** usually 16 mg IV followed by 4 mg PO or IV every 6 hours, results in dramatic reversal of neurologic deficits and alleviation of headaches. Unfortunately, the effect is short-lived (weeks), but further improvement is possible with dose escalation and with definitive treatment. Dexamethasone should be tapered whenever possible.
2. **Anticonvulsant therapy** for patients with mass lesions of the brain is usually administered only to patients with known or suspected seizures (i.e., transient, usually brief, episodes of neurologic dysfunction with a clear onset and termination). They are also given prophylactically to patients for whom surgical resection is planned. Prophylactic use of anticonvulsants in nonsurgical patients is usually reserved for cases of metastatic melanoma because these lesions have a predilection for the gray matter and are hemorrhagic in nature and thus have a high likelihood of inducing seizures.
3. **Radiation therapy** (RT) is the standard treatment of brain metastases. The field usually encompasses the whole brain, and doses range from 2000 to 4000 cGy, administered by larger fractions in the lower-dose regimen.
4. **Surgery** provides a significant survival advantage to patients with brain metastases. Median survival for surgically treated patients is 10 to 12 months, and 12% of patients live 5 years or longer. Candidates for surgical resection should have solitary brain metastases and limited or controlled systemic disease. Surgical resection is considered in other cases on an individualized basis and may be influenced by the need for a tissue diagnosis. RT is given after surgical resection.
5. **Radiosurgery** is a method of delivering a single large dose of radiation to a well-defined target; the steep dose fall-off of this technique ensures that little radiation is delivered to surrounding tissues. It is an effective, minimally invasive outpatient procedure that is a treatment option for patients with small intracranial metastases. Radiosurgery may be used in place of surgical resection or whole-brain radiation therapy or as an adjuvant to either or both treatments. Local control rates appear to be equal for surgery and radiosurgery. Radiosurgery offers an advantage for metastases that are not surgically accessible, for multiple metastases, or for tumor types that are resistant to standard radiation therapy (e.g., renal cell carcinoma, melanoma) where control by radiosurgery appears to be superior.
6. **Chemotherapy.** Cytotoxic agents are generally not used to treat brain metastases, but responses have been documented in patients with metastatic breast cancer, small cell lung cancer, and lymphoma.

II. Metastases to the meninges

A. **Pathogenesis**
1. **Incidence.** Leptomeningeal metastases have been demonstrated at autopsy in 8% of patients with systemic malignancy.
2. **Associated tumors.** Although any systemic tumor can metastasize to the leptomeninges, those that do so most commonly are lymphoma, leukemia (especially acute), lung carcinoma (especially small cell), breast carcinoma, and melanoma.
3. **Mechanism.** Metastasis to the leptomeninges occurs by hematogenous spread through arachnoid vessels or the choroid plexus, by infiltration along nerve roots, and by extension from CNS metastases. The sites of heaviest infiltration are usually at the base of the brain, the major brain fissures, and the cauda equina.
B. **Natural history.** Leptomeningeal metastasis causes an inflammatory response that produces signs of meningismus and results in neurologic symptoms by several mechanisms. Direct invasion of cranial and spinal nerve roots as they traverse the subarachnoid space can cause radiculopathies. Invasion by neoplastic cells in the subarachnoid space can cause focal brain and spinal cord dysfunction. Decreased absorption of cerebrospinal fluid (CSF) due to obstruction of the arachnoid villi can cause hydrocephalus.
C. **Clinical presentation.** The hallmarks of leptomeningeal metastases are evidence of noncontiguous neurologic dysfunction and an excess of neurologic findings

in relation to symptoms. Although the presentation depends on the level of neuraxis involvement and the mechanism of disease production (see above), there are four basic clinical presentations. These may be seen alone or in combination, and meningismus may also be present.

1. **Spinal.** The most common presentation of leptomeningeal metastases is spinal. Signs and symptoms include back pain, radicular pain, weakness and numbness of extremities, and loss of bowel and bladder control.
2. **Cerebral.** About half of patients present with cerebral signs and symptoms, including headache, lethargy, change in mental status, gait ataxia, and seizures (partial and generalized).
3. **Cranial nerve.** Signs and symptoms include visual loss, diplopia, facial numbness, facial weakness, dysphagia, and hearing loss.
4. **Hydrocephalic.** Signs and symptoms of increased intracranial pressure, including headache, decreased level of consciousness, gait apraxia, and urinary incontinence.

D. **Evaluation.** Although the diagnosis of leptomeningeal metastases is often strongly suspected on a clinical basis, it can sometimes be difficult to make a definitive diagnosis. The general approach is to demonstrate disease radiographically and to confirm the diagnosis by examination of CSF.

1. **Imaging studies.** Images of the brain and full spine should be obtained because the entire neuraxis is at risk and requires treatment. MRI after administration of contrast material is the preferred modality. If MRI is unavailable, CT scans of the head, in conjunction with myelography, can be performed instead. Priority should be given to imaging the clinically involved portion of the neuraxis. Hydrocephalus in the absence of an obstructing lesion or contrast enhancement in the distribution of the spinal fluid suggest leptomeningeal involvement. Enhancement is most commonly seen in the basal cisterns, along the sylvian fissures, and along the nerve roots of the cauda equina, but it can also be seen along the sulci of the cerebral hemispheres, around the spinal cord, and rarely within the ventricles.
2. **CSF examination.** To confirm the diagnosis, the CSF is examined for protein and glucose content, cell counts, and cytology. Routine bacterial and fungal cultures should also be performed because the differential diagnosis often includes infectious meningitis. CSF may be obtained by lumbar puncture or, in cases of suspected spinal block, by cervical puncture with radiographic guidance.
   a. **Routine studies.** Elevated protein and pleocytosis (usually lymphocytic) are nonspecific findings consistent with metastatic disease. A low glucose level occurs in about 25% of cases and is thought to indicate more severe disease. The absence of infection should be confirmed.
   b. **Cytologic examination** confirms the diagnosis in about half of cases on the first tap. False-negative cytologic findings are not infrequent. The diagnostic yield increases to about 90% by the third tap.
   c. **Tumor markers** may serve as additional diagnostic tests and are useful in following response to therapy. Such biochemical markers include b-microglobulin and b-glucuronidase (leukemia and lymphoma), lactate dehydrogenase isoenzymes (leukemia and lymphoma), carcinoembryonic antigen (solid tumors such as lung and breast cancer and melanoma), human chorionic gonadotropin and a-fetoprotein (germ cell tumors) and cancer-specific monoclonal antibodies (especially B-cell markers to differentiate leukemic or lymphomatous cells from normal reactive T-cell CSF lymphocytes). Flow cytometry studies, which evaluate DNA abnormalities and estimate the degree of aneuploidy, may also be useful in cases of suspected leptomeningeal metastases (especially leukemic and lymphomatous) with nondiagnostic CSF cytologies.

E. **Management.** The optimal therapy for neoplastic meningitis has not been established. The basic premise is to treat clinically active or bulky disease with RT and to treat the remainder of the neuroaxis with intrathecal chemotherapy. A response can be achieved in about half of patients, but the median survival time is less than 6 months. Patients with breast cancer and lymphoma have the best prognosis.

1. **Dexamethasone** is of limited benefit in patients with leptomeningeal disease. A trial of low doses (4 to 16 mg/day) is warranted, however.
2. **RT** is limited to areas of clinical involvement and areas of bulky disease as defined radiographically to prevent severe marrow depression. The typical dose is 3000 cGy delivered in 10 fractions.
3. **Intrathecal chemotherapy** is used to treat the remainder of the neuraxis. The drug can be administered by lumbar puncture or by intraventricular reservoir. The drug is usually given twice weekly until no abnormal cells are found in CSF and is then given at progressively longer intervals. Preservative-free agents should be used.
   a. **Methotrexate,** 7 mg/m^2 (15 mg maximum) twice weekly followed by leucovorin rescue
   b. **Cytarabine,** 30 mg/m^2 twice weekly
   c. **Thiotepa,** 7 mg/m^2 twice weekly

III. Metastases to the spine can result in epidural cord compression, which is a neurooncologic emergency. Any cancer patient with back pain should receive a prompt and thorough evaluation. Patients with neurologic compromise localizing to the spinal cord or cauda equina require emergent evaluation and treatment.

A. **Pathogenesis**
1. **Incidence.** About 5% of patients with cancer develop clinical evidence of spinal cord compression (about one third the incidence of intracerebral metastases).
2. **Distribution.** About 10% of epidural metastases occur in the cervical spine, 70% in the thoracic spine, and 20% in the lumbosacral spine. About 10% to 40% of cases are multifocal.
3. **Responsible tumors.** Any tumor capable of metastasizing can cause spinal cord compression. Lung cancer accounts for 15% of cases; breast carcinoma, prostate carcinoma, carcinoma of unknown primary site, lymphoma, and myeloma each account for about 10% of cases.
4. **Mechanisms.** Spinal cord dysfunction arises by several mechanisms. The most common is direct extension of tumor from the vertebral bodies (a common site of metastasis) to the epidural space, resulting in cord compression. Other tumors, such as neuroblastoma and lymphoma, encroach on the spinal cord through the intravertebral foramina. Secondary vascular compromise can also occur, resulting in cord infarction that may cause the sudden irreversible deterioration seen in some patients. Direct metastasis to the spinal cord parenchyma is a much less common cause of spinal cord dysfunction in cancer patients.

B. **Diagnosis**
1. **Natural history.** The progression of disease from the spinal column to the epidural space with neural encroachment is manifested clinically as local back pain followed by radicular symptoms and eventually myelopathy.
   a. The initial stage of localized pain can last for several weeks or, in tumors such as breast cancer and lymphoma, for several months.
   b. Radicular symptoms usually herald further progression of the metastatic tumor but are still a relatively early symptom.
   c. After symptoms related to compression of the spinal cord or cauda equina occur, the progression is usually extremely rapid; a complete myelopathy may develop within hours. Rapid progression is especially common with lung cancer, renal cancer, and multiple myeloma.
2. **Clinical presentation** depends on the level of spinal involvement.
   a. **Midline or paravertebral back pain** is the initial symptom in more than 90% of patients with spinal cord compression due to malignancy. The pain is dull and aching and is caused by involvement of bone by the malignancy. Tenderness over the appropriate spinal level is usually readily elicited.
   b. **Radiculopathy** is usually manifested by pain in a dermatomal distribution but can also include sensory or motor loss in the distribution of the involved roots. Cervical disease and lumbar disease usually cause unilateral radiculopathy, whereas thoracic disease causes bilateral radiculopathy, resulting in a bandlike distribution of pain. The pain from thoracic radiculopathies can sometimes be similar to pain from pleurisy, cholecystitis, or pancreatitis. The pain from cervical or lumbar radiculopathies can simulate disk herniation.
   c. **Myelopathy** can rapidly result from further disease progression. Depending on the level of spinal involvement, the signs of myelopathy include bilateral weakness and numbness in the lower extremities and loss of bowel and bladder function. Associated neurologic findings include hyperactive deep-tendon reflexes, Babinski's responses, and decreased anal sphincter tone. Disease at the level of the cauda equina usually causes urinary retention and saddle anesthesia. Unusual presentations of spinal cord compression include ataxia without motor, sensory, or autonomic dysfunction. Metastasis to the spinal cord parenchyma can cause a myelopathy without back pain.
3. **Evaluation.** Because the prognosis worsens when myelopathy develops, the diagnosis of epidural metastasis should be established before the onset of spinal cord injury. The extent of workup depends on the clinician's suspicion for metastatic disease and the degree and rate of neurologic progression of the patient.
   a. **Plain radiographs** correctly predict the presence or absence of epidural metastases in more than 80% of cases. Loss of pedicles, destruction of the vertebral body, and vertebral body collapse are the most common abnormalities of cord compression seen on plain films. Plain films, however, provide no information about the degree and extent of neural impingement and therefore should be used only to evaluate patients without neurologic symptoms or where the index of suspicion is low.
   b. **Bone scans** may be useful in cases in which plain radiographs are normal but there is still a low index of suspicion for epidural cord compression.
   c. **MRI** is usually the procedure of choice for evaluating patients with suspected cord compression. MRI accurately defines the degree of neural impingement and the extent of bone involvement, is noninvasive, and accurately detects other entities in the differential diagnosis of myelopathy. Images should be obtained after the administration of a contrast agent. The procedure is usually performed in patients with neurologic dysfunction or in whom the index of suspicion for cord compression is otherwise high.
   d. **Myelography** may be used when MRI is unavailable, when multilevel disease is suspected and MRI of the entire spine is not feasible, or when CSF sampling is also required. If myelography shows a complete block, contrast material may need to be administered at both the lumbar and high cervical levels to establish the extent of disease. If myelography is performed, CSF should always be sent for routine studies and cytologic examination. Myelography is contraindicated in patients with coagulopathy and may worsen a neurologic deficit below the level of a spinal block.

    e. **Lumbar puncture** is usually performed in patients with epidural cord compression only if there is a suspicion of concomitant leptomeningeal dissemination of tumor.
   4. **Differential diagnosis**
    a. **Structural lesions.** Epidural hematoma (may occur spontaneously or after invasive procedures, especially in patients with a coagulopathy), epidural abscess, benign tumors (e.g., meningioma), herniated disk, osteoporotic vertebral collapse
    b. **Nonstructural lesions.** Paraneoplastic syndromes (see section V), radiation myelopathy (see section VI.B.3), Guillain-Barré syndrome
    c. **Back pain** in the absence of neurologic symptoms or findings in patients with normal imaging studies of the spine may be due to retroperitoneal metastases, which can be diagnosed by CT or ultrasound imaging.
C. **Prognosis.** The outcome is greatly improved if treatment is initiated before spinal cord symptoms appear. Other prognostic factors include the level of spinal cord involvement and the rate of neurologic progression. Patients with breast cancer and lymphoma tend to do better because their tumors progress less rapidly and respond to multimodal therapy. Patients with carcinomas that progress more rapidly and are less responsive to chemotherapy and RT tend to do less well. True paraplegia (strength of 0 on a scale of 0 to 5) that is not reversible with dexamethasone virtually never improves, even with surgical decompression.
D. **Management.** If neurologic symptoms have developed or if there is radiographic evidence of epidural encroachment of tumor, rapid therapeutic intervention is essential.
   1. **Dexamethasone** is useful for alleviating neurologic symptoms and helps to control pain associated with epidural cord compression. Treatment should begin immediately, even before diagnostic studies are performed. Dosing depends on the degree of neurologic involvement. For radiculopathy only, doses are usually 16 mg IV followed by 4 to 6 mg IV or PO every 6 hours. For rapidly evolving disease, or for evidence of myelopathy, treat with 100 mg IV followed by 24 mg IV every 6 hours. Begin tapering after benefit from definitive therapy has been demonstrated or the neurologic deficits become irreversible.
   2. **RT** is the primary treatment for spinal cord compression. It not only retards tumor growth but also greatly alleviates pain. RT is especially useful for tumors that are sensitive to radiation (e.g., lymphoma, myeloma), early and slowly progressive lesions, and metastases below the conus medullaris. The usual dose is 3000 to 4000 cGy over 2 to 4 weeks.
   3. **Surgery** is used in the treatment of some patients with tumor metastatic to the spine. If there is spinal cord compression and severe neurologic symptoms of recent, rapid onset, an emergent decompression can be accomplished by a laminectomy (posterior approach). If both systemic and spinal involvement of tumor are limited, and especially if the tumor is relatively resistant to radiation, the tumor and involved vertebral bodies can be resected from an anterior surgical approach, and the spine can be stabilized with prosthetic devices. RT is performed in addition to surgery, preferably after the operation. Other specific indications for surgery include the following:
    a. Unclear pathologic diagnosis on a clinical and radiographic basis
    b. Progression of neurologic abnormalities during RT
    c. Spinal cord compression in a previously irradiated area
    d. Spinal instability
   4. **Chemotherapy** is not usually used for local treatment of malignant spinal cord compression. Some oncologists may advocate its use in highly responsive tumors, such as lymphoma, if neurologic involvement is limited.

IV. Metastases to the peripheral nervous system

A. **Brachial plexus**
   1. **Anatomy.** The brachial plexus involves the C5 through T1 nerve roots. The upper portion of the plexus (C5 and C6) innervates the proximal arm musculature and sensation to the thumb. The lower portion (C8 and T1) innervates the hand musculature and sensation to the fifth digit. In the axillary region, the lower portion of the plexus is in close proximity to the lymphatic system.
   2. **Mechanism.** Tumor is most likely to involve the brachial plexus by direct invasion. Indeed, lung and breast cancer are the most commonly involved tumors. Other tumors that involve the brachial plexus usually metastasize to the upper lobe of the corresponding lung and then spread to the plexus through the lymphatic system.
   3. **Clinical presentation.** The most common presenting symptom is pain, which tends to radiate from the shoulder to the digits in a radicular fashion and is exacerbated by shoulder movement. Paresthesias and weakness, with loss of deep-tendon reflexes and evidence of muscle atrophy, occur in relation to the extent of involvement of the brachial plexus. Associated findings may include lymphedema of the arm, a palpable axillary or supraclavicular mass, and Horner's syndrome.
   4. **Differential diagnosis.** The primary entity to be differentiated from metastatic brachial plexopathy is radiation plexopathy. Other causes of plexopathy include surgical trauma, trauma secondary to poor limb placement during anesthesia, and radiation-induced tumors of the plexus. Metastatic tumors tend to involve the lower trunk of the plexus because of its close proximity to lymphatic vessels, whereas RT plexopathy is more likely to involve the upper trunk.
    a. **Metastatic plexopathy** is suggested by early severe pain, hand weakness, and Horner's syndrome.
    b. **Radiation plexopathy** is suggested by absent or mild pain, weakness of the shoulder girdle, and progressive lymphedema.
   5. **Evaluation.** Imaging with CT or MRI may be useful in demonstrating tumor mass in the region of the plexus. Surgical exploration and biopsy may be required to confirm the diagnosis, but false-negative biopsy results are not uncommon. Epidural disease due to infiltration along nerve roots is seen in some patients with metastatic plexopathy; therefore, additional imaging of the spine may be required, especially in patients with Horner's syndrome.
   6. **Management.** The tumor is treated with RT or chemotherapy as indicated. The primary management problem is usually pain control, as neurologic function usually does not return. Many patients develop chronic pain that is refractory to analgesics. Consultation for ablative procedures is often required.
B. **Lumbosacral plexus**
   1. **Mechanism.** Malignant lumbosacral plexopathy is caused mostly by direct extension of intra-abdominal tumors, but one fourth of cases are from metastases of extra-abdominal tumors. Nearly half of patients with metastatic plexopathy also have spinal epidural disease. Radiation plexopathy can result from pelvic irradiation and can present in a similar fashion.
   2. **Clinical presentation.** The most common presenting symptom is pain; usually unilateral, severe, unremitting low back or pelvic pain radiates into the leg. Pain is later followed by paresthesias, weakness, and loss of deep-tendon reflexes. Bladder function is usually preserved.
   3. **Evaluation.** CT scans are useful for detecting presacral masses or sacral erosion. Evaluation of the spine, usually by MRI, may also be required.
   4. **Management.** RT and chemotherapy are used to treat the malignancy as indicated. The goal of treatment is usually pain control, which is often difficult to achieve.
C. **Peripheral nerves.** Spread of systemic tumors to peripheral nerves is an unusual neurologic complication of malignancy. It occurs primarily in two settings:
   1. **Infiltrative polyneuropathy** can result from invasion of the endoneurium by lymphoma and leukemia. This syndrome is underrecognized by autopsy reports. Over weeks to months, it causes a widespread, asymmetric, multifocal neuropathy, which may be fulminant in some cases and lead to death. The diagnosis is made by biopsy of an involved sensory nerve.
   2. **Perineural spread of tumors** is seen with cutaneous and primary cancers of the head and neck (i.e., cancers of the larynx, pharynx, and tongue). Tumors invade the perineural space, spread proximally along the nerve, and may even enter the intracranial cavity and extend into the brain stem. The trigeminal and facial nerves are most commonly involved, often together, probably because of their rich coinnervation of the face. Orbital nerves may also be involved. The tumors most likely to disseminate along nerves are spindle cell variant and atypical squamous cell carcinomas. The diagnosis is based on clinical suspicion and is confirmed by biopsy. CT scans may show thickened, enhancing nerves.

V. Paraneoplastic syndromes are rare neuromuscular complications of cancer. They are important to recognize because they may herald early, potentially curable malignant disease. Paraneoplastic syndromes frequently present before the cancer is diagnosed and can be associated with neoplastic disease that is not yet radiographically detectable. Patients with paraneoplastic syndromes are believed to have a prolonged survival time with respect to the underlying malignancy. An autoimmune pathogenesis has been demonstrated for some of these disorders, and specific antibodies are associated with many of the paraneoplastic disorders. It is important to realize that clinically identical disorders may occur in patients without cancer, but such patients do not demonstrate these autoantibodies.

A. **Paraneoplastic cerebellar degeneration** (PCD) is a syndrome of pancerebellar dysfunction of subacute onset. Manifestations include truncal and appendicular ataxia, dysarthria, and nystagmus (often down-beating); patients are usually so severely affected that they are bedridden, have unintelligible speech, and are unable to care for themselves. Associated neurologic syndromes such as dementia or neuropathy may be present, but they tend to be much less severe.
   1. **Pathogenesis.** This disorder is associated with circulating antibodies that bind to both tumor and cerebellar tissue samples. The tumors in patients with PCD express antigens normally present only in the cerebellum, and the paraneoplastic syndrome is believed to result as a consequence of an immune response against the tumor. About half of affected patients have antitumor antibodies. The most common is anti-Yo (also called APCA, or anti-Purkinje's cell antibody), which binds to Purkinje's cells of the cerebellum and is seen in women with breast and gynecologic malignancies. Other antibodies that may be associated with this syndrome include anti-Hu (mostly with small cell lung cancer), anti-Ri (breast cancer), and anti-Tr (mostly in male patients with Hodgkin lymphoma).
   2. **Diagnosis.** The diagnosis should be suspected on clinical grounds because the neurologic presentation is distinct. A definitive diagnosis is possible in patients with anti-Yo, anti-Hu, and anti-Ri antibodies. Other diagnostic features include inflammatory cells in the CSF, normal brain scans, and the absence of other causes of cerebellar dysfunction. If there is no known underlying malignancy, a thorough systemic search for cancer must be undertaken. The diagnosis is sometimes not made until autopsy, when an occult malignancy is discovered, and examination of the brain shows loss of Purkinje's cells of the

cerebellum.

   3. **Therapy is ineffective.** Patients with PCD do not respond to plasmapheresis, immunosuppressive treatment with steroids and cytotoxic agents, or treatment of the underlying malignancy.

B. **Paraneoplastic sensory neuronopathy** (PSN), also referred to as *dorsal root ganglionitis,* is a syndrome of subacute progressive loss of proprioception and vibratory sense. Pain, temperature, and touch modalities of sensation are also affected, but to a lesser degree. Painful dysethesias and paresthesias are usually present. The result is a severe sensory ataxia that leaves patients bedridden. The neuropathy may affect the autonomic system, causing urinary retention, hypotension, pupillary changes, impotence, and hyperhidrosis. Sparing of the motor system is a hallmark of the syndrome, although patients are usually so impaired that they may have mild weakness from disuse atrophy. In patients with more widespread neurologic disease, such as dementia, myelopathy, or cerebellar dysfunction, the disorder is referred to as *paraneoplastic encephalomyelitis* (PEM).

   1. **Pathogenesis.** A circulating antibody, called anti-Hu (also called ANNA-1 for antineuronal nuclear antibody type 1), has been demonstrated in patients with PSN or PEM and malignancy, mostly small cell lung cancer. This antibody reacts with tumor specimens as well as with neurons throughout the nervous system. Often, the antibody binds predominantly to the dorsal root ganglia, causing inflammation and loss of neurons. The source of this antibody appears to be present in most small cell carcinomas. The paraneoplastic syndrome is thought to occur as a result of cross-reactivity during an immune response directed against the tumor. Despite the widespread presence of the antigen in tumors, only certain patients develop the antibody. Anti-Hu antibody causes other neurologic paraneoplastic syndromes associated with small cell carcinoma (see [section A](), [section F](), [section G](), and [section H]()), and sites of antibody binding in the nervous system correlate roughly with the neurologic presentation of patients with these various disorders.

   2. **Diagnosis.** The diagnosis should be expected on clinical grounds because the neurologic syndrome is often highly specific. Electromyographic (EMG) studies in patients with PSN usually show a total absence of sensory action potentials and normal or nearly normal compound muscle action potentials. A definitive diagnosis can be made by detecting the anti-Hu antibody. CSF studies show increased protein, a mild pleocytosis, and oligoclonal bands. A thorough attempt to diagnose an underlying malignancy must be made in patients who present without known cancer.

   3. **Therapy is ineffective.** Plasmapheresis, immunosuppressive therapy, or treatment of the underlying malignancy have not proved to be beneficial.

C. **Opsoclonus-myoclonus.** Opsoclonus is an ocular motility disorder consisting of irregular, involuntary, multidirectional eye movements that persist with eye closure and sleep. It may be associated with myoclonus (brief, jerking contractions of flexor muscles). Opsoclonus-myoclonus is classically associated with neuroblastoma in children, in whom it heralds a good prognosis. Less commonly, it is associated with ataxia and encephalopathy in adults with breast cancer. In the latter disorder, opsoclonus-myoclonus is associated with the anti-Ri antibody (or ANNA-2). Unlike PCD and PSN, opsoclonus-myoclonus can be relapsing and remitting in nature and may resolve spontaneously.

D. **Cancer-associated retinopathy** is a syndrome of visual loss that begins with obscurations and night blindness and proceeds to total blindness. It is most commonly associated with small cell lung carcinoma and melanoma. This disorder is associated with an antibody that recognizes the protein recoverin in the photoreceptor cells of the retina. It can be diagnosed by the presence of this antibody and by electroretinography.

E. **Limbic encephalitis.** Early manifestations of this disorder include personality changes (depression and anxiety), which are followed by a profound loss of short-term memory. Seizures, hallucinations, and hypersomnia may also be present. Limbic encephalitis is most commonly associated with small cell lung cancer and in some cases is attributable to the anti-Hu antibody.

F. **Brain-stem encephalitis** causes vertigo, nystagmus, facial numbness, oculomotor disorders, dysphagia, dysarthria, deafness, and long-tract signs. It is most commonly seen in small cell lung carcinoma and may be associated with the anti-Hu antibody.

G. **Motor neuronopathy, or motor neuron disease,** is a spectrum of disorders involving the motor system for which the association with malignancy is still poorly characterized. Unlike most other paraneoplastic disorders, this syndrome can arise late in the course of the malignancy, even during remission. It is most commonly seen in lymphoma (both non-Hodgkin and Hodgkin lymphoma), where it is frequently associated with a paraproteinemia. A similar condition can be seen as part of the spectrum of disease associated with the anti-Hu antibody and small cell lung carcinoma.

These disorders are characterized by a progressive loss of motor function with sensory sparing that may resolve spontaneously. Loss of anterior horn cells is seen pathologically. A viral etiology has been speculated. EMG studies can help establish the diagnosis.

H. **Neuropathies associated with plasma cell dyscrasias.** A symmetric, distal sensorimotor polyneuropathy can be associated with plasma cell dyscrasias, including monoclonal gammopathy of undetermined significance, multiple myeloma with or without systemic amyloidosis, osteosclerotic myeloma, and Waldenström's macroglobulinemia. The polyneuropathy can be associated with other findings as part of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). It is often associated with a monoclonal paraprotein (often immunoglobulin M- k), which reacts with a myelin-associated glycoprotein, resulting in a demyelinating neuropathy. The neuropathy is progressive, but usually no pain or autonomic involvement occurs. Treatment with plasmapheresis is beneficial in some patients.

I. **Polymyositis and dermatomyositis.** These disorders cause symmetric, proximal muscle weakness, characterized by difficulty rising from a chair, combing hair, and so forth. Only a small minority of cases of polymyositis and dermatomyositis are associated with malignancy. These disorders are discussed further in Chapter 28, [section II.E]().

J. **Myasthenia gravis** causes progressive fatigue with exercise. It occurs in 30% of patients with thymomas; 10% of patients with myasthenia gravis are found to have thymomas. The syndrome is due to an antibody that binds to the acetylcholine receptor at the postsynaptic membrane of the neuromuscular junction. The diagnosis is made by detecting the antibody in the serum, by the response to edrophonium chloride (the Tensilon test), and by the characteristic EMG response to repetitive stimulation. Treatments include pyridostigmine bromide (Mestinon), steroids, plasmapheresis, resection of an associated thymoma, and sometimes resection of the thymus. Myasthenia gravis is difficult to treat, especially during the period of tumor resection. Treatment should be undertaken only by those familiar with the disorder.

K. **Lambert-Eaton myasthenic syndrome** is characterized by proximal muscle weakness, especially of the pelvic girdle. In contrast to myasthenia gravis, the weakness improves with exercise, and therefore the physical examination may fail to substantiate the patient's complaints. Hyporeflexia, muscle tenderness, and autonomic dysfunction (orthostatic hypotension, impotence, dry mouth) may be associated with the condition. Lambert-Eaton myasthenic syndrome results from an autoantibody that reacts with voltage-gated calcium channels of peripheral cholinergic nerve terminals and tumor cell membranes.

   1. **Associated tumors.** Mostly small cell lung cancers are found; may also be seen in association with lymphoma and thymoma, and one third of patients have no malignancy.

   2. **Diagnosis.** Detection of the antibody against P/Q-type VGCC (voltage-gated calcium channels) and by EMG, which should show small compound muscle action potentials that increase after brief exercise or repetitive stimulation at high frequencies (20 to 50 Hz).

   3. **Therapy.** Effective therapies include treatment of the underlying malignancy, guanidine hydrochloride (125 to 500 mg PO three or four times daily), 3-4-diamino-pyridine (5 to 25 mg PO three or four times daily), steroids, intravenous immune globulin, and plasmapheresis.

VI. Adverse effects of radiation to the nervous system

A. **Mechanism.** The nervous system is highly susceptible to damage from radiation. The degree of neural dysfunction depends on the total radiation dose and fraction size, the volume of irradiated tissue, and the time elapsed since RT. Reactions are classified as acute, early delayed, and late delayed. Acute reactions during RT are believed to be due to a transient breakdown in the blood–brain barrier, leading to increased intracranial pressure. The risk for acute reactions increases with larger fraction sizes. Early delayed reactions, occurring weeks to months after irradiation, are usually self-resolving and are thought to be due to demyelination. Late delayed reactions, usually occurring months to years after irradiation, have been demonstrated pathologically as a coagulative necrosis of the involved white matter. Hyalinization of blood vessels is associated with vascular thrombosis and accumulation of fibrinoid material.

B. **Radiation syndromes.** Specific neurologic syndromes occur in response to RT, depending on the site of irradiation. The skin, hair, subcutaneous tissues, and bone are at risk as well. Hair loss occurs when the dose to the brain exceeds 2000 cGy over 2 weeks and is rarely permanent when supervoltage equipment is used. Hair regrowth usually occurs within 3 months, but this may be greatly impeded by chemotherapy.

   1. **Radiation encephalopathy.** Acute encephalopathy manifests as headache, nausea, vomiting, somnolence, and worsening of neurologic deficit. Early delayed encephalopathy often mimics tumor recurrence, both clinically and radiographically, and consists of headache, lethargy, fever, and worsening of neurologic symptoms. In children undergoing prophylactic whole-brain RT for acute lymphoblastic leukemia, this condition is referred to as the *radiation somnolence syndrome.* Chronic radiation encephalopathy is associated with atrophy of the brain and is more likely to occur after whole-brain RT than after focal RT. Clinical findings include memory loss, cognitive dysfunction (learning disabilities in children), gait abnormalities, and urinary incontinence. This chronic disorder sometimes responds to CSF shunting.

   2. **Radiation necrosis** is a late delayed reaction to RT that mimics tumor recurrence. It causes worsening focal neurologic deficits and progressive enhancing lesions on imaging studies. Positron-emission tomography imaging can be useful in differentiating radiation necrosis from tumor recurrence. Because the necrotic lesion has mass effect, surgical extirpation is often useful.

   3. **Radiation myelopathy.** No acute reactions to irradiation of the spine usually occur. Early delayed reactions usually manifest as electric shock–like sensations in the arms or legs that last for several seconds and are precipitated by flexion of the neck (Lhermitte's sign). The condition is usually self-limited. Late delayed damage to the spinal cord results in a progressive myelopathy that may be asymmetric in onset. This disorder is secondary to necrosis of the white matter and usually occurs with doses greater than 5000 cGy given over 5 weeks by conventional fractionation.

   4. **Radiation plexopathy.** Brachial and lumbosacral plexopathy are a late delayed reaction to RT and are discussed in [section IV.A.4](). Early delayed reactions

cause transient, self-limited paresthesias and weakness.

5. **Loss of special senses.** Loss of vision and hearing are relatively common sequelae of cranial irradiation. Visual loss can result from radiation-induced optic neuropathy, retinopathy, glaucoma, cataract formation, and dry-eye syndrome. Hearing loss is due to otitis media (acute or early delayed effect) or to sensorineural damage (late delayed effect).

6. **Hormonal deficiencies** occur as a result of hypothalamic and pituitary dysfunction after irradiation. The most common deficiency involves growth hormone, but thyroid, adrenal, and gonadal dysfunctions also occur.

C. **Management.** Acute and early delayed reactions are self-limited but often respond to treatment with steroids. Late delayed reactions, which are usually due to neuronal and glial necrosis, do not respond to treatment.

D. **Radiation-induced tumors** tend to occur decades after irradiation and include meningiomas, nerve sheath tumors, astrocytomas, and sarcomas.

E. **Radiation-induced cerebrovascular disease** is caused by severe advanced atherosclerosis that occurs years after irradiation. It is thought to be due to occlusion of the vasa vasorum. Patients are at high risk for transient ischemic attacks and strokes.

VII. Neurologic complications of chemotherapy are common and depend on the dose of the chemotherapeutic agent, whether the drug is given as part of a multidrug regimen and whether it is given in conjunction with radiation therapy. Chemotherapeutic agents may be toxic to the entire nervous system or cause more limited neurotoxicity, affecting only the central or peripheral nervous systems, or portions thereof. Various clinical syndromes, therefore, occur.

A. **Encephalopathy** (insomnia, agitation, drowsiness, depression, confusion, headache) usually develops acutely after administration of the offending agent but less commonly can also develop chronically, when it usually presents as dementia. Responsible agents include methotrexate, cytarabine, procarbazine, mitotane, l-asparaginase, ifosfamide, cisplatin, vincristine, 5-fluorouracil, tamoxifen, nitrosoureas, etoposide, interferon- a, pentostatin, tegafur, levamisole, and, rarely, hexamethylmelamine, fludarabine, and 5-azacitidine.

B. **Cerebellar syndrome** (limb ataxia, gait disturbance, nausea and vomiting, nystagmus) can be seen with the use of cytarabine, procarbazine, fluorouracil, and the nitrosoureas.

C. **Seizures** are rarely associated with the use of vincristine, cisplatin, hydroxyurea, l-asparaginase, ifosfamide, and procarbazine.

D. **Peripheral neuropathy** (paresthesias, loss of deep-tendon reflexes, distal extremity weakness) is a common neurologic complication of chemotherapy. Responsible agents include vincristine, vindesine, vinblastine, procarbazine, paclitaxel (Taxol), docetaxel (Taxotere), suramin, hexamethylmelamine, etoposide, teniposide, and cisplatin.

E. **Cranial neuropathy** (loss of hearing, vision, taste) may develop from the use of cisplatin, vincristine, and the nitrosoureas.

F. **Myelopathy** (quadraparesis, paraparasis, bowel and bladder dysfunction) is seen mostly with the use of intrathecal agents, especially methotrexate.

G. **Combined radiation and chemotherapy induced neurotoxicity** is often difficult to substantiate but is known to occur with the use of methotrexate and cisplatin and possibly with carboplatin, the nitrosoureas, cytarabine, and 5-fluorouracil in combination with radiation therapy.

VIII. Other complications of cancer

A. **Cerebrovascular disease** (CVD). Strokes and hemorrhages are the second most common cause of CNS lesions in cancer patients. (Metastases are the most common.) Autopsy series show that 15% of cancer patients have CVD, of whom half have symptoms during their lifetime. In addition to risk factors that apply to the general population, patients with cancer have additional factors that predispose them to CVD.

1. **Cerebral embolisms** can result from the following:
   a. Nonbacterial thrombotic endocarditis, seen especially with adenocarcinoma of the lung and gastrointestinal tract, is the most common cause of cerebral infarction in patients with carcinoma.
   b. Septic emboli from systemic fungal infections, most commonly *Aspergillus* species.
   c. Tumor emboli (uncommon)

2. **Thrombosis** can cause strokes as well as occlusion of the superior sagittal sinus. The latter syndrome presents with headache, obtundation, and sometimes bilateral strokes. Thrombotic disorders in cancer are caused by the following:
   a. DIC
   b. Hyperviscosity syndromes
   c. Chemotherapy, especially with l-asparaginase.
   d. Vasculitis, usually as a complication of infection

3. **Hemorrhages** are especially common in patients with leukemia but are associated with many malignancies. Specific etiologies include the following:
   a. Thrombocytopenia
   b. DIC
   c. Hyperleukocytosis (acute myelogenous leukemia)
   d. Tumor invasion of blood vessels
   e. Bleeding diatheses (e.g., in hepatic failure)

4. **Subdural hematomas** can result from the following:
   a. Metastases
   b. Lumbar puncture

B. **CNS infections** are discussed in Chapter 35, section II.B.

C. **Ocular complications in cancer**

1. **Metastases to the eye and orbit**
   a. **Etiology.** Ocular and orbital metastases occur most frequently in breast cancer. Hematogenous dissemination to the eye also complicates acute leukemia, melanoma, and sarcomas and carcinomas of the lung, bladder, and prostate. Several head and neck cancers can directly invade the orbit.
   b. **Diagnosis**
      1. **Signs.** Patients develop eye pain, diplopia, loss of vision, and exophthalmos. Fundal hemorrhages, leukemic infiltrates, or masses may be evident on ophthalmoscopy.
      2. **CT scans** of the orbits, brain, and surrounding tissues must be obtained in patients with symptoms of ocular or orbital metastases.
      3. **Biopsy** is performed if the retroorbital mass is the sole site of disease.
   c. **Management.** Prednisone, 40 mg/m^2 PO daily, should be given if vision is threatened. RT to the orbit is the treatment of choice for metastatic disease but may result in blindness. On the other hand, emergency treatment of the eye with small doses of RT may prevent blindness in patients with ocular involvement from acute leukemia.

2. **Thrombosis of the central retinal vein**
   a. **Etiology.** Central retinal vein thrombosis occurs in hyperviscosity syndromes associated with Waldenström's macroglobulinemia and occasionally with plasma cell myeloma. Marked erythrocytosis from polycythemia vera may also cause the problem.
   b. **Diagnosis.** Patients develop a sudden, often painless loss of vision. "Sausage-link" widening of conjunctival and fundal veins may be present. The fundus may also have hemorrhages, hard and soft exudates, and microaneurysms.
   c. **Management.** Plasmapheresis is used for malignant paraproteinemias (see Chapter 22), and phlebotomy for polycythemia vera (see Chapter 24, Polycythemia Vera).

3. **Retinal artery occlusion**
   a. **Etiology.** Embolic retinal artery occlusion is most commonly due to atherosclerosis but may rarely be seen with atrial myxoma, marantic endocarditis, and cryoglobulinemia.
   b. **Diagnosis.** Patients develop sudden, painless loss of vision and a pale fundus with a bright red spot over the fovea.
   c. **Management.** Ophthalmologic consultation should be obtained immediately in all cases. Emergent measures include vigorous massage of the eye, administration of tolazoline (Priscoline, 75 mg IV) as a vasodilator, and aspiration of aqueous humor.

4. **Amaurosis fugax** can occur in patients with marked thrombocytosis (usually greater than 800,000/µL) caused by myeloproliferative diseases, especially primary thrombocythemia or polycythemia vera. Treatment consists of antiplatelet drugs (e.g., aspirin, 300 to 900 mg/day) and chemotherapy. Plateletpheresis may also be used in severe cases.

Suggested Reading

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Chapter 33 Bone and Joint Complications

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I. Metastases to cortical bone Metastases to bone marrow are discussed in Chapter 34, Cytopenias, section I.A.

A. **Pathogenesis.** The bones most frequently involved with metastases are the femur, pelvis, spine, and ribs. Tumor cells may metastasize to vertebral bodies or the skull without entering the systemic circulation by seeding through Batson's vertebral venous plexus (a valveless system of veins along the entire vertebral column that communicates with other venous systems, from the pelvis to the brain).

1. **Mechanisms.** Osteoclast-mediated destruction and direct tumor cell-mediated destruction are the two mechanisms by which skeletal metastases destroy bone. Stimulation or inhibition of osteoblastic activity also occurs. The relative balance of osteoclastic and osteoblastic activity determines whether a lesion is lytic or blastic. Malignant cells secrete many factors known to both stimulate the proliferation and activity of osteoclasts and produce osteolysis, possibly indirectly through the osteoblasts. These factors include the following:

    a. Transforming and fibroblastic growth factors; tumor necrosis factors

    b. Prostaglandins; interleukin-1 (IL-1), IL-6, and IL-11

    c. Parathyroid hormone–related protein

    d. Bone morphogenic proteins

    e. Matrix-degrading proteins, such as specific metalloproteinases

    f. Osteonegrin, a natural inhibitor of osteoclastic development

2. **Frequency.** A relatively small number of malignancies account for most tumors that spread to bone.

    a. **Tumors that commonly metastasize to bone.** Carcinomas of unknown primary site, the lung, breast, kidney, prostate, and thyroid; plasmacytoma; melanoma; and Ewing's sarcoma

    b. **Tumors that rarely metastasize to bone.** Ovarian carcinoma and most soft tissue sarcomas

B. **Natural history.** Bone metastases are usually confined within the bony substance and generally do not cross joint spaces. They lead to pain, pathologic fracture, neurologic compromise, and progressive immobility.

1. Cervical spine metastases compressing the cord may result in myelopathy and weakness of the muscles of respiration, resulting in paralysis, pneumonia, and possibly death. Thoracic spine metastases compressing the cord can result in paraplegia.

2. Dense sclerosis of bones (e.g., with prostate cancer) or extensive involvement of bone marrow spaces can result in refractory pancytopenia.

3. Crippling bone disease can make bedridden patients susceptible to decubitus ulcers, hypercalcemia, and infections.

4. Pathologic fracture is less likely in the osteoblastic variant of metastatic prostate cancer.

C. **Prognosis.** The expected survival of patients with skeletal metastasis varies. Patients with lung cancer survive only a few months. The median survival of patients with breast cancer and only skeletal metastases, however, is 2 years. The median survival time of patients with stage IV renal cancer is 11 months, but 20% to 30% of those with a solitary metastasis survive 5 years after the lesion is surgically resected. About 20% of patients with skeletal metastases from prostate cancer survive 5 years.

D. **Diagnosis**

1. **Symptoms and signs**

    a. **Dull, aching, or boring pain** that is worse at night and improves with physical activity is characteristic of pain from bone metastases. This pain pattern also occurs with malignant invasion of retroperitoneal structures without bony involvement. These characteristics are directly opposite to the typical pain of degenerative diseases.

    b. **Bone pain intensified by activity** is often the first symptom of imminent fracture. On the other hand, pathologic fractures can also be painless. Patients often report falling down, but it is often not clear whether the fracture was the cause or effect of the fall.

    c. **Spinal instability** can cause excruciating pain, which is mechanical in origin. The patient is comfortable only when lying absolutely still, and any movement reproduces severe pain.

    d. **C7 to T1 vertebral pain** is usually referred to the interscapular region; radiography of both cervical and thoracic spines is essential in these patients.

    e. **T12 to L1** vertebral pain is usually referred to the iliac crest or sacroiliac joint.

    f. **Sacral pain** is usually referred to the buttocks, perineum, and posterior thighs. The pain typically is exacerbated by sitting or lying down and relieved by standing.

2. **Serum alkaline phosphatase levels** are usually elevated in patients with bone metastases. Elevations appear to reflect an osteoblastic (or healing) response to tumor destruction. In pure osteolytic tumors, such as plasma cell myeloma, the serum alkaline phosphatase level is normal. Nonneoplastic causes of increased bone alkaline phosphatase include the following:

    a. Primary hyperparathyroidism, thyrotoxicosis, acromegaly

    b. Renal disease

    c. Paget's disease

    d. Osteomalacia

    e. Healing fractures

    f. Physiologic increases occur in the following circumstances:

        1. Pediatric age group (before bony epiphyseal closure)

        2. Pregnancy (placental source)

3. **Radionuclide bone scan,** using ^{99m}Tc-methylene bisphosphonate, is the most effective screening test for skeletal metastases. The scan often detects metastases several months before radiologic changes are evident. Radionuclide bone scans reflect osteoblastic activity; thus, purely lytic lesions with a preponderance of osteoclastic activity may not be apparent on a bone scan.

    a. **Specificity.** Patients with a known cancer and bone pain have positive bone scans in 60% to 70% of cases; patients without bone pain have positive scans in 10% to 15% of cases.

        1. Multiple "hot spots" are more specific than one or two. In cancer patients without known metastases, the appearance of new abnormalities on bone scan represents metastasis in only 10% of patients with one lesion and in 25% of patients with two lesions.

        2. Retroperitoneal tumors often cause a bony response, characterized by diffuse isotope uptake over the anterior aspect of the spine.

        3. Patients with metastases from breast or prostate cancer, when clinically responding to endocrine therapy, may develop new abnormal areas on scans because of bone healing and increased osteoblastic activity.

        4. Multiple myeloma is the most frequent cause of false-negative bone scans. These patients rarely have positive bone scans except in fractured areas.

        5. Decreased uptake of radioisotope is seen in irradiated bone that never did contain metastases and thus cannot be interpreted as a sign of absence of metastases or of reduced tumor burden.

    b. **Benign conditions that can cause a positive bone scan**

        1. Bone healing after fracture

        2. Radiation osteitis

        3. Arthritis and spondylitis

        4. Osteomyelitis

        5. Osteonecrosis

        6. Regional osteoporosis

        7. Paget's disease of bone

        8. Hyperostosis frontalis interna

        9. Osteopetrosis (Albers-Schönberg disease)

        10. Osteogenesis imperfecta

4. **Plain radiographs** remain essential for the diagnosis and characterization of bone metastases. Metastatic lesions must involve 30% to 50% of bone matrix to

be visualized on plain radiographs. Some tumors typically produce osteolytic or osteoblastic metastases, but both processes are accelerated in affected bone, and most tumors produce mixed lesions (Table 33.1). *Diffuse osteoporosis* may be the only radiologic abnormality in some patients with extensive bony involvement (e.g., multiple myeloma). *Skeletal infections* with many pyogenic bacteria are frequently associated with sclerotic reactions; chronic granulomatous infections, however, may result in purely lytic lesions.

Table 33.1 Radiologic characteristics of bone metastases

    a. **Indications.** Radiographs should be obtained and compared with previous films of the involved areas in patients with the following conditions:
        1. Bone pain
        2. Abnormalities on physical examination suggestive of fracture
        3. Asymptomatic abnormalities in bone scans
    b. **Routine skeletal surveys** are not indicated except in patients with plasma cell myeloma that may be associated with painless osteolytic lesions in crucial bone sites, such as the femora or cervical spine.
    c. **Vertebral involvement** from metastatic cancer is manifested by loss of the pedicles or lateral spinous processes and vertebral collapse with sparing of the intervertebral space. Infections that involve the intervertebral disk space destroy it. Some chronic infections (e.g., tuberculosis or brucellosis), however, may involve the vertebrae and not the intervertebral spaces, result in vertebral collapse, and thereby mimic malignancy.
    d. **Postirradiation osteitis** produces irregular, diffuse (rather than localized) lytic or mixed lesions confined to the radiation portal.
  5. **Computed tomography** (CT) scan is useful to diagnose early metastases of bone, particularly the spine, when hot spots are detected on the radionuclide scan but corresponding plain radiographs are normal. CT scans elucidate cortical erosion, subtle fractures, and matrix calcification or ossification. In addition, they are useful to evaluate epidural compression, the extent of metastases (e.g., in the femur), and areas difficult to image by conventional radiographs (e.g., costovertebral junction, sternum, and sacrum).
  6. **Magnetic resonance imaging** (MRI) scanning is best at delineating the extraosseous extension of a soft tissue mass through the bone cortex (e.g., epidural compression). This technique is also ideal for demonstrating the intraosseous extension of tumor into the cancellous bone.
  7. **Biopsy.** If a fracture has already occurred, care must be taken to sample the tumorous area adequately rather than the healing area of fibrous tissue and osteoid formation. Specific expertise in bone histopathology must be available. If only a single bone is involved, the biopsy must be approached as if the lesion were resectable for cure. Potentially curable lesions include a solitary renal cell metastasis and sarcoma.
    a. **Indications.** If other sites associated with a lower risk for morbidity are not available, biopsy is done on an accessible site. Bone biopsy for the differential diagnosis of cancer is indicated in patients with the following conditions:
        1. An isolated bone lesion that the radiologist interprets as being compatible with a primary bone tumor
        2. An osteolytic bone lesion in a crucial area (e.g., cervical spine or femoral neck) and no history of cancer
        3. A history of a cancer that metastasizes to bone, localized bone pain, normal radiographs of the area, equivocal bone scan and alkaline phosphatase results, and no evidence of disease elsewhere
        4. Isolated bone pain in a region that was previously irradiated and radiographic findings that are not typical of postirradiation osteitis
    b. **Contraindications.** Bone biopsy should not be done in symptomless patients with isolated, osteolytic lesions in noncrucial areas that are suspected to be benign lesions or metastatic disease. Biopsy in these patients often results in chronic pain at the biopsy site. If a cancer is discovered, it is a metastasis for which treatment could have awaited the development of symptomatic disease.

E. **Management**
  1. **Medical management** is necessary in patients with multiple painful metastatic sites.
    a. **Chemotherapy and endocrine therapy** are useful for treating metastatic tumors known to respond to these modalities. Chemotherapy doses may need to be attenuated because of compromised marrow function from neoplastic invasion or irradiation.
    b. **Bisphosphonates.** Pyrophosphonates are natural compounds that are potent inhibitors of osteoclast-mediated bone resorption and contain two phosphonate groups bound to a common oxygen. Bisphosphonates (such as pamidronate or clodronate) are analogues of the endogenous pyrophosphonate with a carbon replacing the oxygen atom. The wide variety of alternative carbon substitutions results in marked differences in antiresorptive properties and side effects. Bisphosphonates have become the standard treatment for tumor-induced hypercalcemia (see Chapter 27, section I), have been successfully used in the treatment of conditions characterized by increased osteoclast-mediated bone resorption (such as Paget's disease of bone or osteoporosis), and are a valuable form of therapy for bone metastases.
        1. These drugs are poorly absorbed and often poorly tolerated when administered orally. They are highly concentrated in bone and become biologically inactive once the drug becomes a part of bone that is not remodeling. As a result, continued administration of bisphosphonates is required to achieve the desired lasting inhibition of bone resorption.
        2. *Intravenous* **pamidronate** (90 mg IV every 4 weeks) as a supplement to antitumor therapy substantially reduces morbidity and subsequent skeletal events in patients with myeloma or breast cancer with bone metastasis. Pain is improved in about half of patients given pamidronate even without anticancer treatments. Oral clodronate is also helpful but appears to be less effective than intravenous pamidronate. The use of bisphosphonates in other cancers, including prostate cancer, is not yet substantiated by double-blind trials.
        3. Bisphosphonates may also have an antitumor effect; some randomized trials have showed a reduction in both skeletal and visceral metastases in patients with myeloma or breast cancer. Third-generation bisphosphonates (e.g., zoledronate and ibandronate) are undergoing clinical trials.
    c. **Criteria for response of bone metastases to therapy.** The appearance of new osteoblastic lesions on radiographs or bone scans or increasing size of sclerotic lesions does not necessarily indicate progression of metastases. Indeed, these findings may represent clinical improvement. Although the response of bone metastases to treatment is difficult to quantitate, it may be evaluated by assessing the following:
        1. Pain relief and quality of life
        2. Serum tumor markers
        3. Biochemical markers of bone resorption (e.g., hydroxyproline urinary excretion)
        4. CT scans
    d. **Bracing of the vertebral column** helps relieve pain and protect neurovascular structures while the lesions are resolved with radiation therapy (RT) or chemotherapy. Bony strength to resist gravitational forces must be adequate. Bracing of the extremities is seldom helpful.
  2. **RT** ameliorates pain and may produce bone union and prevent fracture. The optimal dose of RT has not been defined. Smaller doses (e.g., 800 cGy given once) may be as effective as 2500 to 4000 cGy given over 2 to 4 weeks. This undoubtedly convenient, single or very short dose schedule, however, may not be adequate for patients with a relatively good prognosis.
    a. **Pathologic fractures.** The administration of RT after orthopedic fixation of pathologic fractures is generally considered standard therapy, but the clinical benefit of this additional treatment *has not been demonstrated.* After orthopedic fixation, the bone encompassing the entire prosthesis is typically included in the radiation portal. RT may begin as soon as the patient can be moved if the incision can be spared; otherwise, treatment is delayed until the skin has healed.
    b. **Isolated sites of bone pain.** RT controls local pain from bony metastases in more than 80% of patients within 2 weeks to 3 months. Irradiating a few severely painful sites may reduce the analgesic dose needed to manage patients with multiple sites of pain.
    c. **Asymptomatic osteolytic lesions** of the cervical spine and long bones are irradiated to prevent complications.
    d. **Hemibody irradiation** is used by some centers for control of pain caused by bone metastases. The treatment is effective in about 60% of patients, but it is associated with gastrointestinal upset and hematosuppression, particularly transfusion-dependent anemia.
  3. **Radiopharmaceuticals,** especially [85]Sr (Metastron), can decrease pain for several months in about 75% of patients with skeletal metastases from breast or prostate cancer. Such agents are useful when endocrine therapy fails to control the disease (see Chapter 2, section IV.B).
    a. [89]Sr is preferentially taken up and retained at sites of increased bone mineral turnover; uptake in bone adjacent to metastases is up to five times greater than for normal bone. This agent appears to provide effective adjuvant therapy to local-field RT with decreased new sites of pain, decreased need for further RT, decreased analgesic requirement, and improved quality of life.
    b. Hematologic toxicity is the major precaution but is usually transient. Other agents (including ^{32}P, [153]Sm, and [186]Re) generally are associated with more hematologic toxicity or have undergone fewer clinical trials than [89]Sr.
    c. Unfortunately, substantial numbers of patients achieve incomplete pain resolution, and some patients get no pain relief at all. None of the radiopharmaceuticals affects survival. Relatively few patients exhibit antitumor activity when treated with radiopharmaceuticals.
  4. **Surgery** plays a crucial role in managing bony metastases that endanger neurologic function or ambulation. Surgery can usually be avoided when RT or chemotherapy is effective and adequate stability of the bone permits natural repair.

Orthopedic consultation should be obtained in all patients with metastatic lesions of the femoral neck or shaft or with pathologic limb fracture. When considering operative treatment, the major factors include the patient's general medical condition, functional goals, and comfort and quality of life; the

anticipated responsiveness of the tumor to RT alone; the ease of delivering nursing care; and the morbidity of the contemplated procedure.

- a. **Methyl methacrylate,** an acrylic bone cement, replaces deficient bone and greatly enhances the ability to use metal implants. It increases compressive strength and torque capacity, promotes hemostasis, and should be used with fixation devices whenever bone stock is inadequate to permit rigid fixation or implantation. The use of methyl methacrylate entails considerable potential for local complications, and the circulating monomer may be associated with intraoperative systemic complications.
- b. **Complications.** Surgical treatment for pathologic fractures is associated with an operative mortality rate of about 8% and an infection rate of about 4%. The risk for infection increases in previously irradiated sites and in immunocompromised patients. Common reasons for failure of internal fixation include poor initial fixation, improper implant selection, and progression of disease within the operative field.
- c. **Embolization.** Blood loss during surgical stabilization or biopsy of a metastatic lesion may be life-threatening. Metastatic breast and particularly renal cell cancers are notoriously hypervascular. Preoperative angiography and occlusion of feeding vessels, particularly for lesions of the acetabulum or spine, may be indicated. The embolization of vertebral lesions, however, is associated with a risk for spinal cord injury.
- d. **Rehabilitation.** Patients treated surgically for pathologic fractures caused by metastases are good candidates for intensive rehabilitation programs unless they have hypercalcemia or require parenteral narcotics, which are associated with very short survival times.

F. **Surgical management of the appendicular skeleton.** The threshold to treat lower extremity lesions is lower than that for upper extremity disease as a result of the weight-bearing function of the legs. However, lifting and pulling with the arms generate high distractive forces. In addition, patients with metastases to the lower extremities often require crutches or a walker, which generate high compressive loads in the bones of the arms. These issues must be factored into the decision of how to best treat an upper extremity (usually humeral) lesion.

1. **Surgical methods** for metastases to long bones of the limbs include the following:
   - a. **Reinforcement of the involved bone** with internal splints (bone plates, hip nails, intramedullary rods). Whenever possible, intramedullary fixation (nails or endoprostheses) is preferred over extramedullary fixation (plates) because the former results in smaller dissections, stronger fixation, and more rapid return to weight bearing.
   - b. **Removal of the metastatic tumor** from the bone (either by surgical excision or débridement), insertion of an internal fixation device or prosthesis, and supplemental fixation with bone cement.
   - c. **Reconstruction of the articular surfaces** of the proximal humerus, hip, or knee after *en bloc* excision of involved segments of periarticular bone with either total joint arthroplasty or hemiarthroplasty. Prosthetic arthroplasty is useful in the following circumstances:
     1. Reconstruction of large destructive areas that are not amenable to internal fixation
     2. Salvage of failed internal fixation devices
     3. Salvage of lesions in which there are no RT options to prevent disease progression
   - d. **Amputation of dysfunctional extremities** riddled with tumor in patients with intractable pain, reasonable life expectancy, and an absence of limb-sparing treatment options

2. **Upper extremities.** Small lesions involving the humerus that are unlikely to fracture and that are sensitive to RT may be treated successfully with nonoperative measures, including RT. Lesions that are larger and in patients using walkers or crutches may be best treated with prophylactic fixation or endoprosthetic replacement followed by RT.

   Pathologic fracture of the humerus usually occurs at the junction of its proximal and middle thirds and in the past was often treated by stabilizing the extremity in a cast or sling. Internal fixation or prosthetic replacement is now the treatment of choice for these patients because the risk for nonunion and infection increases when surgery is performed on an irradiated limb, and pain relief is predictable with modern orthopedic techniques.

3. **Lower extremities: prophylactic orthopedic surgery.** Prophylactic internal fixation, followed by RT to inhibit further tumor growth, is always considered in patients with lytic lesions in the femoral neck or shaft that are at risk for pathologic fracture. Prophylactic surgery should be considered in the following circumstances:
   - a. The patient is in good general medical condition, and
   - b. The lytic lesion of the femur or tibia is more than 2.5 cm in diameter or involves more than half of the total cortical width (implies a 50% likelihood of fracture if untreated), or
   - c. Spontaneous avulsion of the lesser trochanter has occurred, or
   - d. Pain from lytic lesions persists despite RT.

4. **Lower extremities: pathologic fractures.** Untreated pathologic fractures rarely heal, and although RT may achieve local control, bony union remains unlikely. Internal fixation is indicated for pathologic fractures of the femur or tibia to decrease pain and to permit early ambulation.
   - a. **Femoral head and neck fractures.** Internal fixation may be considered but is usually inadequate. A standard cemented femoral hemiarthroplasty is safe, provides long-lasting relief from pain, permits early ambulation without the need for postoperative RT, and is preferred. Prosthetic replacement is particularly required if extensive cortical destruction would not allow a stable construction even with bone cement augmentation. If the articular cartilage and subchondral bone of the acetabulum are intact, a bipolar or standard endoprosthesis is used. The complication rate is 20%.
   - b. **Intertrochanteric fractures.** Nail-plate devices are used when sufficient residual bone is present to allow stable bony fixation and to support body weight, but intramedullary devices are frequently required. Prosthetic replacement is considered if there is extensive bony loss, if pathologic fracture has developed slowly resulting in extensive destruction, or if there is no possibility of obtaining structural stability; the complication rate, however, is substantial.
   - c. **Subtrochanteric fractures** are more difficult to repair because the fracture often extends into the intertrochanteric area or femoral shaft. The fractures are usually stabilized with a reconstruction nail. Nail-plate devices are associated with a high frequency of implant failure, but intramedullary devices are helpful, especially with the use of methyl methacrylate. Extensive destruction may require the use of a modular oncologic or calcar-replacing prosthesis, but local morbidity is significant, and an ideal device to attach the abductor muscles to the prosthesis has yet to be devised.
   - d. **Femoral shaft fractures** require intramedullary fixation supplemented with interlocking screws and bone cement if there has been extensive cortical loss.
   - e. **Lesions of the acetabulum** may respond to chemotherapy, but they still leave the patient with a painful hip if subchondral collapse and deformity have already begun. Reconstructive surgery with total-hip replacement is often beneficial in patients with reasonable life expectancy (e.g., those with breast cancer). This procedure is demanding because acetabular support and fixation may require the use of flexible Steinmann pins in the superior ilium and across the sacroiliac joints to transmit the weight-bearing stresses to intact bone. A protrusio acetabulum ring is often needed to provide additional structural support.

G. **Management of the axial skeleton.** Most cancer patients with mild mechanical instability of the spine and neck or back pain can be successfully treated with bracing and RT. Surgery is associated with a significant rate of complications (about 20%) but can be very important when the spine becomes unstable. Segmental spinal fixation systems use hooks and screws to attach rods to the posterior spine at multiple vertebral levels. Newer techniques use combinations of bone cement, allograft bone, and metal devices to replace or supplement diseased vertebral bodies. Patients may get out of bed on the first postoperative day and typically require a custom-fitted low-profile plastic orthosis.

Patients in whom spinal instability is likely to develop should undergo surgical stabilization before RT. Whenever possible, adjuvant RT should be delayed 3 to 6 weeks after surgery to maintain spinal alignment and to minimize wound complications.

1. **Surgery for spinal metastases** may be indicated in the following circumstances:
   - a. The diagnosis of metastatic cancer has escaped diagnosis at other sites. Percutaneous trocar biopsy may be necessary when needle biopsy fails to provide a diagnosis.
   - b. Mechanical instability from fracture causes pain and progressive deformity.
   - c. Pathologic fracture causes compression of the spinal cord or nerve roots.
   - d. A symptomatic tumor is known to be resistant to RT (e.g., renal cell carcinoma).
   - e. A spinal tumor continues to progress despite adequate RT.

2. **Restabilization of the spine may not be indicated** in the following circumstances:
   - a. Multiple osseous and soft tissue metastases exist.
   - b. More than two or three vertebrae are destroyed and need replacement.
   - c. The patient has poor nutritional, immunologic, or pulmonary status or severe disease not related to the malignancy.

3. **Cervical spinal metastases** must be irradiated regardless of symptoms and often require immobilization of the head and neck. A soft cervical collar is the least uncomfortable method but should be used only in patients with minimal disease. A rigid collar-like brace is adequate support if there is some intrinsic stability. If there is gross instability and the integrity of the spinal cord is in jeopardy, it may be necessary to rigidly fix the head with a special halo device and placement of screws into the skull. These prosthetic devices are often used until the patient succumbs.

4. **Thoracolumbar spinal metastases**
   - a. **Painful lesions** should be irradiated. MRI should be done first to search for potential sites of epidural compression and to plan radiation fields. Many

patients have a soft tissue mass extending around the involved vertebrae. These masses compress nerves, contribute to pain, and should be included in the radiation port. Fiberglass braces and corsets may reduce back pain and help stabilize the spine.

    b. **Rapidly progressive metastases** that are refractory to RT may be manifested by increasing pain, worsening destruction on radiographs, or the development of neurologic deficits. Open decompression of the spinal cord and internal fixation to permit early mobility (1 to 3 weeks) should be considered, but the outlook for these patients is poor.

5. **Spinal decompression**

    a. **Laminectomy** provides direct access to posterior and posterolateral tumors but compromises the stability of the spine. Spinal cord compression is usually a result of tumors of the vertebral body (i.e., anterior to the spinal cord); thus, laminectomy does not reliably relieve symptoms. Below the level of the third cervical vertebra, laminectomy should only be used for lesions in the dorsal elements, laminae, and pedicles.

    b. **Anterior surgical decompression** of the spinal cord is performed using thoracotomy or laparotomy, especially for RT-resistant tumors (e.g., renal cell carcinoma). Anterior decompression involves the removal of the vertebral body and all tumor anterior to the spinal cord (vertebrectomy). The spinal column is reconstructed with a graft or cage, and a second, posterior stabilization is usually needed. Custom-shaped methyl methacrylate in combination with plates is often used for fixation; bone grafts are preferred in patients when life expectancy exceeds 6 months because any purely mechanical construct will eventually fail if there is no bony healing. The anterior route provides immediate mechanical stability and the best chance for neurologic recovery. The associated success rate is reported to be 75% to 90%, with less blood loss and fewer complications than laminectomy.

    c. **Posterolateral surgical decompression** is an alternative for the technically difficult lesions above the sixth thoracic vertebra and is useful in more debilitated patients. Patients are able to sit in a chair on the night of surgery and to begin walking the next day.

        1. Posterolateral decompression removes a part of the rib and lamina to gain access to the vertebral body and decompress the anterior aspect of the spinal cord from the side. After completing vertebrectomy and removing the disks, the surgeon inserts a vertical strut (graft or cage) between the end plates of the healthy vertebrae above and below the tumor site. Posterior fixation rods, which can be placed through the same incisions, provide immediate stability.

        2. The advantage of this approach is that it does not require thoracotomy. Posterior spinal instrumentation can be carried out at the same time as tumor removal, often with video-assisted endoscopic techniques. This procedure may reduce patient morbidity, days in intensive care, and days of hospitalization while providing the same quality of neurologic recovery and maintenance of function as anterior resection. Access to the tumor, however, is usually limited because the surgeon is working around the spinal cord. Neurologic recovery has been less reliable than with a formal anterior approach.

    d. **Vertebroplasty** is a promising new procedure consisting of the percutaneous injection, under fluoroscopic guidance, of methyl methacrylate into a diseased vertebral body. The procedure is most commonly used to treat osteoporotic compression fractures, but experience in treating myeloma and metastatic carcinoma has been accumulating. A variant of this procedure uses a balloon to restore vertebral height and compress both cancellous bone and tumor before injecting the cement.

II. Occurrence of cancer in connective tissue disorders
The associations of rheumatic conditions with the development of malignancies probably reflect immune dysregulation, chronic immune stimulation, and the use of immunosuppressive drugs in their treatment.

A. **Sjögren syndrome** is associated with a 44-fold increased risk for non-Hodgkin lymphoma (NHL), particularly of the monocytoid B-cell type. An intermediate stage of "pseudolymphoma" may persist for years.

B. **Dermatomyositis and polymyositis.** Various kinds of malignancy develop in about 25% of patients with these disorders, particularly dermatomyositis. The cancer may present at the time of diagnosis or at a significantly later time. Thus, an extensive radiographic or invasive search for malignancy at the time of diagnosis is not recommended.

C. **Rheumatoid arthritis** is associated with a four-fold increased incidence of malignancies (which are usually hematopoietic) in the United States and an increased risk for oropharyngeal carcinomas in Japan. Felty's syndrome, which has been extended to include the presence of increased numbers of circulating CD16-positive large granular lymphocytes, is associated with a 13-fold increased occurrence of NHL. The use of cytotoxic agents is believed to be involved in the pathogenesis of malignancies in rheumatoid arthritis, but patients have developed cancer without such exposure.

D. **Scleroderma** with pulmonary fibrosis has previously been reported to be associated with bronchoalveolar cell carcinoma, but this association has not been observed in more recent series. Fibrosing disorders that resemble scleroderma and are associated with a significant risk of malignancy include the following:
1. **Palmar fasciitis with inflammatory polyarthritis.** This syndrome is accompanied by thickening of the palmar fascia, which can progress to Dupuytren's contracture. The syndrome can precede recognition of the malignancy by several months and is most often associated with ovarian carcinoma.
2. **Reflex sympathetic dystrophy syndrome** shows several clinical features of the palmar fasciitis syndrome and is associated with Pancoast's tumor when it affects the upper extremities and with gynecologic tumors when it affects the lower extremities.

E. **Vasculitis**
1. **Cutaneous hypersensitivity (leukocytoclastic) vasculitis** is the form of vasculitis that is most strongly associated with coexistent malignancy, including both hematopoietic neoplasms and solid tumors. This association is strongest for hairy cell leukemia, which is also associated with a high occurrence of polyarteritis nodosum.
2. **Sweet's syndrome** (acute febrile neutrophilic dermatitis) is associated with malignancy in 15% of cases, usually acute leukemia. The syndrome comprises fever, leukocytosis, and a characteristic eruption of painful, erythematous papules on the head, neck, and upper extremities.
3. **Erythema nodosum,** a variety of panniculitis, is associated with Hodgkin lymphoma and leukemia.
4. **Mixed cryoglobulinemia** is associated with hepatocellular carcinoma, NHL, and hepatitis C virus infection.

F. **Other connective tissue diseases**
1. **Systemic lupus erythematosus.** About 5% of patients develop malignancies, usually hematopoietic and probably related to the use of immunosuppressive drugs.
2. **Lymphatoid granulomatosis** affects the lungs and may result in NHL.
3. **Gout.** Two thirds of patients with myeloproliferative disorders have hyperuricemia and hyperuricosuria. The occurrence of acute gouty arthritis in these patients has been markedly reduced with the routine prescription of allopurinol.

III. Paraneoplastic bone and joint conditions

A. **Hypertrophic osteoarthropathy** is manifested by clubbing of the fingers, pain and effusion in large joints, and periosteitis. The ankles, knees, elbows, and wrists are the most frequently involved joints. The extremely painful periosteal reaction usually involves the extensor surfaces of the legs and forearms. The change in the overlying skin resembles cellulitis with induration, erythema, and *peau d'orange.*
1. **Associated tumors.** Hypertrophic osteoarthropathy develops most frequently with lung adenocarcinomas, less frequently with other lung carcinomas, and occasionally with gastrointestinal adenocarcinomas and intrathoracic sarcomas.
2. **Benign causes of clubbing**
    a. Hereditary clubbing
    b. Lung abscess
    c. Bronchiectasis
    d. Tuberculosis
    e. Endocarditis
    f. Biliary cirrhosis
    g. Crohn's disease
    h. Cyanotic congenital heart disease
3. **Diagnosis.** Clubbing should be self-evident; patients should be questioned about the duration of the abnormality. Sponginess, by palpation, of the proximal nail beds may indicate early clubbing. Radiographs of painful joints or long bones often show periosteal reactions.
4. **Therapy.** Control of the associated tumor usually alleviates symptoms of hypertrophic osteoarthropathy. The pain can be relieved by a variety of nonsteroidal antiinflammatory drugs (NSAIDs). Patients with severe pain require narcotic analgesics.

B. **Pachydermoperiostosis** associated with lung cancer consists of a dense overgrowth of periosteum resulting in clubbing and leonine facies (see Chapter 28, section II.I).

C. **Joint pain, subcutaneous fat necrosis (panniculitis), and eosinophilia** occasionally constitute the presenting features of pancreatic cancer.

D. **Hypercalcemia and hypocalcemia.** See Chapter 27, section I.A and section II.A.

E. **Rheumatic manifestations that suggest an occult malignancy.** No distinguishing features of rheumatic syndromes define the coexistence of cancer. The following manifestations should strongly suggest a thoughtful search for malignancy, *particularly if they first occur at 50 years of age or older.* They may improve or disappear with therapy directed at the malignancy.
1. Explosive seronegative polyarthritis, first occurring at 50 years of age or older and presenting with swollen and tender joints, with a predilection for the lower extremities sparing the small joints and wrists, and with mild nonspecific synovitis identified by synovial biopsy.

2. Monoclonal gammopathy in a patient with typical rheumatoid arthritis
3. Palmar fasciitis and polyarthritis
4. Eosinophilic fasciitis unresponsive to steroidal therapy
5. Raynaud's phenomenon first occurring at 50 years of age or older (often with asymmetric involvement of the fingers and progression to necrosis)
6. Cutaneous leukocytoclastic vasculitis, first occurring at 50 years of age or older and presenting as if apparently idiopathic

F. **Direct infiltration of malignancy into articular tissues**
   1. **Sarcomas** can present as primary malignancies of any joint.
   2. **Metastases** can affect any joint and mimic inflammatory arthritis.
   3. **Acute leukemic arthritis** is caused by leukemic infiltration of synovium. It is usually symmetric and may resemble rheumatic fever or juvenile rheumatoid arthritis. Effusions may occur. In 25% of cases, adjacent bone may develop lytic lesions, osteoporosis, or osteoblastic changes. Brief symptomatic responses can be obtained with ibuprofen or aspirin. Treatment of the underlying leukemia resolves with arthritis.
   4. **Chronic leukemic arthritis** is uncommon; it is usually symmetric but is otherwise similar to the acute type both in radiographic patterns and response to therapy.
   5. **Myeloma-induced amyloidosis** produces carpal tunnel syndrome and, rarely, a rheumatoid arthritis-like syndrome. Synovial tissues may be densely infiltrated with myeloma cells.

IV. Adverse effects of radiation to bone

A. **Radio-osteonecrosis of the mandible** may complicate RT of head and neck cancers. The problem occurs more often in patients with large tumors, bone invasion, history of large alcohol intake and heavy smoking, poor dentition, poor oral hygiene, and poor nutritional status. The mandible becomes brittle and superinfected, resulting in pain, fractures, and draining fistulas.
   1. **Diagnostic criteria**
      a. Localized pain and tenderness
      b. Mucosal ulceration or necrosis (occasionally, a fistula) with exposure of bone and, occasionally, cutaneous fistulas
      c. Loose teeth in the suspected area
      d. Radiographs showing a lytic lesion of the mandible, sometimes with a radiodense sequestrum or involucrum
      e. Manifestations should not be clinically evident for at least 4 months after completion of treatment.
   2. **Prevention** of radio-osteonecrosis involves proper dental extractions before RT and oral hygiene and fluoride treatment regimen during and after RT. If possible, the patient should not have any dental extractions for 2 years after RT. Even with these precautions, osteonecrosis develops in 5% to 10% of patients when a high-dose RT portal overlies the mandible.
   3. **Treatment**
      a. **Conservative management**
         1. Frequent mouthwashes with dilute hydrogen peroxide, or a baking soda and salt solution
         2. Systemic antibiotics, usually penicillin
         3. Topical nystatin or bacitracin ointment
         4. Analgesics
         5. Gentle débridement
      b. **Aggressive management**
         1. Hyperbaric oxygen treatments
         2. Surgical resection of the nonviable portion of the mandible
         3. A combination of hyperbaric oxygen and surgical resection

B. **Radiation osteitis** may mimic bony metastases. Differentiation of these disorders is discussed in section I.D. Postirradiation pathologic fractures of the femoral neck may rarely complicate pelvic irradiation.

C. **Radiation-induced bone sarcomas** have been reported after high-dose irradiation of both benign and malignant lesions. The incidence is less than 0.1% of all 5-year survivors; the latent period is more than 5 years.

D. **Premature closure of bone epiphyses and apophyses** can result in shortening, kyphosis, and asymmetry of osseous structures in children who have received RT.

V. Adverse effects of chemotherapy on bone

A. **Aseptic necrosis of the hip** is a complication of high doses of glucocorticoids. The risk is proportional to the dose of drug and not to the duration of therapy. Increased pressure in the intramedullary space causes the sudden onset of hip pain. Capsular irritability is demonstrated by flexing the hip and medially rotating the thigh. Early diagnosis is best established by MRI. Radionuclide bone scan is the diagnostic test of second choice. Removal of bony cores from the necrotic areas predictably, if incompletely, relieves pain and may favorably alter the natural history of osteonecrosis if done before the occurrence of secondary changes, such as collapse of subchondral bone and articular cartilage.

B. **Postchemotherapy rheumatism** is a syndrome of myalgias and arthralgias that develops within 1 to 3 months after completing adjuvant chemotherapy for breast cancer using cyclophosphamide and 5-fluorouracil. Mild periarticular swelling occurs in some cases. NSAIDs are not effective. Symptoms are self-limiting and generally resolve over several months. Extensive workups for breast cancer recurrence or for inflammatory rheumatologic disease are not needed in this setting.

C. **Raynaud's phenomenon** is a common toxicity of treatment with cisplatin, vinblastine, or bleomycin.

D. **Arthralgias** associated with **paclitaxel** therapy usually begin 2 to 3 days after treatment and resolve within 5 days. Problematic arthralgias have also been reported in rare patients treated with **tamoxifen.**

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Chapter 34 Hematologic Complications

Dennis A. Casciato

Increased Blood Cell Counts

I. Erythrocytosis (polycythemia) Erythrocytosis is defined as an elevation of the hematocrit, hemoglobin, and red blood cell (RBC) count above the *upper limits of normal*. Normal limits in adults are as follows:

	Men	**Women**	
Hematocit	52%	47%	
Hemoglobin	17.7 gm/dl	15.7 gm/dl	
Red cell count	$5.9 \times 10^6/\mu L$	$5.2 \times 10^6/\mu L$	
Red cell mass	36 ml/kg	32 ml/kg	(or, >25% above mean normal predicted value)

  A. **Relative polycythemia** is characterized by normal RBC mass and decreased plasma volume. Causes of relative polycythemia include dehydration, diuretics, burns, capillary leak, decreased oncotic pressure ("third- spacing"), hypertension, and stress ("Gaisböck's syndrome").

  B. **Primary polycythemia** is caused by intrinsic defects of hematopoietic progenitors.
    1. **Acquired primary polycythemia** (polycythemia vera [PV]) develops independently of serum erythropoietin (EPO) concentration. Uncontrolled proliferation of marrow elements results in an increased RBC mass. Diagnostic criteria for PV are discussed in Chapter 24, Polycythemia Vera, section I.A.
    2. **Primary polycythemia due to truncation of the EPO receptor** can be congenital or familial. An increased proliferation of erythrocytes, elevated RBC mass, hypersensitivity of erythroid progenitors to EPO, low serum EPO levels, normal hemoglobin oxygen dissociation, and absence of progression to leukemia characterize this rare disorder. Other gene defects in addition to that affecting the EPO receptor usually are also present in a high percentage of affected families.

  C. **Secondary polycythemia** is associated with increased RBC mass due to extrinsic stimulation of progenitors by circulating substances such as EPO.
    1. **Appropriate erythrocytosis**
      a. **Chronic hypoxemia** is a potent stimulus for erythropoietin production. Causes of hypoxemia include pulmonary diseases, right-to-left intracardiac shunts, low atmospheric pressure (high altitudes), and alveolar hypoventilation (brain disease or pickwickian syndrome). Intermittent arterial desaturation and erythrocytosis may be caused by supine posture, particularly in obese patients with pulmonary disease.
      b. **Heavy smoking.** Excessive and sustained exposure to carbon monoxide from cigarettes or cigars, which produces an increased affinity between the remaining oxygen and the hemoglobin molecule, is a common cause of erythrocytosis.
      c. **Congenital disorders** include hemoglobinopathies with high oxygen affinity (abnormal oxyhemoglobin dissociation), overproduction of EPO, and familial deficiency of 2,3-biphosphoglycerate (rare).
      d. **Androgen therapy** stimulates erythropoiesis.
    2. **Inappropriate erythrocytosis** occurs with elevated EPO levels in the absence of generalized tissue hypoxia and is seen in a variety of diseases.
      a. **Renal diseases** account for about 60% of all cases of inappropriate erythrocytosis, and renal adenocarcinomas account for half of those cases. Cysts, other tumors, hydronephrosis, and transplantation make up the remaining renal causes of erythrocytosis.
        1. **Renal cell carcinoma** is associated with erythrocytosis in 1% to 5% of cases. The tumor cells are the site of EPO synthesis.
        2. **Renal transplantation** is associated with erythrocytosis in 10% of patients. The erythrocytosis has been ascribed to transplanted artery stenosis, graft rejection, hypertension, hydronephrosis, diuretic use, and EPO overproduction from residual renal tissue, especially in polycystic disease.
      b. **Hepatocellular carcinoma and cerebellar hemangioblastoma** each account for 15% to 20% of cases of inappropriate erythrocytosis in the literature.
      c. **Other causes** of inappropriate erythrocytosis are rare. Huge uterine leiomyomas and ovarian carcinoma can cause renal hypoxia or ectopic EPO production. Pheochromocytomas and aldosteronomas cause erythrocytosis through multiple mechanisms.

  D. **Evaluation of patients with polycythemia**
    1. **Screening evaluation.** The following studies are obtained in all patients with persistent polycythemia:
      a. **Perform a complete history and physical examination** to search for known causes of erythrocytosis. Search for treatments that are associated with erythrocytosis (androgen therapy, renal transplantation). Diligently search for splenomegaly, which would suggest PV.
      b. **Evaluate for intravascular volume depletion** (e.g., are diuretics being administered?); replete the volume and then reassess.
      c. **Analyze the complete blood count** (CBC). The presence of granulocytosis, eosinophilia, basophilia, or thrombocytosis suggests PV.
      d. **Measure arterial oxygen partial pressure and saturation.** The RBC mass is roughly proportional to the degree of arterial desaturation. Arterial oxygen saturation less than 90% and a Pao_2 of less than 60 to 65 mm Hg may result in erythrocytosis.
      e. **If the patient smokes tobacco, measure the carboxyhemoglobin concentration;** values of more than 5% are associated with erythrocytosis. Note that smoking may also cause granulocytosis.
    2. **Special diagnostic studies**
      a. **RBC mass** determination is paramount for distinguishing absolute polycythemia from relative polycythemia. RBC mass must be measured with ^{51}Cr-labeled erythrocytes to confirm absolute erythrocytosis. Plasma volume is measured concomitantly with ^{125}I-labeled albumin to demonstrate relative erythrocytosis.
      b. **Abdominal radiography** (intravenous pyelogram, renal ultrasonography, or abdominal computed tomography [CT] scanning) is indicated in all patients with absolute erythrocytosis that is not explained by either PV or appropriate erythrocytosis because the frequency of renal causes is high.
      c. **Serum EPO concentration** can be measured if the diagnosis is in doubt. If the EPO level is high in the presence of erythrocytosis, EPO is being produced inappropriately. If the EPO level is not high, primary polycythemia is present.
      d. **Oxyhemoglobin dissociation curve** is indicated in patients with a family history of unexplained erythrocytosis.
      e. **Other diagnostic studies** for inappropriate erythrocytosis are obtained *only ii* the screening evaluation exposes abnormalities that could indicate pathology of a specific organ.
      f. **Bone marrow examination** is not diagnostic of any disorder associated with erythrocytosis. Fibrosis is present in some PV cases. Cytogenetic studies and *in vitro* studies of hematopoiesis may be helpful in difficult cases when PV is suspected.

II. Granulocytosis

A. **Definitions**
 1. **Granulocytosis.** The upper limit of normal for neutrophils is 8000/µL.
 2. **Leukemoid reactions.** The term *leukemoid reaction* should be restricted to granulocytosis with circulating promyelocytes and myeloblasts.
 3. **Leukoerythroblastic reactions** are characterized by immature granulocytes in association with nucleated erythrocytes in the peripheral blood. Platelet counts may be normal, increased, or decreased. *Differential diagnosis* includes the following:
   a. Metastatic tumor in the marrow
   b. Marrow fibrosis with extramedullary hematopoiesis
   c. Marrow recovery after severe hematosuppression
   d. Shock, hemorrhage
   e. Brisk hemolysis, hereditary anemias
B. **Causes of granulocytosis**
 1. **Increased proliferation in the marrow** is seen in the myeloproliferative disorders (MPDs), marrow rebound after suppression by drug or virus, and as a chronic response to infection, inflammation, or tumor. The mechanism of tumor-induced granulocytosis most often involves increased production of granulocyte and granulocyte-macrophage colony-stimulating factors (G-CSF, GM-CSF), interleukin-1 (IL-1), and IL-3.
 2. **Increased marrow proliferation and increased granulocyte survival** are seen in chronic myelogenous leukemia (CML).
 3. **Shift from the marrow storage pool into the circulation** is seen in response to stress, endotoxin, corticosteroids, and etiocholanolone.
 4. **Demargination** (resulting in granulocytosis involving only mature neutrophils) is seen in stress, including emotional upset, epinephrine administration, exercise, infection, hypoxia, and intoxication.
 5. **Decreased egress into the tissues** is seen after chronic treatment with corticosteroids.
C. **Differentiation of leukemoid reactions** from MPDs and CML involves complete clinical evaluation, especially for the history and presence of splenomegaly. The leukocyte differential count, neutrophil alkaline phosphatase score, and, occasionally, cytogenetics may be helpful (see Table 24.1 in Chapter 24). Bone marrow biopsies are frequently not diagnostic and may be confusing.

III. Thrombocytosis

A. **Thrombocytosis in cancer patients.** Persistent thrombocytosis may indicate cancer. Thrombocytosis in neoplastic disease may be idiopathic or the result of bleeding or bone marrow metastases. Generally, thrombocytosis associated with solid tumors is mild, but values may exceed 1,000,000/µL.
B. **Common causes of transient thrombocytosis**
 1. Acute hemorrhage or phlebotomy
 2. Acute infection
 3. Recovery from myelosuppression (viruses, ethanol, cytotoxic agents)
 4. After surgery (persists for about 1 week)
 5. Response to therapy for folic acid or vitamin B_{12} deficiency
 6. Certain drugs (epinephrine, vinca alkaloids, and perhaps miconazole)
C. **Causes of chronic thrombocytosis**
 1. Iron deficiency (the most common cause of thrombocytosis)
 2. MPDs
 3. Neoplasms (idiopathic or bone marrow metastases)
 4. Chronic inflammatory diseases
 5. Hyposplenism (postsplenectomy states, hemolytic anemias, regional enteritis, sprue, and splenic atrophy from repeated infarctions)
D. **Differentiation of causes of chronic thrombocytosis.** After history and physical examination, helpful screening tests for the evaluation of chronic thrombocytosis include the following:
 1. **Peripheral blood.** Megathrombocytes and fragments of megakaryocytes are rarely seen in disorders other than the MPDs and CML. A normal mean platelet volume (MPV) suggests reactive thrombocytosis. The granulocyte differential is helpful for recognizing MPDs and CML. The presence of hypochromia and microcytosis supports iron deficiency.
 2. **Serum iron, iron-binding capacity, and serum ferritin** to evaluate for iron deficiency
 3. **Bone marrow aspirate** examination demonstrates panmyelosis in MPDs and CML. Bone marrow biopsy may detect tumor involvement. Iron staining is unreliable in patients with cancer or chronic inflammatory diseases if the results show low or absent iron stores.

IV. Eosinophilia

A. **Definition.** The upper limit of normal in absolute cell count is 550/µL.
B. **Non-neoplastic causes of eosinophilia**
 1. Allergies and drug hypersensitivities
 2. Skin diseases (many types)
 3. Infection with fungus, protozoan, or metazoan; convalescence after a febrile illness
 4. Eosinophilic gastroenteritis, inflammatory bowel disease
 5. Eosinophilic pulmonary syndromes (e.g., Löffler's syndrome)
 6. Collagen vascular diseases, especially rheumatoid arthritis and polyarteritis nodosa
 7. Contaminated tryptophan eosinophilia-myalgia syndrome
 8. Chronic active hepatitis, pernicious anemia, immunodeficiency syndromes
 9. Hyposplenism (see section III.C.5)
 10. Hypereosinophilic syndromes (see Chapter 23, Hypereosinophilic Syndrome)
C. **Eosinophilia associated with neoplasia**
 1. Hodgkin lymphoma (up to 20% of cases)
 2. MPDs and CML (common)
 3. Acute lymphocytic leukemia and lymphoma (especially T-cell types)
 4. Angiolymphoid hyperplasia with eosinophilia (Kimura's disease)
 5. Pancreatic acinar cell carcinoma (syndrome of polyarthritis, subcutaneous panniculitis, and peripheral eosinophilia)
 6. Tumors undergoing central necrosis or metastasizing to serosal surfaces
 7. Malignant histiocytosis
 8. Eosinophilia related to treatment: RT to the abdomen, hypersensitivity to cytotoxic agents

V. Basophilia

A. **Definition.** The upper limit of normal is 50/µL.
B. **Causes of basophilia**
 1. Hypersensitivity reactions
 2. MPDs
 3. Chronic granulocytic leukemia
 4. Mastocytosis
 5. Hyposplenism (see section III.C.5)
 6. Infections: tuberculosis, influenza, hookworm
 7. Endocrine: diabetes mellitus, myxedema, menses onset
 8. Miscellaneous: hemolytic anemia, ulcerative colitis, carcinoma

VI. Monocytosis

A. **Definition.** The upper limit of normal is 500 to 800/μL.
B. **Causes of monocytosis**
   1. Hematologic neoplasms, myelodysplastic syndromes, hemolytic anemias, and other hematologic disorders
   2. Solid tumors with and without metastases
   3. Tuberculosis, subacute bacterial endocarditis, syphilis, and resolution from acute infection
   4. Inflammatory bowel disease and sprue
   5. Collagen vascular disease
   6. Hyposplenism (see section III.C.5)
   7. Factitious monocytosis may occur when blood samples are taken from finger tips affected by peripheral vascular disease

VII. Lymphocytosis. The differential diagnosis of lymphocytosis is discussed in Chapter 23, Chronic Lymphocytic Leukemia, section III.D.

Cytopenia

Decreased formed elements in the circulating blood can result from decreased or ineffective production within the bone marrow, increased destruction of cells, or sequestration in the spleen. Patients with cancer often have a combination of these abnormalities, but bone marrow failure is the most common cause of cytopenia. The type and duration of cytopenia depend on several factors (Table 34.1).

Table 34.1 Hematopoiesis, cell kinetics, and bone marrow injury

I. Pancytopenia because of bone marrow failure

A. **Metastases to the marrow**
   1. **Occurrence.** Carcinomas of the breast, prostate, and lung are the solid tumors most likely to be associated with extensive marrow metastases. Melanoma, neuroblastoma, and carcinomas of the kidney, adrenal gland, and thyroid also frequently have marrow metastases.
   2. **Findings.** Tumor volume in the marrow does not correlate directly with the degree of hematosuppression. Marrow metastases are often found in patients without any hematologic abnormality. Most patients have bone pain, bone tenderness, radiographic evidence of cortical bone involvement, or elevated serum alkaline phosphatase levels.
      a. **Bone marrow paraneoplastic alterations** can result in qualitative and quantitative abnormalities in hematopoiesis. In the absence of marrow metastases, changes can develop that are comparable to those seen in the primary myelodysplastic syndromes, including myelodysplasia in all cell lines, marked reactive changes, stromal modifications, and bone marrow remodeling.
      b. **Desmoplastic reactions** to metastases can result in myelofibrosis.
      c. **Bone marrow biopsy** is superior to aspiration (with examination of the clot specimen) for detection of metastases; both techniques are complementary. Cytologic preparations of bone marrow aspirates must be inspected at the edges of the smears for clumps of tumor cells.
      d. **Peripheral blood abnormalities.** Nearly all patients with solid tumors and leukoerythroblastosis have demonstrable metastases. Thrombocytopenia (in the absence of RT or chemotherapy) is the next best indicator. Leukocytosis, eosinophilia, monocytosis, and thrombocytosis each is associated with positive marrow biopsies in about 20% of cases.
      e. **Radiographs.** Bone scans are positive in 70% of patients with bone marrow metastases proved by biopsy, and bone radiographs are positive in 80% of cases.
B. **Marrow fibrosis**
   1. **Occurrence.** Extensive primary marrow fibrosis is characteristic of myelofibrosis with agnogenic myeloid metaplasia and late-stage polycythemia vera. Marrow fibrosis may also be secondary to neoplastic infiltration with leukemia or metastatic carcinoma or as a distant effect of some tumors without demonstrable tumor cells in the marrow. *Secondary fibrosis* in the marrow may also be seen in reaction to the following:
      a. Collagen vascular disorders (particularly systemic lupus erythematosus, in which the fibrosis can reverse after treatment with high-dose corticosteroids)
      b. Toxic agents (benzene, radiation, cytotoxic agents)
      c. Infectious agents (especially tuberculosis and syphilis)
      d. Hematologic diseases (myelodysplasia, pernicious anemia, hemolytic anemia)
      e. Miscellaneous disorders (osteopetrosis, mastocytosis, renal osteodystrophy, Gaucher's disease, giant lymph node hyperplasia, angioimmunoblastic lymphadenopathy with dysglobulinemia)
   2. **Findings.** Splenomegaly and a leukoerythroblastic blood smear are characteristic of marrow fibrosis of any cause.
C. **Marrow necrosis**
   1. **Occurrence.** When diagnosed antemortem, marrow necrosis nearly always is due to either sickle cell disease or a malignancy, particularly a hematologic neoplasm. Systemic embolization of fat and marrow frequently occurs. The median survival of patients with marrow necrosis from a malignancy is less than 1 month.
   2. **Findings.** Patients have severe bone pain (in back, pelvis, or extremities), cytopenias, and a leukoerythroblastic blood smear.
      a. **Serum levels** of alkaline phosphatase, lactate dehydrogenase (LDH), uric acid, and bilirubin are usually elevated.
      b. **Radiographs** are normal.
      c. **Bone marrow aspiration** demonstrates characteristic findings: Individual hematopoietic cells are not recognizable, and cells with indistinct margins and intensely basophilic nuclei are usually surrounded by amorphous acidophilic material.
D. **Bone marrow failure secondary to treatment.** Ionizing radiation and most chemotherapeutic agents cause suppression of bone marrow function. Although recovery is usual after chemotherapy, recovery after irradiation is inversely proportional to dose and volume treated and may never be complete. Indeed, after doses in excess of 3000 cGy, the bone marrow may be replaced by fatty and fibrous tissue. The distribution of marrow in the human skeleton is shown in Fig. 34.1. The induction of short-term cytopenias by anticancer therapies is discussed in Chapter 4, Principles, section VI.B.2.

Figure 34.1 Distribution of bone marrow in healthy 40-year-old subjects. Marrow cellularity is relatively decreased and amounts of fat increased in elderly subjects. (Data from Ellis RE. The distribution of active bone marrow in the adult. *Phys Med Biol* 1961;5:255.)

The occurrence of **therapy-related myelodysplasia and acute myelogenous leukemia (AML)** is even more worrisome for the development of treatment strategies. To develop this complication, the patient must have been treated long enough and then live long enough to manifest this long-term toxicity.

   1. **Occurrence.** Nearly half of patients have a primary hematologic malignancy. The risk for AML is increased 10- to 50-fold in patients treated for multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma, ovarian cancer, germ cell tumors, small cell lung cancer, and childhood acute lymphoblastic leukemia (ALL). For children with ALL who achieve complete remission, the risk for therapy-related AML is greater than the risk for developing relapsed ALL. Adjuvant chemotherapy for breast cancer is associated with only a minimally increased risk for AML.
   2. **Leukemogenic agents.** The risk of inducing AML is directly related to the total cumulative dose. The risk may also depend on the schedule of administration; for example, the risk in children with ALL is greatest in those undergoing weekly or biweekly therapy with epipodophyllotoxins.
      a. **Alkylating agents** are the drugs with the most clearly demonstrated leukemogenic potential. Melphalan and chlorambucil are most often associated with AML in this class of drugs.
      b. **Other drugs.** Epipodophyllotoxins (etoposide, teniposide), nitrosoureas, and procarbazine are also leukemogenic. Cisplatin is not a classic alkylating agent and is possibly leukemogenic; however, it is nearly always given in combination with other drugs, some of which are leukemogenic. Hydroxyurea has been implicated as being possibly leukemogenic in the treatment of MPDs.

c. **RT** is associated with a minimally increased risk for AML when given alone but with a synergistically increased risk when combined with leukemogenic drugs.
3. **Chromosome abnormalities,** particularly involving chromosomes 5q or 7q, are found in 70% of therapy-linked AML associated with alkylating agents. These same aberrations are seen in patients developing AML after exposure to leukemogenic solvents and pesticides. In contrast, certain balanced translocations involving 11q23 appear to be characteristic of myelodysplasia and AML occurring after treatment with cytostatic agents acting on DNA topoisomerase II, such as etoposide.
4. **Natural history.** AML develops 3 to 5 years after initiation of therapy but can arise after 10 years or longer; the syndrome rarely develops within 1 year. Therapy-induced AML is usually preceded by months to years of myelodysplasia (see Chapter 25, section I.C). After AML develops, the course is rapid and usually refractory to treatment. Death usually occurs within 2 to 4 months of diagnosis. An important predictive factor for favorable response to intensive antileukemic therapy is the absence of a preceding myelodysplastic phase.

II. Pancytopenia because of hypersplenism

A. **Pathogenesis**
1. **Hypersplenism.** Splenic enlargement from any cause (including carcinomatous metastases) may result in phagocytosis of the circulating blood cells and the development of cytopenias.
2. **Erythrophagocytosis** that causes anemia is a characteristic finding in the bone marrow and in the remainder of the reticuloendothelial system of patients with malignant histiocytosis-hemophagocytic syndrome, which most likely represents a variant of T-cell lymphoma. Erythrophagocytosis by macrophages surrounding tumor sites has also been demonstrated in Hodgkin lymphoma and other lymphomas.
B. **Diagnosis.** The diagnosis of hypersplenism is based on clinical judgment. The only true diagnostic test for hypersplenism is improvement in the cytopenias after splenectomy.
C. **Treatment**
1. **Indications for splenectomy** for hypersplenism are all of the following:
   a. The patient has palpable splenomegaly.
   b. The cytopenia is severe (e.g., anemia requiring frequent transfusions; severe neutropenia associated with recurrent, serious bacterial infections; or thrombocytopenia with hemorrhagic manifestations).
   c. Other causes of cytopenia have been ruled out (e.g., disseminated intravascular coagulation [DIC]).
   d. A reasonable survival time after splenectomy is expected.
   e. The patient's general medical condition is satisfactory enough to make the operative mortality risk acceptable.
   f. Surgeons experienced in performing splenectomy under adverse conditions are available.
2. **Consequences of splenectomy**
   a. **Postsplenectomy blood picture** is characterized by Howell-Jolly bodies, neutrophilia, eosinophilia, basophilia, lymphocytosis, monocytosis, and thrombocytosis.
   b. **Postsplenectomy sepsis** is a potentially fatal complication, especially in children younger than 6 years of age. The most common infecting organisms are *Streptococcus pneumoniae* and *Haemophilus influenzae.* The incidence of sepsis in patients with Hodgkin lymphoma who undergo splenectomy has been reported to be 1% to 3%. Immunization may be helpful. Febrile episodes must be treated immediately and aggressively.

III. Anemia in patients with cancer

A. **Anemia because of blood loss or iron deficiency**
1. **Pathogenesis** includes ulcerating tumors, extensive surgery, benign gastrointestinal (GI) tract diseases, gastrectomy (unable to use heme iron but able to use ferrous salts), and hemosiderinuria from chronic intravascular hemolysis.
2. **Diagnosis.** Patients with known GI tract malignancies must not be presumed to be bleeding from an ulcerating tumor (see Chapter 30, section I).
   a. **Physical examination** may reveal obvious sites of bleeding. Stools should be tested for occult blood.
   b. **Blood studies** may demonstrate microcytosis and hypochromia. Important clues that may signify a recent hemorrhage are polychromasia (often prominent 5 to 10 days after acute hemorrhage) or thrombocytosis (as a reaction to bleeding). Hypoferremia and hypertransferrinemia are often obfuscated in cancer patients by the presence of concomitant anemia of chronic disease; serum ferritin levels are usually more helpful.
   c. **Bone marrow examination** demonstrating the absence of stainable iron is unreliable in patients with cancer. The presence of stainable iron eliminates iron deficiency.
   d. **Therapeutic trials.** Ferrous sulfate, 325 mg PO given three times daily for 30 days, should elevate the hemoglobin concentration in patients with iron deficiency and otherwise intact hematopoiesis.
B. **Anemia because of nutritional deficiencies** results in megaloblastic anemia, macro-ovalocytosis, neutrophil hypersegmentation, and in severe cases, pancytopenia.
1. **Folic acid deficiency** is the most common cause of megaloblastic anemia in cancer patients. Decreased intake of folate is common with any advanced cancer. Increased requirements for folate develop with autoimmune hemolytic anemia, the postoperative state, prolonged intravenous therapy, and competition for use of folate by rapidly proliferating tumor cells. Folate deficiency may also develop after the use of folate antagonist drugs (e.g., methotrexate).
2. **Vitamin B$_{12}$ deficiency** is usually seen in cancer patients who have undergone gastrectomy (the site of intrinsic factor production) or who have malabsorption secondary to lymphoma that involves the ileum (the site of vitamin B$_{12}$ absorption).
C. **Anemia of chronic diseases** (ACD)
1. **Pathogenesis.** ACD is caused by immune activation in reaction to foreign antigens with the production of cytokines that directly inhibit both the action and production of EPO. ACD is more severe with widespread metastases but may be observed in patients with localized tumors.

   The increased levels of tumor necrosis factor (TNF) and IL-1 seen in malignancies and inflammatory conditions result in anemia indirectly by means of interferons (IFNs). TNF stimulates marrow stromal cells to produce IFN-b, and IL-1 acts on T-lymphocytes to produce IFN-g. Both IFN-b and IFN-g inhibit erythropoiesis directly.

   Neopterin levels, which indicate the activation of macrophages by IFN-g, are also increased in malignancies. The hemoglobin concentrations are inversely proportional to the blood concentrations of neopterin and IFN-g. IFN-g also inhibits granulocytopoiesis, but neutropenia is not a manifestation of ACD. IL-1 also stimulates the release of G-CSF and GM-CSF, which can overcome the inhibitory effects of IFN-g.

2. **Diagnosis**
   a. **Hemogram.** The erythrocytes in ACD are usually normocytic and normochromic. Some patients have microcytosis and hypochromia. The reticulocyte count is normal or slightly increased.
   b. **Serum iron studies.** The diagnosis of ACD involves the demonstration of decreased levels of both serum iron and transferrin (total iron-binding capacity). Serum ferritin values are normal or increased.
   c. **Bone marrow studies** demonstrate ineffective erythropoiesis that is manifested by decreased polychromasia of nonnucleated marrow RBCs, shortened RBC life spans, and decreased numbers of sideroblasts. Reticuloendothelial iron may be normal, increased, or decreased.
3. **Treatment.** ACD is rarely severe enough to necessitate RBC transfusions. However, recombinant human EPO can correct ACD in most situations in which it is encountered. Subcutaneous administration of 50 to 150 U/kg three times weekly may decrease the transfusion requirement and increase the quality of life within 8 to 12 weeks of starting treatment.
D. **Anemia caused by parvovirus B19.** Parvovirus B19 is the etiologic agent of transient acute aplastic crises in patients with underlying hemolytic anemias. This complication is also seen in patients receiving chemotherapy, particularly as treatment of leukemia. An acute infection is manifested by worsening anemia, exanthem, and polyarthralgia.

In immunocompromised hosts who are unable to produce neutralizing antibodies against the virus, an infection can persist and cause chronic bone marrow failure, usually manifested by anemia. The viral target is an erythroid progenitor cell. The bone marrow shows erythroid hypoplasia. Treatment with commercial hyperimmune gamma globulins may be helpful.

E. **Pure red cell aplasia** (PRCA)
1. **Pathogenesis.** More than half of cases of PRCA (isolated severe hypoplasia of erythroid elements in the marrow) include an associated thymoma, which is usually noninvasive (see Chapter 19, section I.B.1). Lymphoproliferative disorders and various carcinomas have also been associated with PRCA. Rare

cases of thymoma have been associated with pure neutropenia (see section D for discussion of parvovirus B19).

2. **Diagnosis.** A normocytic, normochromic anemia and reticulocytopenia are present. Bone marrow biopsy demonstrates markedly decreased to absent erythroid precursors and normal megakaryocytes and myeloid elements. Chest radiographs demonstrate a mediastinal mass if associated with thymoma.

3. **Treatment.** Removal of a thymoma results in remission of PRCA in about half of cases. Many patients with and without thymoma have responded to cyclophosphamide therapy.

F. **Warm antibody (IgG) immune hemolysis**

1. **Pathogenesis.** Autoimmune hemolysis because of IgG antibodies most commonly occurs in patients with lymphoreticular neoplasms. More than half of patients in some series have an associated malignancy, but only 2% of cases are associated with solid tumors. This complication has also been reported after treatment with various cytostatic drugs, most recently a rare but severe form with fludarabine. The IgG-coated erythrocytes are removed from the circulation by the reticuloendothelial system, predominantly by the spleen (extravascular hemolysis).

2. **Diagnosis.** Patients with warm antibody autoimmune hemolysis usually have an insidious onset of severe anemia, mild jaundice, and splenomegaly. The blood smear shows polychromasia, a significant degree of spherocytosis, and often, nucleated RBCs. Reticulocytes are typically increased but may be normal if any other cause of anemia is also present. The direct antiglobulin test (DAT, or Coombs' test) is positive with anti-IgG or anticomplement antisera, usually with specificity for the Rh blood group system.

3. **Treatment.** Prednisone and successful treatment of the tumor are necessary. Patients with solid tumors associated with immune hemolysis respond to prednisone infrequently. Patients who have an unsatisfactory response or need chronic corticosteroid therapy require splenectomy if their general condition permits.

G. **Cold antibody (IgM) immune hemolysis**

1. **Pathogenesis.** Cold agglutinins are IgM molecules that attach to RBC membranes at cold temperatures and fix complement. At 37°C, the IgM molecules dissociate from the cell, but the complement remains fixed. Cold agglutinins are most common in lymphoma and are rare in other malignancies. Overt hemolysis (often intravascular) is unusual except in patients with very high titers (greater than 1:1000) of cold agglutinins.

2. **Diagnosis.** Patients with high titers of cold agglutinins may have acrocyanosis or Raynaud's phenomenon. RBC agglutination may be observed on blood smears, but spherocytes are not prominent. The DAT is strongly positive when performed at 4°C but is positive only with anticomplement antisera at 37°C.

3. **Treatment.** There is no satisfactory treatment for cold agglutinin hemolytic anemia except for control of the underlying disease.

H. **Microangiopathic hemolysis** (MAHA) with erythrocyte fragmentation has been described in patients with adenocarcinoma (particularly mucin-producing gastric cancer) and hemangioendothelioma. The pathophysiology of MAHA involves fibrin strands of DIC, pulmonary intraluminal tumor emboli, narrowing of pulmonary arterioles by intimal proliferations, or a side effect of chemotherapy. Most patients with MAHA, however, probably have DIC or chemotherapy-associated thrombotic thrombocytopenia (see section IV.C).

IV. Thrombocytopenia because of increased platelet destruction
Decreased production is by far the most common cause of thrombocytopenia in patients with cancer (see section I). Splenic sequestration may cause thrombocytopenia, almost always in association with anemia (see section II). Increased destruction of platelets is usually associated with normal megakaryocytes in the bone marrow and decreased platelet life spans.

A. **DIC** is the most common cause of increased destruction of platelets in cancer patients (see Coagulopathy, section II).

B. **Idiopathic thrombocytopenic purpura** (ITP) complicates lymphoproliferative diseases, especially malignant lymphoma and chronic lymphocytic leukemia, and is rarely associated with carcinoma. Thrombocytopenia is due to reticuloendothelial system destruction of IgG-coated platelets.

1. **Diagnosis** of ITP is made presumptively in the absence of evidence of DIC or of drug-induced thrombocytopenia with the finding of a nondiagnostic bone marrow containing normal or increased numbers of megakaryocytes.

2. **Treatment.** Control of the underlying disease is essential for satisfactory control of ITP.

   a. Patients are treated with prednisone, 60 to 80 mg/day PO. Single alkylating agents or vinca alkaloids successfully achieve remission in some patients. Splenectomy is indicated in patients who fail the above measures and have symptomatic thrombocytopenia or require relatively high doses of prednisone chronically.

   b. Many cases of ITP are chronic; platelet counts are 50,000 to 80,000/μL. In the absence of symptoms, it is best to observe these patients without giving long-term immunosuppressive therapy.

C. **Chemotherapy-induced thrombotic thrombocytopenic purpura** (TTP) **or hemolytic-uremic syndrome** (HUS). TTP/HUS can develop during the treatment of patients with cancer, particularly when using mitomycin C for adenocarcinoma. Therapy with cisplatin, bleomycin, cyclosporine, or gemcitabine has also been associated with this complication.

Chemotherapy-induced TTP/HUS usually occurs 2 to 9 months after cessation of treatment, even when the cancer is in remission (about one third of patients). Noncardiogenic pulmonary edema develops in 65% of patients with this syndrome, which is rapidly lethal if not successfully treated.

More than 90% of cases have been associated with mitomycin C. About 10% of patients treated with mitomycin C develop TTP/HUS, especially when the cumulative dose is more than 60 mg. Manifestations are often precipitated or exacerbated by transfusion of blood products.

1. **Diagnosis.** TTP/HUS is characterized by the extensive deposition of hyalin-like material in arterioles and capillaries. Diagnostic hallmarks of TTP/HUS are microangiopathic hemolysis and severe thrombocytopenia; other features often include markedly elevated serum LDH levels, rapidly changing neurologic abnormalities, fever, and renal dysfunction. Coagulation abnormalities associated with DIC are absent.

2. **Treatment.** Transfusion of plasma and intensive plasmapheresis has been successful in achieving remissions in classic TTP/HUS, which was formerly considered to be uniformly fatal. Treatment of chemotherapy-induced TTP/HUS with staphylococcal protein A extracorporeal immunoabsorption of circulating IgG immune complexes also achieves significant responses in half of patients. Normalization of platelet counts and LDH values are seen 7 to 14 days after starting treatment.

V. Granulocytopenia.
Granulocytopenia in cancer patients is usually the result of chemotherapy, radiotherapy, other drugs, severe infection, or myelophthisis. An immune or cytokine basis is involved in the granulocytopenia associated with T- g-lymphoproliferative disease (syndrome of large granular T lymphocytes) and rare cases of thymoma. Experimental evidence also supports the existence of paraneoplastic suppression of granulopoiesis. All of these entities are discussed elsewhere in the book.

VI. Blood component therapy
Hematopoietic growth factors are discussed in Chapter 4, Chemotherapeutic Agents, section X.

A. **Transfusion of erythrocytes**

1. **Indications** for transfusion of packed RBCs (PRBC) are to increase blood volume (when acute blood loss threatens the integrity of the cardiovascular system) and to increase oxygen-carrying capacity (when anemia causes or threatens tissue hypoxia). Most patients tolerate chronic, moderately severe anemia (hemoglobin higher than 8 g/dL) well. No specific hemoglobin value mandates transfusion. PRBCs are given to increase the oxygen-carrying capacity of blood for actual or incipient congestive heart failure or to reverse cardiac or central nervous system ischemic symptoms. When the hemoglobin level that precipitated symptoms is determined, patients with chronic anemia are transfused prophylactically to exceed that level.

2. **Transfusion reactions**

   a. **Fever and chills.** Most febrile reactions are caused by antibodies in the recipient directed against granulocytic antigens and specific HLA antigens on leukocytes in the donor blood. Febrile reactions occur in up to 80% of patients who receive multiple transfusions. The reaction usually does not start until 30 to 120 minutes into the transfusion.

   b. **Allergic reactions** involving urticaria or anaphylaxis develop in 5% of transfused patients. Some of these reactions are due to antibodies in the recipient directed against immunoglobulin components and other proteins in the plasma of the donor. These kinds of reactions or anaphylaxis are particularly likely to occur in patients with congenital IgA deficiency (1 per 800 people).

   c. **Major acute hemolytic transfusion reactions** are most likely to occur as a result of human error during blood preparation or administration. Fever and chills usually develop within the first 30 minutes into the transfusion and are often accompanied by tachycardia, hypotension, tachypnea, oliguria, hemoglobinuria, and DIC.

   d. **Delayed hemolytic transfusion reactions** occur 5 to 10 days after transfusion, particularly in association with alloantibodies to antigens of the Kidd blood group system.

   e. **Posttransfusion purpura** is manifested by severe thrombocytopenia developing 5 to 8 days after transfusion and occurs in the 2% of patients who lack the platelet antigen Pl[A1].

   f. **Bacterial contamination** occurs rarely in packed RBC units (usually with cryopathic gram-negative bacteria) but is more likely with platelet packs that are stored (at room temperature) for more than 4 days.

   g. **Viral contamination.** Pre-donation screening interviews and postdonation serologic testing have significantly reduced the incidence of some

transfusion-transmitted viral infections (hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]). These procedures are not successful for other viruses (e.g., cytomegalovirus). The risk for a fatal hemolytic transfusion reaction is 1:100,000. The risks (per unit for blood units that are negative in laboratory testing) of transmitting viruses through transfusion are as follows:

Hepatitis B virus, 1:63,000
Hepatitis C virus, 1:103,000
HIV, 1:500,000
Human T-cell lymphotrophic virus types 1 and 2, 1:641,000

    h. **Graft-versus-host disease** (GVHD) can occur after blood cell transfusion in patients who are undergoing a conditioning regimen for bone marrow transplantation (BMT) or who have acute lymphoblastic leukemia or congenital immunodeficiency. GVHD can also occur in patients who are not immunocompromised if the blood donor is homozygous for one of the HLA haplotypes of the recipient and particularly if the donor is a first-degree relative.

    i. **Other complications** include those associated with massive transfusion (blood volume overload, hypocalcemia, hyperkalemia, hypothermia), iron overload with chronic transfusions, and alloimmunization.

3. **Uses for erythrocyte preparations**
   a. **Fresh whole blood.** None
   b. **PRBCs.** The mainstay of erythrocyte transfusion therapy
   c. **Saline-washed PRBCs.** Patients who have IgA deficiency (particularly those with high anti-IgA titers), prior urticarial reactions with transfusions, or the need to avoid transfusion of complement
   d. **Leukocyte-filtered PRBCs.** Multiple-transfusion patients with prior febrile nonhemolytic transfusion reactions; also, immunocompromised patients in whom reducing the risk for transfusion-transmitted cytomegalovirus (CMV) is sought (particularly when seronegative units for CMV are not available). See section VI.C.2 for important issues involving leukodepletion filters.
   e. **Frozen RBCs.** Source for rare blood types, a backup supply for the common blood types, a substitute for saline-washed or leukocyte-filtered PRBCs when those methods fail to prevent febrile or allergic transfusion reactions, and an additional method of autologous donation. The extensive washing required to remove the cryopreservatives in frozen RBCs renders the suspension totally free of all leukocytes, platelets, and plasma constituents. The major limitations are the cost and the time required to prepare and store cells.
   f. **Gamma-irradiated PRBCs** are given to prevent viable T lymphocytes from causing transfusion-induced GVHD in the recipient. A dose of 1500 cGy is usually administered.
   g. **Directed donor PRBCs** do not decrease the risk for transmission of any virus. Furthermore, these units are associated with an increased risk for GVHD when provided by first-degree relatives to immunocompromised patients.

B. **Transfusion of granulocytes.** Granulocytes collected by apheresis are rarely helpful in treating patients with granulocytopenia. The paramount factor in determining the outcome of sepsis is the recovery of marrow function. Transfusion of leukocytes often results in GVHD and transmission of CMV. Prophylactic transfusions are useless. If granulocyte transfusion is used, the transfused cells should be irradiated for severely immunocompromised patients, and donors who are seronegative for CMV should be used for seronegative recipients.

Granulocyte harvesting from the donor is promoted by the use of G-CSF or corticosteroids. The donor and recipient must be compatible for Rh and ABO erythrocyte antigens. Daily granulocyte transfusions may be occasionally helpful *only if all of the following criteria are met*:

1. Recovery of bone marrow function is a reasonable expectation but is not expected to occur for 1 week.
2. The absolute granulocyte count is less than 200/µL.
3. A serious bacterial or fungal infection is proved by culture.
4. The infection is not responding to the appropriate antibiotics.

C. **Transfusion of platelets**
   1. **Factors influencing the decision to transfuse platelets**
      a. **Platelet count.** Spontaneous hemorrhage rarely occurs with platelet counts above 20,000/µL. Platelet counts of less than 10,000/µL are associated with an increased risk for spontaneous hemorrhage, especially when the thrombocytopenia results from decreased production rather than increased platelet destruction. Progressively worsening thrombocytopenia is more likely to be associated with active hemorrhage than stable or increasing platelet counts.
      b. **Platelet age.** Young platelets (i.e., produced after peripheral destruction) are larger and better able to provide hemostasis than old platelets. Usually, patients with immune or postinfectious severe thrombocytopenia have no serious hemorrhagic sequelae.
      c. **Active bleeding,** uncontrollable by local measures, or bleeding into vital or inaccessible organs, is an absolute indication for platelet transfusion in patients with thrombocytopenia of nearly any severity.
      d. **Fever, infection, and corticosteroid therapy** increase the risk for serious hemorrhage in patients with very low platelet counts.
      e. **Immune thrombocytopenia** usually makes platelet transfusions useless.
      f. **Drugs and diseases adversely affecting platelet function** may necessitate platelet transfusions in times of hemorrhage or surgery despite adequate platelet counts (see section C.6).
      g. **Patients with disease that is refractory to platelet transfusion** may be alloimmunized, but they also may have DIC, TTP/ HUS, or ITP.
   2. **Problems associated with platelet transfusion**
      a. **Alloimmunization.** Compatibility between donor and recipient for both ABO and HLA antigens is important for achieving a successful platelet count increment after transfusion. Alloimmunization requires the presence of class I and class II HLA antigens. Platelets alone do not result in the development of antibodies because they carry only class I HLA antigens and platelet-specific antigens; the class II antigens necessary for the development of alloimmunization are provided by transfused monocytes, lymphocytes, and dendritic cells. Rh antigens play only a minor role in alloimmunization after platelet transfusions.
      b. **Reactions to platelet transfusion.** Infectious contamination occurs rarely, but more commonly than with PRBCs because platelets are stored at room temperature for 5 days. Hemolysis of the small numbers of contaminating donor RBCs in donor platelet concentrates is of minor consequence. Febrile reactions, however, occur often in ABO-compatible platelet transfusions because of the large number of leukocytes that are contained in platelet packs. Febrile reactions occur in response to platelet transfusions because:
         1. **Recipient antibodies to white blood cells** (WBCs) attack donor WBCs after transfusion. This reaction is prevented by effective leukodepletion of platelet packs.
         2. **Cytokines released by leukocytes during storage,** particularly TNF-a and IL-1b (which are exceptional pyrogens), are passively transfused. This reaction is prevented by performing leukodepletion before storage of the platelet packs.
         3. **Recipient antibodies to cells and proteins** in the donor unit form immune complexes that trigger the release of cytokines. This reaction involving incompatible platelets is unaffected by leukodepletion and justifies further testing for HLA antibodies or platelet-specific antibodies, if available.
      c. **Leukodepletion filters** remove donor leukocytes by barrier retention of the filters' microfibers, by adherence to the filter material, and by platelet-leukocyte–mediated interactions. Leukocytes are more thoroughly removed at lower temperatures than at body temperature and when filtration is performed in the blood bank laboratory than at the bedside.
      d. **Hypotensive reactions to transfusions** appear to be caused by elevated bradykinin levels in platelet packs obtained from donors who were taking angiotensin-converting enzyme (ACE) inhibitors and transfused through certain leukodepletion filters at bedside. This reaction does not appear to occur when blood is filtered in the laboratory or when leukocytes are depleted before storage. Until this important complication of platelet transfusion is fully elucidated, patients receiving ACE inhibitors who also require leukodepleted blood components should probably receive blood that has been depleted of leukocytes in the laboratory rather than at the bedside.
   3. **Selection of which preparation to transfuse** depends on expected future transfusions and the presence of alloimmunization.
      a. **Random (ABO-compatible) units** are obtained from multiple donors of whole blood. Platelet concentrates (without regard to ABO compatibility) may be used in patients with transient thrombocytopenia that is not expected to recur and when platelets are needed immediately.
      b. **Single-donor platelets** (plateletpheresis packs) are obtained by density centrifugation. About 6 to 8 units may be obtained from one donor two or three times weekly. Single-donor platelet packs are the preferred blood product in conditions that require recurrent platelet transfusions because alloimmunization is delayed. Alloimmunization may be prevented when using this blood product in patients receiving chemotherapy.
      c. **HLA-compatible platelets.** HLA-matched platelets are required in alloimmunized patients but are not always available. The likelihood of an identical HLA match is 1 in 4 among siblings and 1 in 1000 in the general population.
      d. **Platelets from family members** should be avoided in patients who are possible candidates for BMT. The marrow donor may be used as the source of HLA-identical platelets, however, after the transplantation conditioning program has begun.
   4. **Prophylactic transfusions**
      a. **Acute leukemia.** Prophylactic transfusion of these patients with platelets is recommended to maintain the count above 10,000/µL.

b. **In aplastic anemia,** prophylactic transfusions are avoided if possible.
        c. **Pregnancy.** Platelet packs are administered to patients with a platelet count less than 100,000/μL just before delivery. After delivery, platelet counts should be maintained above 50,000/μL for 1 week. The possibility of DIC should be evaluated in patients with continued or massive postpartum bleeding associated with thrombocytopenia. Pregnant patients with thrombocytopenia induced by myelosuppressive therapy or leukemia are given platelet transfusions empirically.
    5. **Effectiveness of platelet transfusions** is determined by measuring platelet counts just before, 1 hour after, and 24 hours after transfusions. If the patient does not respond with an increase of about 25,000 in the platelet count after 1 hour, the transfusion should be considered a failure. The result at 24 hours can be further affected by concurrent hematologic complications.
    6. **Other measures**
        a. **Diseases affecting platelet function.** Patients with uremia require dialysis, cryoprecipitate, or desmopressin acetate (DDAVP) to improve platelet function. In patients with platelet dysfunction secondary to paraproteins, it is necessary to control the underlying disease or to perform plasmapheresis.
        b. **DDAVP** may be useful in patients with drug-induced platelet dysfunction at a dose of 0.3 μg/kg given over 20 minutes.
        c. **Alloimmunized patients who are refractory to transfused platelets.** High-dose intravenous gamma globulin (400 mg/kg per day for 5 days) occasionally permits better platelet increments in patients who are refractory to platelet transfusion. Cross-matched platelets are now available and may be helpful. Plasma apheresis may be tried empirically in difficult situations.
        d. **Menorrhagia in patients with thrombocytopenia** should be treated with medroxyprogesterone, 20 mg PO daily, to induce amenorrhea. Treatment is continued until the platelet count exceeds 60,000/μL.
D. **Transfusion of plasma proteins**
    1. **Preparations**
        a. **Fresh-frozen plasma** (FFP) contains all coagulation factors and is useful in replacement of all acquired clotting factor deficiencies (e.g., DIC, massive transfusion, liver disease). The indications for FFP are as follows:
            1. Replacement of isolated coagulation factor deficiencies
            2. Reversal of documented coagulation factor deficiencies after massive blood transfusions
            3. Reversal of warfarin effect in patients requiring immediate surgery or having active bleeding
            4. Treatment of antithrombin III deficiency and thrombotic thrombocytopenic purpura
        b. **Cryoprecipitate** contains von Willebrand's factor, fibrinogen (factor I), factor VIII, and factor XIII. Cryoprecipitate is useful in treating acquired deficiencies of fibrinogen and factor VIII (e.g., DIC) when volume overload from plasma treatment is to be avoided and in severe von Willebrand's disease.
        c. **Plasma protein fractionation** has resulted in the following commercially available products:
            1. **Fibrinogen.** This form is never indicated because of the 100% risk for hepatitis.
            2. **Prothrombin complex** (factors II, VII, IX, X, protein C, and protein S) is used in congenital factor deficiencies and in occasional cases of coumarin overdose with life-threatening hemorrhage. The risk for hepatitis with this blood product is 60%.
            3. **Albumin and purified protein fraction** have the same concentration of albumin and the same cost. They are useful for blood volume expansion, but their use in chronic hypoalbuminemia of malabsorption, nephrosis, or cirrhosis or as a nutritional supplement is futile.
            4. **Gamma globulin** is useful for passive immunization.
        d. **Hyperimmune intravenous gamma globulin** must be infused at a rate slower than 1 mL/min to avoid complications. This very expensive product is of definite therapeutic importance in only a few clinical circumstances:
            1. Congenital humoral immunodeficiency states
            2. Acquired humoral immunodeficiency states (e.g., chronic lymphocytic leukemia, lymphoma, myeloma) when complicated by recurrent bacterial infections that do not respond to prophylactic antibiotics
            3. Platelet alloimmunization in conjunction with platelet transfusion
            4. Idiopathic thrombocytopenic purpura when severe or life-threatening hemorrhage occurs, when severe thrombocytopenia refractory to steroids occurs during pregnancy, or when splenectomy is performed and hemostasis is a problem
    2. **Hazards**
        a. **Allergy.** All plasma preparations are associated with a small incidence of serum sickness reactions. Fever, urticaria, or erythema may also occur in reaction to residual leukocyte antigens.
        b. **Volume overload** is an important consideration when administering FFP. Citrate toxicity may occur with very rapid transfusion rates (100 mL/min).
        c. **Venous thrombosis and DIC** occur with prothrombin-complex transfusions.
        d. **Infection** with hepatitis B, hepatitis C, delta agent hepatitis, HIV, CMV, and Epstein-Barr virus is a potential risk for all plasma products.
            1. **Risks for hepatitis**
                a. **Very high risk:** fibrinogen, prothrombin complex, repeated use of cryoprecipitate
                b. **Intermediate risk:** single-donor units screened for hepatitis B surface antigen of plasma
                c. **Very low risk:** gamma globulin, albumin, purified protein fraction
            2. **Risks for HIV transmission:** nil for gamma globulin, albumin, and purified protein fraction

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Coagulopathy

I. Thrombosis ("hypercoagulability") Multiple or migratory venous thrombosis in cancer patients has been repeatedly documented since Trousseau's description in 1865. An accelerated course of intermittent claudication and of ischemic heart disease has also been described in cancer patients and probably represents additional variants of Trousseau's syndrome.

A. **Incidence.** The overall incidence of thrombotic episodes in cancer patients is 10% to 15%, especially during postoperative periods. About 3% of patients with idiopathic venous thrombosis ultimately are proved to have a malignancy, particularly during the first 6 months after diagnosis. Pulmonary emboli have been found at necropsy in about half of patients with disseminated cancer and have antedated the diagnosis of cancer in 1% to 15% of patients. The malignancies most commonly associated with thrombosis are MPDs and carcinomas of the GI tract, lung, or ovary (only 7% of patients with pancreas cancer develop classic Trousseau's syndrome).
B. **Mechanisms**
    1. **Cancer is associated with the following factors:**
        a. The direct production of tissue factor-like procoagulant (which forms a complex with factor VII to activate factor IX and factor X) and the "cancer procoagulant" (a cysteine protease that activates factor X directly)
        b. Increased platelet reactivity secondary to either tumor-platelet interactions or clonal abnormalities (MPDs)
        c. Endothelial cells becoming procoagulant under the influence of inflammatory cytokines, particularly TNF and IL-1
        d. Increased levels of platelets, fibrinogen and factors V, VIII, IX, and XI, and decreased plasma levels of antithrombin-III (AT-III), all of which probably are of minor importance
        e. The formation of fibrin-platelet vegetations on mitral or aortic valves, resulting in noninfectious endocarditis with paradoxical emboli to peripheral organs. Fewer than one third of affected afebrile patients have heart murmurs. Most vegetations, which are smaller than 2 mm, are not detected by echocardiography.
        f. Localized anatomic changes, such as tumor compression and venous stasis, can precipitate thrombosis. The tumor's disruption of blood vessels exposes collagen and basement membrane, which may trigger clotting. Tumor neovascularization activates both factor XII and platelet reactions.
    2. **Comorbid factors,** such as advanced age, bed rest, infection, surgery, and drugs, play a contributory role for blood hypercoagulability to become manifest clinically.
    3. **Cancer therapies** associated with enhanced risk for thrombosis are high-dose chemotherapy with BMT, asparaginase, high doses of estrogen, and tamoxifen. Tamoxifen increases the risk for venous thrombosis slightly (1.5- to 2-fold) when given alone and increases the risk for venous and arterial thrombosis significantly higher when given concomitantly with chemotherapy, particularly to premenopausal women. The presence of activated protein C resistance as a result of the inheritance of factor V Leiden or of the prothrombin G20210A gene mutation increases the risk further.
C. **Diagnosis**
    1. **The clinical diagnosis of thrombosis** is made by physical examination and venous ultrasonography or venography. The presence of venous thrombosis, a heart murmur, and arterial embolism suggests an underlying mucin-producing carcinoma.
    2. **An occult malignancy should be sought** in patients who present with any of the following:
        a. Idiopathic deep-vein thrombosis or pulmonary emboli
        b. Idiopathic deep-vein thrombosis combined with arterial thrombosis
        c. Idiopathic thrombosis that is recurrent or at multiple sites

d. Thrombosis that is resistant to anticoagulation therapy
e. Associated paraneoplastic syndromes
3. **A reasonable screening evaluation for occult cancer** in patients with thrombotic disease includes a thorough history and physical examination (including rectal or pelvic examination), complete blood count, basic chemistry panel, LDH, carcinoembryonic antigen, prostate specific antigen in men older than 50 years, urinalysis, stool for occult blood, and chest radiograph. An abdominopelvic CT scan can be obtained for patients with any of the conditions listed in section C.2.b, section C.2.c, section C.2.d and section C.2.e.
4. **Laboratory tests of coagulation** can be obtained during the first idiopathic venous thromboembolic event in an otherwise healthy person to seek a possible biologic defect predisposing to thrombosis. Such assays would include the following:
    a. Assay for lupus anticoagulant and serologic tests for antiphospholipid antibodies
    b. Functional assays for protein C and AT-III
    c. Functional assays for protein S (immunologic assays of total and free protein S)
    d. Clotting assay for resistance to activated protein C (genetic test for factor V Leiden if clotting assay is positive)
    e. Screening for dysfibrinogenemia (thrombin time, immunologic and functional assays of fibrinogen)
    f. Total plasma homocysteine
    g. Genetic test for prothrombin gene mutation (prothrombin 20210A)
D. **Management of recurrent thrombosis in cancer patients** is difficult because it is often resistant to therapy and because patients often have worrisome sites for potential hemorrhage.
1. **Anticoagulant therapy.** Standard-dose intravenous heparin, extended minidose heparin (5000 to 10,000 IU/day SC), adjusted-dose SC heparin (while monitoring the partial thromboplastin time), and weight-adjusted low-molecular-weight heparin (LMWH) are options for initiating therapy, depending on the clinical and social circumstances. Experience with LMWH is limited in cancer patients, but the available results are promising. The attractiveness of LMWH is the ability to treat venous thrombosis outside of the hospital setting without the need for monitoring clotting tests; the switch to oral warfarin is made after 8 to 12 days. For difficult cases, treatment with LMWH may be extended well beyond the usual transition period to oral therapy with warfarin, which is usually begun 1 day after starting unfractionated heparin.

   If there are concerns about potential bleeding, low-dose warfarin may be used with an international normalized ratio (INR) target of 1.4 to 1.9. The dose of warfarin can be increased to maintain a higher INR for recurrent thrombosis. The necessary duration of warfarin therapy in cancer patients is unclear; for patients with truly idiopathic thrombosis and without cancer, more than 6 months of treatment is recommended (perhaps indefinitely).

2. **Contraindications to anticoagulant therapy** include the following:
    a. Preexisting clotting defect or bleeding source
    b. Inaccessible ulceration (e.g., GI tract)
    c. Recent hemorrhage or surgery in the eye or central nervous system
    d. Severe hypertension or bacterial endocarditis
    e. Regional or lumbar anesthesia; T-tube drainage
    f. Pregnancy (if anticoagulation is mandatory, heparin is used because it crosses the placenta less readily than warfarin)
3. **Vena caval interruption,** usually with a Greenfield filter, is performed if anticoagulants are contraindicated. The filter is effective for preventing pulmonary embolism, but the risk for recurrent venous thrombosis increases 1 to 2 years after placement of the filter.
4. **Graduated compression stockings** should be used if practical.
5. **Removal of the tumor** may control thrombotic episodes but is often impossible.

II. DIC is a frequent complication of metastatic cancer. Local or diffuse thrombosis or hemorrhage, in all combinations, can occur. The incidence depends on the definition and assays used. Severe DIC is common in only two malignancies: carcinoma of the prostate and acute hypergranular promyelocytic leukemia (type M3).

A. **Diagnosis**
1. **Clinical features**
    a. **Type of bleeding.** Patients with severe DIC bleed from at least three sites simultaneously. Patients with chronic DIC (the usual DIC in malignancy) may have minimal bleeding.
    b. **End-organ damage.** Microangiopathic hemolysis, hypotension, oliguria, and renal failure are frequent complications of serious DIC.
2. **Laboratory tests.** No single test is diagnostic for DIC.
    a. **Blood smear.** The numbers of circulating platelets are estimated and fragmented erythrocytes or microspherocytes identified. Schistocytosis is present in about half of cases.
    b. **Platelet count.** Thrombocytopenia occurs nearly always, but DIC rarely causes platelet counts of less than 50,000/μL.
    c. **Clotting tests.** Prothrombin time and activated partial thromboplastin time (PTT) may be slightly shortened, normal, or prolonged. Thrombin time (TT) prolongation occurs with severe hypofibrinogenemia (less than 50 mg/dL) or clinically significant elevation of fibrin degradation products; the TT can also be prolonged with heparin therapy, dysfibrinogenemia, or malignant paraproteinemia.
    d. **Fibrinogen titer** is usually decreased. Fibrinogen concentrations greater than 50 mg/dL (normal range is 200 to 400 mg/dL) should not result in abnormalities of the TT.
    e. **Paracoagulation tests** for fibrin monomers (protamine sulfate) or d-dimers are positive in more than 95% of patients with DIC.
3. **DIC versus primary fibrinolysis.** Although primary fibrinolysis is rare and DIC is common, differentiation between these disorders is important to plan treatment. These disorders are compared in Table 34.2. The platelet count, paracoagulation test, and euglobulin lysis separate the disorders.

Table 34.2 Comparison of acute disseminated intravascular coagulation (DIC) and primary fibrinolysis

4. **Severity of DIC manifestations** depends on the underlying diagnosis, the acuteness of the DIC, the integrity of the reticuloendothelial system, and the intensity of secondary fibrinolysis. Some patients hemorrhage profusely and have marked abnormalities of all of the tests for DIC. On the other hand, DIC may be subclinical and manifested only by a positive paracoagulation test and mild thrombocytopenia.
B. **Management.** Few patients are helped if the underlying problem is not corrected. Patients should be treated *if* the triggering process is ongoing (e.g., an active, acute infection) *and if* DIC is causing end-organ damage. Treatment is not necessary for laboratory manifestations alone. The following sequence is recommended:
1. **Treat the underlying disease.** For patients with cancer, this is often futile, but the possible advantages of antimicrobial therapy, further surgery, RT, or chemotherapy should be considered.
2. **The clotting process should be stopped** with heparin unless there are contraindications.
3. **Administration of blood components.** Platelet packs are given in the presence of thrombocytopenia and serious bleeding. One to four units of FFP or 15 bags of cryoprecipitate usually improve factor deficiencies unless the clotting process is severe. Cryoprecipitate is useful in patients with borderline cardiac reserve who cannot tolerate large volumes of FFP.
4. **Fibrinolysis is inhibited only if necessary,** that is, if the patient has documented primary fibrinolysis or DIC with life-threatening bleeding and evidence of extensive secondary fibrinolysis (i.e., shortened euglobulin lysis time). Fibrinolysis may be inhibited by epsilon-aminocaproic acid (EACA, Amicar); renal failure is a relative contraindication for EACA use. A loading dose of 5 g is followed by 1 g/hour IV or 2 g every 2 hours PO. If the episode of DIC has abated, EACA may be given alone. If the status of DIC is uncertain or ongoing, heparin should be given with EACA.
5. **Antiplatelet drugs** (aspirin and dipyridamole) may be useful in patients with chronic DIC who are not bleeding.
6. **Patient surveillance.** The platelet count, paracoagulation test, and clinical evaluation are the most useful factors to follow. The *reptilase time* (performed like the TT) is sensitive to the presence of fibrin degradation products; unlike the TT, the reptilase test is not affected by heparin.

III. Primary fibrinolysis Primary fibrinolysis occurs essentially only in prostatic carcinoma, advanced cirrhosis of the liver, heat stroke, or amniotic fluid embolism.

A. **Malignancies** may promote fibrinolysis by releasing plasminogen activators, such as urokinase or other proteolytic enzymes. Extensive metastatic liver disease may result in decreased clearance of plasminogen and its activators.
1. **Prostatic carcinoma** and, to a lesser extent, benign prostatic conditions are capable of triggering both thrombosis and fibrinolysis.
2. **Other cancers** that have been reported to activate fibrinolysis are sarcoma and carcinomas of the breast, thyroid, colon, and stomach.

B. **Diagnosis of primary fibrinolysis.** See [section II.A.3].
C. **Management of primary fibrinolysis.** See [section II.B.4].

IV. Other hemostatic defects associated with cancer

A. **Platelet function abnormalities** are common in malignancies.
   1. **Mechanisms**
      a. Coating of platelet surfaces by fibrin degradation products with DIC
      b. Coating of platelets by paraproteins with myeloma
      c. Concomitant azotemia.
      d. Inherent platelet dysfunction associated with myelodysplastic disorders or MPDs
      e. Patients may be taking drugs with antiplatelet activity.
   2. **Diagnosis**
      a. **Signs** of platelet dysfunction include easy bruisability, gingival bleeding with toothbrushing, and other minor mucosal bleeding.
      b. **Laboratory studies.** The template bleeding time is the best available clinical tool for demonstrating abnormal platelet function. A variety of *in vitro* platelet function tests have uncertain clinical validity. Thrombocytopenia, DIC, and azotemia should be ruled out by appropriate tests.
   3. **Treatment.** Patients with bleeding and platelet dysfunction require treatment of the underlying disorder and may require platelet transfusions. DDAVP, 0.3 μg/kg, may also be helpful temporarily.
B. **Paraproteinemia.** Hemostatic abnormalities associated with plasma cell myeloma were discussed in Chapter 22, [section VIII.A.1.a.(1)].
C. **Liver metastases,** when extensive, can result in inability to synthesize clotting factors. Treatment with vitamin K is ineffective. Bleeding must usually be controlled by the administration of FFP.
D. **Dysfibrinogenemia.** Dysfibrinogens are abnormal fibrinogen molecules, which may be inherited or acquired in association with hepatocellular carcinoma or liver metastases. The PT, PTT, and TT are all markedly abnormal. Fibrinogen concentrations are low when measured by clotting methods but are normal when measured by immunologic or physical precipitation methods. Hemorrhage is not common with dysfibrinogenemia but may occur.
E. **Acquired circulating inhibitors of coagulation** occur in a wide variety of tumors (e.g., a heparin-like inhibitor has been described in mastocytosis). It is doubtful that these inhibitors are responsible for hemorrhage in the absence of other causes, such as uremia or thrombocytopenia.
F. **Specific factor deficiencies**
   1. **Factor XIII deficiency or dysfunction** is common in patients with cancer but usually does not cause clinical problems. The PT, PTT, and TT are normal, but the assay for factor XIII is abnormal. Hemorrhagic episodes are treated with FFP, 5 mL/kg weekly.
   2. **Factor X deficiency** may occasionally be an isolated coagulation abnormality in patients with amyloidosis. Hemorrhagic episodes are treated with FFP or prothrombin complexes.
   3. **Factor XII and Fletcher factor (prekallikrein) deficiencies** have been described in patients with cancer but have little clinical significance.
   4. **Acquired von Willebrand's disease** has been reported in cancer patients, particularly in the MPDs.
G. **Hemostatic abnormalities associated with cytotoxic agents**
   1. **Hypofibrinogenemia** or dysfibrinogenemia is an almost universal complication of treatment with l-asparaginase.
   2. **Vitamin K antagonism** occurs with actinomycin D therapy.
   3. **DIC** is a common complication of administration of mithramycin.
   4. **Primary fibrinolysis** has been reported to be activated by the anthracyclines.
   5. **Platelet dysfunction** (of questionable significance) has been reported with cytarabine, daunorubicin, melphalan, vincristine, mitomycin C, l-asparaginase, and high-dose chemotherapy in preparation for BMT.
   6. **Budd-Chiari syndrome** is associated with dacarbazine therapy.

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Chapter 35 Infectious Complications

Jeffrey E. Galpin

I. Granulocytopenia with fever and sepsis

A. **Principles.** The development of fever in patients with granulocytopenia must always be regarded as a medical emergency caused by infection until proved otherwise. The presenting features of infection are altered by the absence of neutrophilic exudation in infected tissues.
   1. **Predisposition**
      a. **Defects in the normal mechanical barriers** to infection provide routes for bacterial and fungal invasion. Examples of such defects are mucositis from tumor erosion, viral ulcerative diseases (i.e., herpes simplex virus [HSV] or varicella zoster virus [VZV]), chemotherapy, or radiation therapy (RT); indwelling catheters and intravenous sites; organ obstruction or erosion from tumors or catheters; and disturbed cutaneous integrity from shaving or skin metastases and ulceration.
      b. **Neurologic dysfunction,** such as peripheral neuropathy, neurogenic bladder, or loss of gag reflex, predisposes patients to pyelonephritis or aspiration pneumonia.
      c. **Impairment of cell-mediated immunity** predisposes patients to infections with fungi (such as aspergillosis, cryptococcosis, or candidiasis), obligate intracellulare microbes (such as *Pneumocystis carini* and *Nocardia* species), and is thought to be responsible for severe primary infections with VZV, rubeola, and cytomegalovirus (CMV, which occurs after allogeneic bone marrow transplantation [BMT]).
      d. **Absence or impairment of splenic function** makes patients susceptible to overwhelming septicemia with encapsulated organisms (e.g., *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae*).
      e. **Hospitalization** predisposes patients to any nosocomial infection.
   2. **Risk.** Granulocytopenia carries the risk for bacterial infection and, if prolonged, fungal infection. The risk for infection increases slightly with granulocyte counts below 1000/μL, rises sharply with counts below 500/μL, and is highest with counts below 100/μL. The more rapid the rate of granulocyte decline, the higher the risk for infection. The qualitative function of granulocytes is equally important as numbers in determining risk for bacterial or fungal infection.
   3. **Infecting organisms.** About 80% of infections in neutropenic patients arise from the patient's endogenous flora. About 75% of septicemias are caused by gram-negative organisms. Fungal infections are increasing in incidence and occur after prolonged periods of granulocytopenia or antibiotic therapy.
   4. **The outcome of a febrile illness** depends on the duration of leukopenia and restoration of normal granulocytes.
B. **Diagnostic methods.** Blood cultures and biopsies remain the pivotal investigations for diagnosis in granulocytopenic patients.
   1. **History and physical examination.** A careful history should be taken. Despite the lack of physical signs of a normal inflammatory response, physical examination should give special attention to the skin, ocular fundus, sinuses, central nervous system (CNS), pelvis, and rectum.
   2. **Surveillance cultures.** Blood cultures have been shown to be the only useful surveillance cultures and are performed during periods of persistent fever in these patients.
   3. **Special laboratory procedures.** [67]Ga scans can help define and localize areas of inflammation but may also give false-positive results in patients with hematologic malignancies. Radiolabeled immunoglobulin scans may contribute to early diagnosis and offer better specificity for localization of infections.
C. **Initial therapy.** Emergent and empirical treatment with intravenous antibiotics is mandatory for febrile neutropenic patients. The most effective choices for empiric initial intravenous antibiotic therapy in granulocytopenic patients with clinical sepsis are as follows:

Ceftriaxone, 2 g IV every 24 hours alone (for patients who have no other symptoms and are stable),

or

Ceftriaxone, 2 g IV every 24 hours, plus either gentamicin, 7 mg/kg per day, or amikacin, 500 mg IV every 12 hours, or

Ceftazidime, 2 g IV every 8 hours, plus piperacillin–clavulanic acid (Timentin), 3.1 g IV every 6 hours,

or

Imipenem-cilastin (Primaxin), 500 mg IV every 6 hours alone, or
Piperacillin-tazobactam (Zosyn), 3.375 g IV every 8 hours alone, or
Meropenem (Merrem), either as a 2 g IV loading dose followed by 3 g continuous IV infusion over 24 hours, or by intermittent administration of 2 g IV every 8 hours

The first two regimens are cost-effective and have lower toxicity. The last four of these regimens cover *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa,* and *Staphylococcus aureus.* These four bacteria account for 85% of pathogens in this setting.

   1. **Growth factors and immunoglobulins.** Colony-stimulating factors (CSFs) should be initiated immediately in patients with granulocytopenia and clinical sepsis. Recombinant granulocyte CSF (G-CSF, filgrastim) and granulocyte-macrophage CSF (GM-CSF, sargramostim) decrease the duration of neutropenia by 2 to 4 days. GM-CSF appears to be particularly effective in patients with chronic lymphocytic leukemia (CLL) who have history of recurrent infections. Intravenous hyperimmune gamma globulin may be effective in prophylaxis for CLL patients with hypogammaglobulinemia and recurrent skin and respiratory infections.
   2. **Toxicity of antibiotics** is minimal with all of these regimens, although seizures are associated with high doses of imipenem (1 gm IV every 6 hours). Diarrhea is more frequent in patients receiving cefoperazone, whereas nausea occurs more often with imipenem. Superinfections caused by b-lactam–resistant, gram-negative bacilli are uncommon but occur more frequently with double b-lactam therapy than with imipenem monotherapy. Use of carbapenems (imipenem, meropenem) in a hospital environment may result in the emergence of nosocomial infections due to multiresistant *Stenotrophomonas maltophilia* in high-risk patients, with a limited choice of antibiotics for therapy.
D. **Ongoing therapy**
   1. If patients improve on empiric antibiotic therapy, it should be continued for 9 or 10 days, despite negative cultures.
   2. If patients do not improve on empiric therapy after 4 days, antibiotics should be stopped and cultures repeated. Patients are probably either on the wrong antibiotics or have a condition for which antibiotics are ineffective (e.g., viral or fungal infection, abscesses, or noninfectious causes). Antibiotics should be resumed if patients become worse or the fever persists.
   3. If fevers persist after 7 days of antibiotic therapy, granulocytopenic patients benefit from empiric antifungal therapy (fluconazole, 200 mg PO or IV every 24 hours). The presence of mucositis or esophagitis should prompt empiric antifungal therapy even earlier. The overall survival rate decreases in adults with acute leukemia if antifungal therapy is not initiated empirically before documentation of filamentous deep fungal infection. Fluconazole has replaced amphotericin B for this purpose because of its ease of administration and low toxicity. Resistant fungal infections may benefit from the use of liposomal amphotericin preparations, such as Abelcet (5 mg/kg IV over 3 hours, with premedication every 24 hours).
E. **Prevention of infection**
   1. **General measures**
      a. Handwashing by the staff before touching patients is the most important preventive technique.
      b. Skin care may be important in preventing infections with *S. aureus* and other pathogens. Occlusive antiperspirants are avoided. Electric shavers are preferred; not shaving at all may be best.
      c. Avoidance of fresh flowers and foods with high bacterial contents (such as fruits, uncooked foods, and tap water) has no established value.
      d. Teeth should be brushed daily. Procedures involving the use of tubes, tapes, and instruments should be minimized because they may be sources of infection.

2. **Isolation methods**
    a. Reverse isolation (caps, masks, gloves, and gowns) has no established benefit. In fact, it probably deters good patient care by limiting patient contact with the hospital staff and family.
    b. High-efficiency particulate air filters and laminar air-flow rooms, which are expensive, are of questionable benefit.
3. **Prophylactic antibiotics.** Using prophylactic antibiotics in granulocytopenic patients hypothetically lowers the endogenous flora (particularly in the gastrointestinal tract [GI]) of potential pathogens.
    a. **Prophylaxis with quinolones** (e.g., ciprofloxacin, 500 mg PO twice daily; floxin, 400 mg PO twice daily) significantly reduces the occurrence of gram-negative bacteremia and delays the onset of fever during periods of neutropenia (thus reducing the number of days that intravenous antimicrobial agents are required). These drugs do not reduce mortality or the occurrence of fever, however. They do spare the anaerobic normal bowel flora. Subsequent infections are mainly due to resistant gram-positive cocci.
    b. **Prophylaxis with Bactrim plus colistin.** Treatment with Bactrim (trimethoprim-sulfamethoxazole [TMP-SMZ, 80 mg/400 mg], 1 ampule IV or 1 tablet PO every 8 hours) plus colistin (400 mg PO twice daily) is associated with fewer infective complications and fewer febrile days compared with treatment with quinolones. Subsequent infections are due to resistant gram-negative rods.
F. **Investigational agents** attempt to reduce mortality in septic shock syndrome caused by gram-negative bacteria by attacking the mediators of inflammation. Such agents include anti–tumor necrosis factor (anti-TNF), E5 (mouse antiendotoxin monoclonal antibody), and HA-1A (human monoclonal IgM antibody that recognizes the lipid A component of lipopolysaccharide). HA-1A acts through immune complex clearance of endotoxin and reduces production of TNF- a, interleukin-1b (IL-1b); and IL-6.

Intravenous immune globulins are being investigated as supplemental treatment of sepsis, septic shock, and systemic inflammation in critically ill patients, although this indication has been only partially validated. Likely beneficial mechanisms of action may include the improvement of serum bactericidal activity due to neutralizing and opsonizing immunoglobulins, stimulation of phagocytosis, and neutralization of bacterial endotoxins and exotoxins. Another attractive possible mode of action may be immune globulin–mediated modification and specific suppression of proinflammatory cytokine release from endotoxin- and superantigen-activated blood cells. Investigational use of IL-2, interferon- g (IFN-g), IL-10, and IL-12 directly or through stimulation of CD4 $^+$ cytotoxic clones is promising.

II. Other infections in the compromised host

A. **Pulmonary infections**
  1. **Differential diagnosis**
      a. **Noninfectious causes.** About 25% to 30% of cases of fever with pulmonary infiltrates in cancer patients are due to noninfectious causes, which include radiation pneumonitis, drug-induced pneumonitis, pulmonary emboli and hemorrhage, lipid emboli after lymphangiography, and leukoagglutinin transfusion reaction.
      b. **Predicting the infecting agent.** Acute, severe symptoms that progress in less than 1 day suggest a common bacterial pathogen or noninfectious process (pulmonary emboli, pulmonary hemorrhage). A subacute course (over several days) suggests a virus, pneumocystis, or occasionally, aspergillosis or nocardiosis. A chronic course (over several weeks) is more typical of mycobacterial or fungal infections, radiation fibrosis, or drug-induced pneumonitis. Prediction from chest radiographs is not valid.
          1. **Infection acquired outside the hospital.** Despite the susceptibility to opportunistic infections, *S. pneumoniae* and influenza virus are the most likely pulmonary infections in cancer patients.
          2. **Infection acquired inside the hospital.** *Klebsiella, Serratia, Pseudomonas,* and *Acinetobacter sp, E. coli,* and *S. aureus* are the most frequently acquired nosocomial pathogens. *Candida* and *Aspergillus sp, Legionella pneumophila,* and *P. carini* are also hospital acquired.
          3. **The association between lung carcinoma and pulmonary tuberculosis** is not fortuitous but is related to the increased susceptibility to opportunistic infections and tuberculosis in cancer patients. Diagnosis of tuberculosis in patients with carcinoma requires pathologic evidence from biopsies or bacteriology samples. In case of tuberculosis, surgical treatment of early-stage bronchopulmonary carcinoma may have to be postponed or even contraindicated. Inversely, chemotherapy and radiotherapy may result in extension of the tuberculosis.
          4. **Primary pulmonary lymphoma related to AIDS** (acquired immunodeficiency syndrome) represents one of several examples of chronic infection leading to malignancy. Patients are typically immunodeficient at the time of diagnosis. Chest radiography shows one or more marginated nodules or a large mass. Computed tomography (CT) scan often shows a cavitary lesion, and no lymph node enlargement or specific pleural effusion is usually found. Diagnostic criteria for this sequel of human immunodeficiency virus (HIV) includes: (1) histologically proven lymphomatous pulmonary involvement; (2) absence of mediastinal and hilar adenopathy on chest radiography; and (3) absence of extrathoracic extension of lymphoma.
  2. **Diagnostic approach**
      a. **Sputum examination.** If the sputum contains neutrophils or macrophages and fewer than 10 epithelial cells per low-power field, the results are probably valid. Problems with interpretation include the following:
          1. Granulocytopenic patients usually have no neutrophils in the sputum.
          2. Mouth flora may cause aspiration pneumonia.
          3. Many patients show negative sputum examination even when *S. pneumoniae* is the responsible organism.
          4. Many opportunistic organisms that produce pneumonia are infrequently retrieved in sputum (e.g., *Mycobacterium tuberculosis, Nocardia asteroides, Aspergillus sp* and *Cryptococcus sp*).
          5. The various classes of penicillins can inhibit recovery of *N. asteroides* in culture. Aminoglycosides inhibit *M. tuberculosis* and *L. pneumophila.*
      b. **Serology** is useful for identifying infection from *Coccidioides immitis, Cryptococcus neoformans, Aspergillus sp, L. pneumophila, Mycoplasma pneumoniae, Toxoplasma gondii,* and CMV. No serologic test can help diagnose acute infections.
      c. **Blood cultures** must be obtained in all patients. Cultures are useful as surveillance in patients with pneumonia, granulocytopenia, and persistent fever.
      d. **High resolution CT** (HRCT). Patients with normal chest radiographs and normal HRCT scans, particularly patients with neutropenia, have a low risk for pneumonia during follow-up. Neutropenic patients with fever of unknown origin and normal chest radiographs should undergo HRCT to detect occult inflammatory pulmonary disease.
      e. **Thoracentesis** should be performed in patients with pleural effusion.
      f. **Lung biopsy procedures.** Diagnosis is paramount in the immunocompromised host. The highest yield and best control of bleeding is by direct visualization with open-lung biopsy. This procedure may be mandatory when the patient is rapidly deteriorating. If the pneumonic process is less rapid, then bronchoscopy with lavage appears to be the best approach. When a mass or consolidation is present, fine-needle biopsy is more frequently performed because the chance of complication is less. Invasive techniques are often not justified late in the course of malignancy because they often add morbidity without hope of palliation. Empiric antibiotic therapy is justified in these cases.
  3. **Therapy** for acute pneumonia should be initiated immediately after cultures are obtained. Patients with acid-fast bacilli, *N. asteroides, C. neoformans,* or *Aspergillus fumigatus* should not be regarded as colonized and should be treated.
B. **CNS infections.** Infections of the CNS can present either with simple changes of cognition or motor skills or with seizures and coma. Meningismus is a hallmark of disease, but this condition may be absent. A magnetic resonance imaging (MRI) scan is indicated when cerebral edema, abscess, or demyelinating encephalitis is suspected. This scan is particularly useful in defining viral encephalitis and areas where enhanced foci are seen, such as in toxoplasmosis.

Special considerations in cancer patients suspected or proved to have CNS infections are as follows:

  1. **Meningitis.** Cancer patients have an increased incidence of atypical pathogens. These may occur as a direct result of immune suppression, CNS involvement, or opportunistic infections after craniofacial surgery.
      a. **Granulocytopenic patients** rarely develop gram-negative meningitis despite a high incidence of gram-negative bacteremias. When meningitis does develop, the pathogens usually are the enterobacteriaceae, *P. aeruginosa, Bacillus subtilis,* or *Listeria monocytogenes.* Meningitis caused by aspergillosis or zygomycosis has also been described.
      b. **Patients with defects in cell-mediated immunity.** *L. monocytogenes* and *C. neoformans* are the most likely pathogens. Meningitis and meningoencephalitis from VZV, HSV, JC virus (progressive multifocal leukoencephalopathy), *Clavispora lusitaniae,* HIV, CMV, *T. gondii,* and *Strongyloides stercoralis* also occur.
  2. **Brain abscesses** are most likely caused by mixed aerobic and anaerobic bacteria. In the immunocompromised patient, brain abscesses are often due to aspergillosis, mucormycosis, nocardiosis, or toxoplasmosis. Toxoplasmosis can produce meningitis, necrotizing encephalitis, or abscess. In atypical cases, brain biopsy is performed at the time of surgical drainage.
  3. **Lumbar puncture** (LP)
      a. **Papilledema.** An emergency CT scan of the brain must be performed first. Patients with space-occupying lesions on CT scan should have LP or cisternal puncture performed by a qualified neurologist or neuroradiologist.
      b. **Thrombocytopenia.** Spinal subdural hematoma occasionally complicates LP in patients with severe thrombocytopenia. Clinical evidence of CNS

infection, however, supersedes consideration of risks. The following guidelines are recommended:

  1. If the platelet count is below 20,000/μL, transfuse platelet packs just before performing LP. Transfuse additional platelet packs if pain or neurologic signs develop.

  2. The most skilled physician available should perform the LP using a 22-gauge needle. The patient should be observed closely afterward. The role of needle aspiration and surgical intervention in patients who develop spinal subdural hematomas induced by LP has not been determined.

 c. **Cerebrospinal fluid should be evaluated** for the following:

  1. Glucose and protein concentrations, cell counts, routine bacterial culture and sensitivity, Gram stain, and cytology. The white blood cell (WBC) count in the cerebrospinal fluid is greater than 100/μL in about 90% of patients with bacterial meningitis and exceeds 1000/μL in 15% to 20%. Neutrophils constitute more than 80% of the WBC in 80% to 90% of patients; occasionally, lymphocytes predominate in the cerebrospinal fluid, especially in neutropenic patients and in about 25% of patients with meningitis caused by *L. monocytogenes.*

  2. Acid-fast culture and stain, fungal cultures, India ink preparation, cryptococcal antigen, and coccidioidiomycosis serology (depending on geography and predominant soil fungus)

  3. Polymerase chain reaction (PCR) assays for HIV, JC virus, herpesvirus, toxoplasmosis, tuberculosis, listeriosis, or other pathogens should be performed only if clinical or laboratory findings suggest the likelihood of that specific infection.

  4. IgG synthesis assays are useful in suggesting certain viral infections. HIV antigen and index are indicated for high-risk patients.

C. **Skin infections**

 1. **Neoplasms invading the skin** (e.g., mycosis fungoides) are associated with infections involving common pathogens such as *S. aureus.*

 2. **Cell-mediated immunity deficiencies** are typically associated with skin infection by VZV or HSV. Kaposi's sarcoma is highly associated with human herpesvirus type 8 (HHV-8). HHV-8 has also been associated with Castleman's disease, which is discussed in Chapter 21, [Non-Hodgkin Lymphoma, section VI.E.](#)

 3. **Granulocytopenic patients** may have skin infections with atypical or few physical findings. *S. aureus* and *Streptococcus pyogenes* are common. More serious manifestations represent systemic infections; these include bullae, raised ecchymotic plaques or nodules, black necrotic ulcers, or ecthyma gangrenosum. These manifestations of systemic infection may be produced by *Pseudomonas, Candida, Zygomycetes,* or *Aspergillus* species or by *Aeromonas hydrophila.*

D. **Alimentary tract and intraabdominal infections**

 1. **Esophagitis** may be from candidiasis or HSV.

 2. **Colitis** with ulceration is commonly produced by CMV. Aspergillosis and zygomycosis may also involve the GI tract. HHV-8 in the form of Kaposi's sarcoma is commonly seen disseminated in the bowel.

 3. **Intra-abdominal abscesses** develop when the bowel or genital tract becomes obstructed, necrotic, or perforated because of tumor. Mixed infections with gram-negative enteric organisms are frequent, particularly with species of *Bacteroides* and *Clostridium. Streptococcus bovis* abscess and sepsis may occur with colon, pancreatic, or mouth carcinoma.

 4. **Perirectal abscesses** frequently develop in granulocytopenic patients, especially those with acute leukemia; usually, they are caused by mixtures of aerobic and anaerobic bacteria.

 5. **Liver infections.** Hepatitis A, hepatitis B, and hepatitis C viral infections are common. Multiple abscesses secondary to systemic bacterial or fungal infection also occur. Even viruses such as VZV, HSV, HHV-8, CMV, or Epstein-Barr virus (EBV) can present as mass or necrotic lesions in the liver of immunocompromised patients. The liver is mildly or moderately involved in many opportunistic infections and may be cultured with biopsy specimens.

E. **Urinary tract infections** are frequent in cancer patients because of obstructive uropathies, the use of urinary catheters, and prolonged and repeated hospitalizations. These infections are often due to resistant gram-negative bacteria or *Candida* species.

F. **Bone marrow infections** are usually due to systemic disease, particularly with tuberculosis, fungi, salmonellosis, listeriosis, or DNA viruses. **Bone marrow suppression** mimicking aplastic anemia occurs with parvovirus B19, mycobacteria, histoplasmosis, and brucellosis.

G. **Central line infections.** The incidence rates of central line infections for external (e.g., Hickman) and subcutaneous ports (e.g., port-A-Cath) are equal. Most central line infections are caused by coagulase-positive or coagulase-negative *Staphylococcus* species, and about 80% of these infections can be treated with 10 days of antibiotics without removing the line. Vancomycin, 500 mg IV every 6 hours, can be used, depending on renal function; if the patient is sensitive, oxacillin, 500 mg IV every 6 hours can be given. **The central line must be removed** in the following circumstances:

 1. Exit site infections with *P. aeruginosa*

 2. All tunnel infections

 3. All line infections caused by fungi or *Candida* species

 4. Bacteremia persisting beyond 24 hours of antibiotic therapy or caused by *Bacillus* species, JK diphtheroids, or most gram-negative organisms

III. Vaccination of immunosuppressed patients

A. **Vaccines contraindicated in immunosuppressed patients** are those that contain living organisms. These include measles (rubeola), varicella (chickenpox), rubella, mumps, oral poliovirus, smallpox, yellow fever, and anthrax.

B. **Permissible vaccines.** Immunosuppressed patients often do not attain an effective response to active immunization. Permissible vaccines, however, are those for diphtheria, tetanus, pertussis, typhoid, cholera, plague, influenza, hepatitis A and B, and pneumococcus. The pneumococcal vaccine is strongly indicated for all cancer patients. The overall effectiveness is 75% to 90%. Diminished efficacy in severely immunosuppressed patients is not well defined.

IV. Viral infections

A. **EBV** is the recognized pathogen for infectious mononucleosis, Burkitt lymphoma in Africa, and nasopharyngeal carcinoma in Asia. The virus is ubiquitous: about 15% of healthy adults, 25% of patients with solid tumors, 60% of renal transplant recipients, and 80% of all patients with leukemia or lymphoma are seropositive for EBV. The virus is transmissible in blood transfusions.

 1. **Diagnosis.** Histologic findings are consistent but not helpful.

  a. **EBV-specific antibodies**

   1. Antibodies to viral capsid antigen (VCA) develop early and persist for life. In contrast, early IgM components of VCA antibodies persist for 4 four to 8 weeks.

   2. Early antigen antibodies, including anti-D and anti-R, are associated with severe disease and with the neoplasms linked to EBV infection.

   3. EBV nuclear antigen antibody (EBNA) types 1, 2, and 3 appear after 1 month of illness, persist for life, and are useful in diagnosing heterophil-negative cases. Anti-EBNA types 1, 2A, and 6 are simultaneously 4 to 10 times higher in chronic reactivation EBV syndromes than in acute EBV disease. Only anti-EBNA type 1 is elevated in nasopharyngeal carcinoma (NPC). Individual EBNA subtype titers appear to be normal in patients with Hodgkin lymphoma and other lymphomas.

   4. The plasma level of sCD23 is a sensitive and useful marker of EBV-related polyclonal or B-cell monoclonal proliferation in transplanted patients with immunosuppression.

   5. IgA antibodies to EBV membrane antigen indicate a high risk for developing NPC. This enzyme-linked immunosorbent assay (ELISA) has potential use in the diagnosis of NPC and for large-scale screening of patients at risk for NPC.

  b. **Nucleic acid hybridization techniques** can detect EBV in human tissues. **Southern blot analysis** distinguishes latent EBV from infectious EBV and determines the clonality of infected tumors with respect to the viral terminal repeat sequence structure. **PCR** is exquisitely sensitive for detecting viral DNA.

 2. **Syndromes associated with EBV**

  a. **Mononucleosis syndrome** is typically manifested by fever, malaise, pharyngitis, lymphadenopathy, splenomegaly (50% of patients), and a peripheral blood smear showing lymphocytosis with atypical cells. Complications include hepatitis, myopericarditis, meningoencephalitis, Guillain-Barré syndrome, cold agglutinin hemolysis, and thrombocytopenia. Infectious mononucleosis occurring in elderly patients may mimic lymphoma or lymphocytic leukemia. Mononucleosis syndrome may also result from infection with CMV, hepatitis virus, mycoplasma, toxoplasma, brucella, mycobacteria, *Yersinia* species, or streptococcus.

  b. **Chronic infectious mononucleosis syndrome** is distinguished by subjective findings of fatigue, malaise, low-grade fever, and mild lymphadenopathy associated with depression of cognitive functions. Occasional patients probably do have this illness, but many more are diagnosed inappropriately because they carry chronic antibodies.

  c. **Chronic active EBV** (CAEBV) is associated with significantly increased numbers of a cytotoxic T-lymphocyte (CTL) subset (CD8$^+$, CD11$^-$ lymphocytes).

   1. Defective EBV-CTL activity and anti-EBNA antibody responses are frequently observed both in children with CAEBV and in their parents, which may suggest a familial basis for the abnormal immune response to EBV.

   2. Antibodies to the EBV VCA are associated with regression of out-growths of virus-transformed B cells and their viral load. Decreases of virus- and cell-associated growth are also associated with sequential increases in IL-2 and IFN-g and with low levels of IL-6 and GM-CSF. Conversely, little or no decrease in cells infected chronically with EBV is associated with undetectable levels of IL-2, low levels of IFN-g, high levels of IL-6 and GM-CSF, and

an increased frequency of cells bearing the phenotypes CD20 and HLA-DR.

    d. **Virus-associated hemophagocytic syndrome** is characterized by high fever, liver dysfunction, coagulation abnormalities, pancytopenia, and a benign histocytic proliferation with prominent hemophagocytosis in bone marrow, lymph node, spleen, and liver. EBV-associated hemophagocytic syndrome has been fatal, particularly in Japan.

3. **Malignancies and lymphoreticular disorders associated with EBV**
   a. **Nasopharyngeal carcinoma** in Asia
   b. **Epidemic Burkitt lymphoma**, an EBV-associated non-Hodgkin lymphoma, is endemic in an area of Africa known as the "Lymphoma Belt." This zone is demarcated by climatic requirements of temperature and rainfall. The plant *Euphorbia tirucalli,* which possesses EBV-activating substances, can induce the characteristic 8:14 translocation of Burkitt lymphoma in EBV-infected lymphoblastic cell lines *in vitro.* Its distribution conforms closely to the climatic requirements of the lymphoma.
   c. **Cutaneous T-cell lymphoma** (CTCL) is associated with both human T-cell lymphotrophic virus type I (HTLV-I) and EBV. Three distinct clinicopathologic subgroups are associated with EBV (types II, III, and V). No EBV genome has been thus far detected in type I CTCL (classic mycosis fungoides) or in type IV CTCL (HTLV I–associated adult T-cell lymphoma).
      1. Type II CTCL (large cell T lymphoma) is either positive or negative for Ki-1 antigen (CD30). Most affected patients have Ki-1–negative lymphoma, which is a fulminant disease, whereas the course of the Ki-1–positive cases is benign.
      2. Type III CTCL (angiocentric T-cell lymphoma, or "lymphomatoid granulomatosis") presents with chronic ulcers or violaceous papules.
      3. Type V CTCL is secondary to systemic EBV-associated T-cell lymphoma. The common features of these EBV-associated CTCLs are resistance to conventional chemotherapy, poor prognosis, and the terminal manifestation of a hemophagocytic syndrome.
   d. **Adult T-cell leukemia-lymphoma** (ATLL) is associated with HTLV-I. It is hypothesized that both EBV and HTLV-I may infect the same T cells in early life and may have a role in the oncogenesis of ATLL.
   e. **Pyothorax-associated lymphoma** is a rare tumor associated with EBV and long-standing tuberculous pyothorax. Most of these cases are high-grade B-cell lymphomas. More than 50 cases have been reported in Japan.
   f. **Gastric carcinoma.** EBV is associated with lymphoepithelioma-like gastric carcinoma with marked lymphocytic stroma. The close relationship between EBV and undifferentiated gastric carcinomas and the variable association with gastric adenocarcinomas suggests fundamentally different roles for the virus in the etiology of these two malignancies.
   g. **Warthin's parotid tumor.** In distinct neoplastic cell types of multiple or bilateral Warthin's tumor of the parotid gland, the EBV genome is frequently detected by *in situ* hybridization technique.

4. **Management** is supportive. Corticosteroids are not used except in the presence of severe anemia, airway obstruction, myopericarditis, or neurologic complications. High-dose acyclovir (800 mg PO four times daily) may have some benefit early in acute EBV syndromes but does not eliminate persistent EBV infection from the oropharynx. Therefore, this agent does not necessarily prevent lymphoma development. Ganciclovir, foscavir, or specific cytokine therapy may also have potential benefit for this infection.

B. **CMV** often presents as EBV-negative mononucleosis. Fever, interstitial pneumonia, and alimentary canal ulcerative disease are the most common manifestations of CMV in adults with neoplasms. CMV, which is tropic for endothelial cells, also causes retinitis, encephalitis, and peripheral neuropathy.

  CMV can suppress cell-mediated immunity, reticuloendothelial cell function, and granulocyte reserves. Cells infected with CMV stimulate production of IL-1 and TNF. Thus, CMV often coexists or activates other opportunistic infections.

1. **Infection, latency, and recurrence.** Primary CMV infection can occur perinatally or later in life and inevitably results in latent infection. Infection is especially likely after transfusions of blood that contains granulocytes.

  Latent CMV burden and risk for recurrence are related to the extent of virus multiplication during primary infection. The risk for CMV recurrence is high in immunocompromised patients and only after neonatal infection in normal hosts.

2. **CMV infection of the GI tract** can cause serious inflammatory or ulcerative disease in immunocompromised patients. Manifestations include pain, ulceration, bleeding, diarrhea, and perforation. All levels of the GI tract, particularly the stomach and colon, may be involved. Pathologic examination reveals diffuse ulcerations and necrosis with scattered CMV inclusions.
3. **Diagnosis**
   a. **Culture.** CMV is slow growing (up to 6 weeks), and culture is generally not practical. Early antibody detected by application of ELISA in cultures does accelerate identification.
   b. **Histiocytology** shows the characteristic enlarged cells with dense nuclear inclusions and wide periinclusion halos. Cytoplasmic inclusions are frequent, but multinucleation is absent.
   c. **Serologic assays**
      1. Seropositivity for antibodies against CMV is indicative of latent infection but is insufficient as a predictor for the risk for recurrence.
      2. Elevated IgM antibody showing four-fold titer increases is highly suggestive of acute disease.
      3. Anticomplementary immunofluorescent assay, ELISA, and indirect fluorescent antibody (FA) assays are sensitive indicators of infection. IgG antibody occurs during the acute phase of the illness and persists for life, whereas IgM antibodies occur early and often disappear after 4 to 8 weeks. Recurrent IgM spikes occur in certain patients, indicating either partial immunity to CMV or exposure to new variants of the virus.
      4. Use of monoclonal antibodies to detect antigens that are amplified through coculturing with lymphocytes is becoming the best means of identifying active CMV disease.
   d. **PCR assay,** both *in situ* and in DNA extracted from gross specimens, is the most useful new tool to isolate and identify the presence and location of CMV in clinical disease.
4. **Management**
   a. **Ganciclovir** (9-[1,3-dihydroxy-2-proxymethyl]-guanine, DHPG)
      1. The efficacy of this drug for CMV retinitis and colitis is well documented, but it is less effective with CMV pneumonia or meningoencephalitis. After BMT, the prophylactic administration of ganciclovir abrogates CMV pneumonitis and considerably reduces the incidence of CMV infection.
      2. Ganciclovir is given for 14 days at a dose of 5 mg/kg IV every 12 hours. Patients with AIDS often require maintenance treatment (5 mg/kg per day). Dosage is modified according to the predicted creatinine clearance and absolute neutrophil count. An oral form of ganciclovir is usually administered at a dose of 1 g four times daily. A slow-release ophthalmic injectable package works well in CMV chorioretinitis.
   b. **Foscarnet** is useful for many ganciclovir-resistant isolates of CMV but must be monitored for renal toxicity and electrolyte, calcium, and magnesium imbalance. Ganciclovir and foscarnet are probably synergistic, and combination therapy is useful in patients when ganciclovir alone is ineffective. Foscarnet therapy is begun with a dose of 60 mg/kg IV every 8 hours in 1 L of normal saline for 2 weeks. Maintenance therapy (90 to 120 mg/kg per day) is required in patients with AIDS. Dosing is adjusted for predicted creatinine clearance. In a comparative trial of foscarnet and ganciclovir therapy in patients with AIDS, foscarnet prolonged survival longer than ganciclovir.
   c. **Cidofovir** is the first acyclic phosphonate nucleoside antiviral agent to be approved for general use in the United States. Although the half-life of cidofovir in plasma is only 2.6 hours, the intracellular half-life may be much longer, allowing biweekly maintenance dosing. *In vitro,* cidofovir appears to be equally or more effective than the other agents available for the treatment of CMV. *In vivo,* cidofovir appears to delay the progression of CMV retinitis. Current dose recommendations are 5 mg/kg IV once weekly for two doses (induction), and then 5 mg/kg IV once every other week (maintenance). Because cidofovir is cleared almost entirely by the kidneys, dosage adjustments must be made in patients with impaired renal function. Disadvantages of cidofovir primarily include its risks for adverse drug reactions, such as nephrotoxicity, which is likely to occur in up to 50% of patients if appropriate preventive measures are not taken. Neutropenia and constitutional reactions to probenecid are also commonly encountered during the course of cidofovir therapy.
   d. **Hyperimmune CMV globulin** appears to be protective and therapeutic in certain patients.

C. **Herpes zoster.** VZV is the most common infective agent to complicate lymphoproliferative diseases. Zoster (shingles) is the reactivation of VZV. Vesicles form in clusters on erythematous bases, usually distributed along one to three dermatomes. Several lesions outside a dermatomal distribution does not necessarily indicate dissemination. Disseminated VZV infections may be manifested by encephalopathy, Guillain-Barré syndrome, transverse myelitis, myositis, pneumonia, thrombocytopenia, hepatitis, and arthritis.

1. **Diagnosis.** It is fruitless to search for an underlying undiagnosed tumor in patients with zoster if the history, physical examination, and routine screening studies are normal.
   a. **Histocytology** (multinucleated cells with intranuclear inclusions) is suggestive.
   b. **Culture.** Inoculate early vesicular fluid.
   c. **Serology.** Complement fixation (CF) antibody titers are useful, although they may not rise for 3 to 4 weeks in immunocompromised patients. Using a PCR method to detect VZV DNA before antibody is produced, contacts of patients with varicella have been shown to carry this infection in their nasopharynx. These patients can be a threat to those who are either immunocompromised or have never been exposed to VZV.
2. **Management.** VZV is transmissible, and patients should be isolated.

a. **Acyclovir, famciclovir, and valacyclovir** have similar effects on herpes zoster; famciclovir and valacyclovir can be administered less frequently. Acyclovir is the treatment of choice for zoster that occurs in immunocompromised patients and for disseminated VZV in any patient. The dosage is 250 mg/m² IV every 8 hours or 800 mg PO four times daily for 7 to 10 days. Famciclovir is administered 500 mg PO three times daily and valacyclovir 1000 mg PO three times daily. All immunocompromised patients with zoster should be treated in the first 72 hours of illness.
b. **Zoster immune globulin** modifies or prevents illness in immunocompromised hosts. Passive immunization can be used instead of drug therapy when a rare toxicity is feared.
c. **Ganciclovir** has considerable activity for VZV as well as for CMV.
d. **VZV live vaccine** is available for primary immunization against chickenpox but has no role in the immunocompromised patient.
D. **HSV.** Patients with reticuloendothelial neoplasms, T-lymphocyte defects, or cytotoxic chemotherapy treatment may develop HSV viremia. The viremia often produces alimentary tract ulceration and hemorrhage, hepatitis (occasionally manifested by abscess-like lesions), and respiratory tract infections.

Patients with Sézary's syndrome or atopic dermatitis can develop progressive fulminant mucocutaneous disease (eczema herpeticum), which can recur and disseminate to visceral organs. HHV-6 sequences are frequently detected by PCR in lymph nodes from patients with angioimmunoblastic lymphadenopathy–like lymphoma, suggesting a possible involvement of this lymphotrophic virus in the pathogenesis of at least some cases of the disease.

1. **Diagnosis**
a. **Histocytology** demonstrates the characteristic intranuclear mass surrounded by marginated chromatosis and often a periinclusion halo. Cytoplasmic inclusions are absent. Electron microscopy analysis of vesicular fluid, which can be performed in less than 30 minutes, strongly suggests the diagnosis. Immunofluorescence for HSV antigen is also rapid and specific.
b. **Culture.** HSV grows rapidly in tissue cultures (24 to 72 hours) and produces a unique cytopathologic picture.
c. **Assays.** Hemagglutination and indirect FA titers are useful if four-fold increases are demonstrated. Differentiation of IgG from IgM antibody assists in clarifying recent infection. An HSV IgG-capture ELISA has demonstrated intrathecal synthesis of antibodies to the virus. Furthermore, a PCR assay has demonstrated amplification of HSV DNA in cerebrospinal fluid. Both ELISA and PCR are rapid, noninvasive means of diagnosing HSV encephalitis in a very early stage of the disease.
2. **Management**
a. **Topical idoxuridine,** especially using dimethyl sulfoxide as a carrier, is effective for HSV keratitis.
b. **Acyclovir** is safe, effective treatment for HSV infections in normal and immunocompromised patients. The dose is 200 mg PO five times daily or 10 to 15 mg/kg IV three times daily for 7 to 10 days. As an ointment, acyclovir is useful for primary local infections but does not appear to prevent recurrent disease. **Famciclovir** and **valacyclovir** are now superseding acyclovir because they have easier dosing regimens of 500 mg PO three times daily and have evidence of better penetration into tissue.
c. **Vidarabine** is effective topically for keratitis.
d. **Ganciclovir** has excellent activity against HSV, although its primary usefulness has been directed at CMV.
e. **Vaccines** are under development both for viral glycoproteins and for viral-induced mammalian cell antigens.
E. **Human parvovirus.** The family of Parvoviridae is composed of small, nuclear-replicating viruses that have no envelope and contain an essentially single-stranded, linear DNA genome.
1. **Oncosuppressive activity.** Certain parvoviruses have the remarkable capacity to prevent the formation of spontaneous and induced tumors in laboratory animals. Epidemiologic studies in humans have correlated serologic evidence of parvoviral infection with a lower incidence of certain cancers. Certain parvoviruses preferentially lyse initiated or stably transformed cells *in vitro.* Parvoviruses can also have a cytostatic effect, causing the reversion of transformation traits, parallel to the down-modulation of the expression of defined genes, particularly oncogenes.
2. **Parvovirus B19.** The pathogenic human parvovirus B19 has extreme tropism for human erythroid progenitor cells. B19 is a known cause of erythema infectiosum ("fifth disease") and aplastic crisis in patients with hemolytic anemias (see Chapter 34, Cytopenia, section III.D).
F. **HHV-8** (also known as Kaposi's sarcoma herpesvirus [KSHV]) is associated with AIDS-related anaplastic large cell lymphoma. The association of HHV-8/KSHV infection is now well established with primary effusion lymphoma (or, body cavity–based lymphoma), multicentric Castleman's disease of the plasma cell type, and Kaposi's sarcoma. A possible pathogenic role of HHV-8/KSHV in other lymphoid tumors, including primary CNS lymphoma, multiple myeloma, some atypical lymphoproliferations, and sarcoidosis has also been suggested, but these associations remain controversial.
G. **HHV-6**, a b-herpesvirus with two variant groups (A and B), is a very common infective agent, approaching 100% in seroprevalence. Primary infection with HHV-6B causes roseola infantum or exanthem subitum, a common childhood disease that resolves spontaneously. After primary infection, the virus replicates in the salivary glands and is shed in saliva, which is the recognized route of transmission for variant B strains. It remains latent in lymphocytes and monocytes and persists at low levels in cells and tissues. HHV-6 is not usually associated with disease in the immunocompetent but is a major cause of opportunistic viral infections in the immunosuppressed, typically in AIDS patients and transplant recipients. In immunosuppressed patients, HHV-6 infection or reactivation may culminate in rejection of transplanted organs and death. Another disease whose pathogenesis may be correlated with HHV-6 is multiple sclerosis.
H. **JC virus** of the papovavirus family is associated with the development of progressive multifocal leukoencephalopathy. See Chapter 36, section V.C.
I. **Human papillomavirus** (HPV) is closely associated with anal and cervical dysplasia and carcinoma. See Chapter 36, section IV.D.2.

V. Bacteria

A. **Mycobacteria.** Active tuberculosis (TB) develops in 0.5% to 1% of patients with malignancies. Infection is predominantly pulmonary in 70%, is disseminated in 20%, and involves lymph nodes or other nonpulmonary sites in 10% of cases. The mortality rate approaches 100% for acute TB pneumonia and 90% for disseminated TB when cellular immunity is significantly depressed.
1. **The incidence** of atypical mycobacterium infection (particularly with *Mycobacterium kansasii* and *M. avium* complex [MAC] is significantly higher in patients with cancer, HIV, or AIDS than in the general population. *M. kansasii* infection has been associated with hairy cell leukemia. *M. malmoense* is an opportunistic pathogen mainly isolated in northern Europe, most often from patients with pulmonary infections. *M. genavense* affects children with severe HIV infection. All of these organisms are commonly resistant to isoniazid or rifampin.
2. **Pathogenesis.** Natural resistance to TB depends on the ability of the macrophage to control intracellular growth of the organism. The resistant host develops a chronic infection primarily affecting the lungs, whereas the highly susceptible host develops a rapidly fatal generalized illness. Survivors of the initial infection then develop resistance to reinfection by a mechanism based on sensitized T cells. When this system is only partially successful, the host becomes infectious if mycobacteria are shed into open airways. Cutaneous anergy and treatment with corticosteroids, cytotoxic agents, or irradiation predispose to reactivation of *M. tuberculosis.*

Mycobacterial infection is associated with an initial copious release of both IFN- a and IFN-g and of IL-10. IL-10 production increases as the infection progresses, and IFN-a and IFN-g levels diminish. IL-10 may have a negative effect on resistance to mycobacterial infections due to decreased macrophage activity, at least in part.

3. **Resistant TB.** Immigration from high-prevalence countries, coinfection with HIV, and outbreaks in congregative facilities are primarily responsible for the increased incidence of TB cases during the past decade. Coincident with the increase in TB, outbreaks of multidrug-resistant (MDR) TB have occurred. MDR TB occurs late in the course of HIV infection and is refractory to treatment. A history of antituberculosis therapy is the strongest predictor of the presence of resistance.
4. **Diagnosis**
a. **Chest radiographic** evidence of infiltrates in apical or posterior segments of the upper lobe or superior segment of the lower lobe are the most frequent manifestations of postprimary TB. Radiographic features may be confusing in immunosuppressed patients, however, in whom intrathoracic adenopathy, pleural effusions, miliary infiltrates, or cavities are important clues to the presence of TB.

Chest radiographs are normal in 10% to 15% of immunosuppressed patients with tuberculosis. Patients with low CD4 $^+$ T-cell counts or decreased CTLs often have intrathoracic adenopathy without parenchymal infiltrate. When infiltrates do occur in these patients, lower lobe consolidation or diffuse infiltrates are much more common than upper lobe abnormalities, and cavitation is uncommon. Pneumocystis and other opportunistic pathogens may produce radiographic abnormalities indistinguishable from tuberculosis in immunosuppressed patients.

b. **Smears and cultures.** Although the tuberculin skin test is often negative in immunocompromised patients with tuberculosis, the diagnosis of tuberculosis can be established by visualizing the organism, performing PCR, or culturing *M. tuberculosis* from sputum or from extrapulmonary sites; blood culture may be positive. Three sputum cultures are necessary for routine culturing; more samples do not increase the yield. Expectorated sputum is the best culture source. Aerosol-induced sputum is superior to gastric juice aspiration in patients who produce little sputum. Diagnostic yield can be further increased using transbronchial biopsy when other material is not diagnostic. The use of PCR in the blood, spinal fluid, and tissue is the most sensitive, specific, and

rapid assay available.

c. **Effusions.** Pleural fluid samples yield about 30% positive cultures, and percutaneous needle pleural biopsies (three biopsies in three locations) yield about 75%. Culture of pericardial fluid yields 50% positive results, and pericardial biopsy yields 80% positive results on either histology or culture. Analysis of ascitic fluid findings are not helpful unless the fluid is concentrated; peritoneal biopsy is preferred.

d. **TB meningitis.** Spinal fluid analysis is variable, although mononuclear cell pleocytosis and low glucose concentrations are common. Concentrated spinal fluid reveals TB bacillus on smear in 30% to 50% of cases and on culture in about 50%. PCR is becoming the best assay to diagnose mycobacterial meningitis.

5. **Management**

a. **TB prophylaxis in cancer patients.** Any patient who is to receive immunosuppressive therapy must be skin tested for TB and anergy. Prophylaxis with isoniazid (INH), 300 mg/day for 1 year, should be given to any cancer patient who has a positive tuberculin skin test.

b. **Active TB.** Because of increasing drug resistance, the U.S. Public Health Service has issued new guidelines for the initial treatment of TB. Until drug susceptibility data are available, patients with active TB should be treated with daily administration of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. In communities with documented isoniazid resistance rates below 4%, only isoniazid, rifampin, and pyrazinamide are required. After 2 months of such therapy, the regimen for patients with drug-sensitive organisms should be changed to isoniazid and rifampin administered daily or two or three times weekly for an additional 4 months or until sputum cultures are negative for 3 months. Alternative regimens are recommended for patients who require directly observed therapy to ensure compliance.

c. **MDR TB** is readily transmitted among hospitalized patients with AIDS. The management of MDR TB is exceedingly difficult, and early diagnosis with individualized therapy is crucial. To interrupt the transmission of MDR TB, stringent isolation procedures and aggressive chemotherapy with a combination of drugs are essential. The choice of agents depends on susceptibility testing, but until such results are available, the drugs most likely to be effective include pyrazinamide, streptomycin, ciprofloxacin, ofloxacin, cycloserine, and ethambutol. The management of patients exposed to MDR TB is also difficult. Such patients should be evaluated for the closeness of their contact with infected patients and their immune status. People at high risk are candidates for chemoprophylaxis; possible regimens include pyrazinamide plus ethambutol in standard doses or pyrazinamide in standard doses plus ciprofloxacin (750 mg twice daily) or ofloxacin (400 mg twice daily).

d. **MAC.** Treatment for dissemination should include either azithromycin or clarithromycin and ethambutol (used as a second drug when tolerated). When resistance to a two-drug regimen or multisystem disease develops, one or two additional drugs should be selected from the following: clofazimine, rifabutin, ciprofloxacin, or in some instances, amikacin.

B. *Nocardia asteroides* **infection (nocardiosis)**. Several types of cell-mediated immune defects have been described in association with nocardiosis. About 20% of cases occur in patients receiving corticosteroids.

In immunocompromised subjects, 75% of nocardiosis cases occur in the lung. Nocardiosis can be asymptomatic, heal spontaneously, or produce a lower lobe bronchopneumonia with cavities, abscesses, or empyema. Disseminated nocardiosis typically involves subcutaneous tissue, muscle, and CNS tissues. Apparently localized soft tissue abscesses or osteomyelitis frequently disseminate.

1. **Diagnosis.** Gram stain of sputum reveals gram-positive, beaded, branching filaments. Sputum should also be examined with modified Ziehl-Neelsen stain. Some organisms are acid-fast. Sabouraud's dextrose and beef heart infusion culture media is incubated aerobically.

2. **Management**
a. Sulfadiazine, 6 to 10 g/day PO in divided doses, is used for 6 weeks to 3 months. Most authorities suggest 1 year of therapy for severe infection.
b. Chloramphenicol (4 g/day PO), chlortetracycline (2 g/day PO), or Bactrim-DS (2 tablets every 8 hours PO) can be used in addition to sulfadiazine for severe disease.
c. Cycloserine (15 mg/kg PO in four divided doses), alone or as an adjunct to sulfadiazine, shows promising results.

C. *Listeria monocytogenes* may be confused with gram-positive cocci, *H. influenzae,* or diphtheroids on Gram stain of specimens. Infections are more common in patients with defects in cell-mediated immunity. *L. monocytogenes* is the most common cause of bacterial meningitis in patients with carcinoma and in patients receiving corticosteroids or other immunosuppressive therapy, especially for lymphoma.

CNS infection with cerebritis or brain abscess accounts for 80% of cases. The mortality rate for CNS infections is 15% to 45%. Bacteremia or sepsis accounts for 20% of cases in adults. Pulmonary involvement is always in the form of an empyema.

1. **Diagnosis**
a. **Culture.** After *L. monocytogenes* is isolated, the organisms have a unique tumbling motion when viewed in a hanging drop.
b. **Spinal fluid.** Either lymphocytes or polymorphonuclear neutrophils are predominant. Spinal fluid protein concentration ranges from normal to 1 g/dL. Glucose levels are low in only half of cases.

2. **Management**
a. **Sepsis.** Ampicillin, 200 mg/kg per day IV, or penicillin, 300,000 U/kg per day IV, are given in six divided doses. Erythromycin and tetracycline are alternative drugs. Gentamycin can be added to ampicillin initially for synergy.
b. **Meningoencephalitis** is treated in the same manner as sepsis. Intrathecal gentamicin, 3 to 5 mg every 24 hours, may be synergistic with intravenous antibiotics.

D. *Legionella pneumophila.* Legionnaires' disease can affect normal and immunosuppressed hosts, especially patients receiving glucocorticoids. The disease typically produces lobar pulmonic consolidation evolving from patchy infiltrates. Features that suggest legionnaires' disease include nonproductive cough, nodular pulmonary consolidation, diarrhea, hyponatremia, and confusion.

1. **Diagnosis**
a. **Cultures** on supplemented Mueller-Hinton agar should be obtained.
b. **Tissue examination.** Dieterle staining can be used to detect bacteria in tissue. Positive direct FA examination of tissue strongly suggests legionnaires' disease. PCR assay is available as a research tool.
c. **Serology.** Antibody titers do not help early in the disease course.

2. **Management**
a. Erythromycin, 1 g IV every 6 hours, should be given for 3 weeks. Newer macrolides, such as clarithromycin and azithromycin, and several quinolones have efficacy.
b. Rifampin, 300 to 600 mg/day PO, is effective as an alternative and can be added if the patient does not respond to erythromycin.

E. **Salmonella.** Malnutrition, malignancy, gastrectomy, necrotic or ischemic tumor masses, and corticosteroid therapy predispose patients to infection with *Salmonella* species. Salmonella enterocolitis, bacteremia, enteric fever, and localized infection are the predominant infections in patients with neoplastic disease.

1. **Diagnosis.** Culture is done on selective media. Serology is of minimal value.
2. **Management.** Ampicillin, 100 mg/kg per day PO, or chloramphenicol, 50 mg/kg per day PO in four divided doses for 2 weeks is most often used. Osteomyelitis, endocarditis, or deep-seated abscesses may take 4 to 6 weeks of therapy. TMP-SMZ (Bactrim) should be used for resistant strains. Abscess formation necessitates surgical drainage.

F. *Helicobacter pylori* is a small, highly motile, curved, microaerophilic gram-negative rod that is uniquely adapted to survive in the highly acidic gastric environment. Primary gastric lymphoma of mucosa-associated lymphoid tissue (MALT) represents a distinct histopathologic entity. Epidemiologic, histomorphologic, molecular-biologic, and experimental data clearly indicate that *H. pylori* infection of the gastric mucosa plays an important role in both the development and progression of MALT lymphoma. Strains of *H. pylori* that are cagA-positive have been reported to be associated with peptic ulcer or malignancy more often than cagA-negative strains. *H. pylori* infection is also associated with an increased risk for gastric adenocarcinoma; the control of *H. pylori* infection, by means of eradication or immunization, may offer the potential to prevention this malignancy (see Chapter 9, Gastric Cancer, section I.B.2).

1. **Diagnosis.** A direct diagnostic test for *H. pylori* is biopsy through an endoscope, which has a sensitivity and specificity of more than 95% in experienced hands, provided at least two biopsies are taken from the gastric antrum and two from the gastric body. Culture of the organism adds little in terms of diagnosis but can facilitate the choice of treatment by allowing the performance of antibiotic-susceptibility testing.

Among the indirect tests, ELISA for *H. pylori* antibodies has a sensitivity and specificity of more than 90% for initial diagnosis, but at least half of patients remain antibody-positive after effective therapy. Breath testing after the administration of [13]C- or ^{14}C-labeled urea, which is metabolized by *H. pylori* urease, has a sensitivity and specificity of more than 95% and is particularly suited to the performance of serial studies to evaluate the efficacy of therapy. Because proton-pump inhibitors, such as lansoprazole and omeprazole, can suppress *H. pylori* without eradicating it, their use should be avoided for 2 weeks before the urea breath test is administered.

2. **Management.** Numerous multidrug regimens to eradicate *H. pylori* have been studied, but none has emerged as the clear treatment of choice. Antimicrobial agents include metronidazole, tetracycline, amoxicillin, and clarithromycin. Regimens administered for 14 days are most popular, although 10-day courses

may be as effective. A 2-week regimen consisting of the proton pump inhibitor, omeprazole, and clarithromycin is convenient but expensive and has a success rate of only 64% to 74%. Two-week courses of a three-drug regimen that includes lansoprazole, clarithromycin, and amoxicillin have a success rate close to 90%. It is possible that 1-week or 10-day regimens with omeprazole, amoxicillin or metronidazole, and clarithromycin will be as effective as longer regimens.

VI. Fungi

A. **Cryptococcosis.** Patients receiving corticosteroids and those with sarcoidosis or Hodgkin lymphoma have the highest incidence of infection with *C. neoformans.* About one third of these patients show anergy to cryptococcal skin antigens.
  1. **Clinical presentation.** Pulmonary infection can be asymptomatic. Chest radiographs reveal local bronchopneumonia, lobar involvement, or discrete nodules that may cavitate. CNS infection usually presents as insidious meningoencephalitis. The onset can be rapid in immunosuppressed patients.
  2. **Diagnosis**
      a. **Culture.** *C. neoformans* is an encapsulated, yeastlike fungus that replicates by budding; pseudomycelia are not produced. Sputum culture on Sabouraud's agar that reveals cryptococci in an immunocompromised host must be regarded with alarm. The normal population can harbor this organism without symptoms, however.
      b. **Cerebrospinal fluid** reveals an elevated opening pressure and lymphocytic pleocytosis in cryptococcal meningoencephalitis. A low glucose concentration is found in half of cases. India ink preparation is positive in only one third of patients. Centrifugation of spinal fluid may reveal the organisms. PCR assays for cryptococcal disease appear promising.
      c. **Serology.** The presence of cryptococcal polysaccharide antigen in spinal fluid or blood is key to the diagnosis (detection in 90% of cases of meningitis). Antibody assays are less useful because cryptococcal antibodies are prevalent in the uninfected population. Skin tests are not useful. Low serum cholinesterase and elevated serum blood urea nitrogen are useful surrogate markers that predict high mortality rates, with death occurring within 2 weeks after fungemia.
  3. **Management**
      a. **Pulmonary disease.** Uncomplicated pulmonary disease usually does not need to be treated. Patients with pulmonary infections who are immunocompromised must be treated with agents such as fluconazole or itraconazole (see section F.1). If these fail, amphotericin B with flucytosine should be tried (see section F.2). Salvage therapy with a combination of imipenem, cotrimoxazole, and a prolonged course of itraconazole has also proved acceptable.
      b. **Meningitis or disseminated disease** is treated with fluconazole at a dose of 400 mg/day either PO or IV as long as creatinine clearance is normal. The combination of a reduced dose of amphotericin B plus flucytosine for about 6 weeks is a second-line regimen (see section F.2). Intrathecal amphotericin B (see section F.3.c) is indicated only as a salvage therapy when fluconazole has failed. Failure of any regimen is associated with depressed spinal fluid glucose, extremely abundant cryptococci in the spinal fluid, CNS obstruction, or poor renal function.
B. **Candidiasis.** The major risk factors for systemic candidiasis include treatment with immunosuppressives, antibiotics, glucocorticoids, or hyperalimentation. Indwelling catheters, intravenous drug abuse, and underlying diseases that produce defects in polymorphonuclear neutrophil function or cell-mediated immunity (e.g., leukemia, lymphoma, diabetes mellitus) also are associated with this infection.
  1. **Clinical presentation.** Localized candidiasis can involve the skin, mouth, esophagus, rectum, or vagina. Disseminated candidiasis can present with fever alone, sepsis, endophthalmitis, skin nodules, renal disease, arthritis, or myositis. *Candida albicans* and *Candidia tropicalis* show discrete, yellow-white retinal lesions.
  2. **Diagnosis**
      a. **Cultures.** Finding hyphae in the urine is more suggestive of infection than finding blastospores or positive culture, but positive blood culture is far more important. Although candida grow well in routine, biphasic, and Sabouraud's agar, they may not produce turbidity in liquid media because they sink to the bottom (the laboratory should be informed when this pathogen is suspected).
      b. **Serology.** Agglutinins are usually not helpful. Precipitins, which do not appear until 10 to 14 days after infection, suggest candidal infection when titers exceed 1:8.
      c. **Esophagogram** shows a typical shaggy, moth-eaten appearance in cases of esophageal candidiasis.
  3. **Management.** Infected foreign bodies, such as prosthetic valves or indwelling catheters, must be promptly removed.
      a. **Local therapy.** Nystatin is used either as an ointment or in liquid suspension (100,000 U/mL). Oral candidiasis is treated with 500,000 to 2,000,000 U every 4 to 6 hours. If this fails, clotrimazole (Mycelex troches), five times daily, or ketoconazole, 200 to 400 mg once daily, should be used.
      b. **Prophylaxis.** Fluconazole, 200 mg PO once daily or 200 mg IV every 24 hours, can be used for prophylaxis in patients in whom chemotherapy is initiated and neutropenia is anticipated. Prophylactic fluconazole prevents colonization and superficial infections by *Candida* species other than *Candida krusei.* This agent is used until recovery of the neutrophil count, development of proven or suspected invasive fungal infection, or the occurrence of a drug-related toxicity.
      c. **Systemic therapy** (see also section F)
          1. Fluconazole also remains the first-line therapy in invasive candidiasis for most species other than *C. krusei.*
          2. Incorporation of amphotericin B into small unilamellar liposomes (AmBisome) alters the pharmacokinetic properties of the drug but allows it to retain significant *in vitro* and *in vivc* activity against fungal species, including *Candida, Aspergillus,* and *Cryptococcus* species, and parasites of the genus *Leishmania.* Liposomal amphotericin can be used at a much higher dosage (5 mg/kg per day IV) with less adverse reactions and better efficacy than amphotericin B alone.

            Amphotericin B (20 mg/day IV for 2 weeks) is recommended only as a second-line therapy for most adult patients with single-organ involvement or candidemia. In severe disease, doses up to 50 mg/day IV should be given for 6 to 10 weeks or until a total dose of 1.5 to 2 g is reached.

          3. Flucytosine, effective in 80% of patients, can be used in conjunction with amphotericin when the disease is severe, particularly with CNS infection (see section F.3 for dose). This regimen is a salvage attempt.
C. **Aspergillosis.** The typical presentation for aspergillosis in immunosuppressed patients is fever and pulmonary infiltrates, often with infarction, hemoptysis, and gangrene from vascular invasion. Nearly one third of patients have no radiologic abnormalities early in the disease. Dissemination complicates pulmonary disease in 25% to 50% of cases. Various skin lesions, multiple abscesses, brain infarction, or GI ulceration with hemorrhage can result.

    Aspergillosis is the second most frequent fungal infection that affects the face and mouth of patients receiving chemotherapy. In these patients, bone marrow recovery or the use of CSFs may lead to the liquefaction of pulmonary foci. Potentially lethal erosion bleeding may then occur because of the vasotropic nature of the infection.

  1. **Diagnosis.** Sputum examination showing septate, acutely branching organisms is highly suggestive of aspergillosis. This finding represents a serious problem in immunosuppressed patients. Methenamine silver stains of lung tissue are usually diagnostic. The value of serologic tests is unproved.
  2. **Management**
      a. **Antifungal treatment** should include the combination of amphotericin B and flucytosine during periods of granulocytopenia, followed by itraconazole after bone marrow recovery (see section F for dosages). Itraconazole appears to contribute significantly to therapy, but the drug is not effective during granulocytopenic episodes. Liposomal amphotericin B is a promising drug for this disease.
      b. **Fluconazole** may obscure the onset of aspergillosis. When aspergillosis is seriously suspected, fluconazole should be given neither prophylactically nor for fever of unknown origin.
      c. **Surgical resection** of localized invasive pulmonary aspergillosis with a cavitating lesion may prevent hemoptysis and recurrence in selected patients. In leukemic patients, the achievement of complete remission combined with aggressive antifungal therapy leads to markedly increased cure of aspergillosis. The combination of a fibrinolytic agent and an antifungal drug may be considered for intractable aspergillus infections because these organisms are angioinvasive.
D. **Zygomycosis.** Zygomycetes infection has been recognized with increasing frequency in patients who have leukemia or lymphoma (but not solid tumors). Infections caused by *Cunninghamella bertholetiae* (a fungus of the Zygomycetes class, Mucorales order) are being identified with increasing frequency in immunocompromised patients, including patients undergoing chemotherapy. Other predisposing factors include acidosis, uremia, immunoincompetence, glucocorticoid therapy, diabetes mellitus, malnutrition, and burns.
  1. **Manifestations.** The genera *Rhizopus, Absidia,* and *Mucor* produce similar pathologic and clinical manifestations because of neutrophil exudation, tissue necrosis, and vascular invasion (resulting in thrombosis and infarction).
      a. **Pneumonia** can be associated with a dry cough or hemoptysis. Radiographs may show interstitial infiltrates, lobar consolidation, or cavitation.
      b. **Cerebral disease** is usually secondary to pulmonary involvement. Coma and focal neurologic signs represent brain infarcts or abscesses. Spinal fluid studies are not usually helpful. **Rhinocerebral disease** occurs most frequently in uncontrolled diabetes mellitus. Manifestations include bloody nasal

discharge, orbital infection, periorbital and perinasal swelling, ptosis, proptosis, loss of vision, trigeminal anesthesia with ophthalmoplegia, facial pain, and facial nerve palsy.

   c. **Disseminated disease** can result in gastroenteritis, bowel perforation or hemorrhage, peritonitis, or abscess in any organ.

2. **Diagnosis.** Zygomycetes organisms have broad, nonseptate hyphae in tissue specimens and, in culture media, mycelia with hyphae and sporangia. Diagnosis is made by demonstrating the organism by culture or hematoxylin-eosin, periodic acid–Schiff, or methenamine silver stains of preparations.

3. **Management.** Early diagnosis is paramount. Amphotericin B or its liposomal form is the drug of choice (see section F). Mortality rates remains high.

E. **Diagnosis of other systemic mycoses**

1. ***Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis*** have diagnostic culture results and histopathologies. These common human pathogens can also present as opportunistic infections in patients who are immunocompromised. Dissemination is often associated with cutaneous anergy.

2. ***Trichosporon beigelii*** causes white piedra and an emerging opportunistic mycosis that is frequently difficult to diagnose. This mycosis is associated with a high attributable mortality rate. Systemic infection has been most frequently described in neutropenic patients receiving chemotherapy.

   a. Cutaneous involvement occurs in about 30% of patients and frequently presents as purpuric papules and nodules with central necrosis or ulceration. Biopsy specimens of these lesions reveal dermal invasion by fungal elements. Culture is positive in more than 90% of cases. Antigen detection in the blood is an early manifestation of disseminated infection.

   b. The antifungal triazoles, fluconazole and SCH 39304, are most active. Amphotericin B and liposomal amphotericin B appear to be ineffective.

3. ***Hansenula anomala*** is rarely pathogenic, but this infection has occurred in patients with small cell lung cancer. Fluconazole treatment appears to be effective.

4. ***Pseudoallescheria boydii,*** an uncommon cause of infection, may cause CNS disease and positive blood cultures in patients with leukemia. Although infections are usually resistant to amphotericin B, they may respond to itraconazole.

5. **Fusariosis.** Members of the genus *Fusarium* are ubiquitous fungi uncommonly associated with infection. Disseminated fusariosis typically occurs in neutropenic patients, carries a high mortality rate, and presents with fever and diffuse cutaneous maculopapular necrotizing nodules. *Fusarium verticilloides* can be isolated from culturing the biopsy of skin lesions (hyphae are often observed on direct microscopy) or bronchial aspirates of lung lesions. Liposomal amphotericin B (see section F.3.b) for 3 to 6 weeks may eradicate this infection, although amphotericin B by itself appears ineffective.

6. **Alternariosis,** another uncommon fungal infection resembling aspergillosis, has been described in both immunocompromised and immunocompetent hosts. Cutaneous alternariosis can occur during neutropenia in BMT patients who are receiving antifungal prophylaxis with fluconazole. Therapy requires surgical excision and amphotericin B.

7. **Fungemic shock.** As the use of empiric antibiotics or prophylaxis for bacteria has increased, organisms such as *C. albicans, Aspergillus niger, Fusarium solani,* and *Acremonium strictum* have been implicated in septic shock occurring in immunocompromised patients.

8. **Radiation port dermatophytosis** is an uncommon condition in which patients receiving RT concurrently have tinea corporis confined primarily to the irradiated skin. Because the cutaneous manifestations may be misinterpreted clinically as acute radiation-induced dermatitis, this condition may be more prevalent than reports suggest.

F. **Therapy of systemic fungal infections**

1. **Fluconazole and itraconazole** have become the primary antifungal agents used in systemic infections. These agents are far safer than amphotericin B or even liposomal amphotericin B and have excellent efficacy. The use of oral polyenes along with fluconazole shows promise in clinical research trials.

   a. **Administration.** Because of their safety, these azole agents can be used with little monitoring. Creatinine clearance and liver function dictate significant changes in dosage. Fluconazole can be given up to 400 mg PO or IV twice daily. Itraconazole can be given at a dose of 100 to 600 mg PO daily depending on the infection.

   b. **Toxicity.** Fluconazole can be associated with GI disturbances and headache. Severe but unusual sequelae are exfoliative skin disorders, thrombocytopenia, and hepatotoxicity. Itraconazole is also mildly toxic, but unlike fluconazole, it has no effect on concomitantly administered warfarin, cyclosporine, or insulin.

2. **Flucytosine** is useful only in combination with amphotericin B for treating *Cryptococcus* and *Candida* species infection and other fungi. The drug penetrates the spinal fluid well (thereby having an advantage in CNS infections) and is excreted primarily by the kidneys.

   a. **Dosage** is 150 mg/kg per day PO in four divided doses, adjusted to maintain a serum level of 50 to 75 µg/mL. When the two drugs are given in combination, the dose of amphotericin B is reduced to 0.3 to 0.5 mg/kg per day, and the dose of flucytosine is decreased to 100 mg/kg per day.

   b. **Toxicity.** Granulocytopenia, thrombocytopenia, and elevation of serum levels of hepatic enzymes and creatinine are common side effects. CNS and GI disturbances occur less frequently.

   c. **Dosage modification.** Dosages must be reduced with leukopenia, thrombocytopenia, or deterioration of renal function. (Note: amphotericin B frequently results in decreased renal function; therefore, toxic levels of flucytosine occur when amphotericin B and flucytosine are used simultaneously.)

3. **Amphotericin B** (and its promising congener liposomal amphotericin B) remains the choice for specific deep-seated or systemic fungal infections or for fluconazole or itraconazole failures. Initially, a test dose of 1 to 5 mg is given. Diphenhydramine (Benadryl), 50 mg PO, is given before the infusion. Hydrocortisone sodium succinate, 25 to 50 mg, and aqueous heparin, 100 U, are added to the amphotericin infusion bottle.

   a. **Dosage.** A dose of 20 mg in 250 mL of 5% dextrose in water is infused over 30 minutes the day after the test dose is given. The dose is slowly raised in 5-mg increments until a maximum of 1 mg/kg per day is reached. Usually, no more than 50 to 60 mg/day is given. Most deep-seated fungal infections necessitate 2 to 3 g of amphotericin when used alone or 1.5 to 2 gm when used with flucytosine.

   b. **Liposomal amphotericin B** (AmBisome) is given at a dose of 3 to 5 mg/kg per day. It is far better tolerated than amphotericin B.

   c. **Intrathecal amphotericin** doses for CNS fungal infections begin at 0.025 mg; the daily dose does not exceed 0.50 mg. The drug is administered every 2 to 7 days either into a reservoir (e.g., Ommaya valve), cisterna, or ventricle, or by LP using a hypertonic technique.

   d. **Toxicity.** Side effects include fever, chills, hypotension, nausea, vomiting, and azotemia. Permanent reduction of glomerular filtration, renal tubular acidosis, phlebitis, anemia, and headache are frequent complications. Serum creatinine and potassium levels are measured daily.

VII. Parasites

A. **Toxoplasmosis.** The incidence of asymptomatic disease based on serology ranges from 10% to 40% in the United States to 96% in western Europe. Of those patients with AIDS who are seropositive for *T. gondii,* about 25% to 50% originally developed toxoplasmic encephalitis. This percentage has decreased dramatically because combination therapy for HIV-1 has become the accepted therapy.

Patients with symptomatic disease present with a low-grade febrile illness characterized by localized or generalized lymphadenopathy, hepatosplenomegaly, malaise, and fatigue. Any organ may become involved. Infection in patients with abnormal cellular immunity may mimic brain tumor or lymphoproliferative disorder.

1. **Diagnosis**

   a. **Histology.** Identification of trophozoites rather than cysts is important because cysts can persist for decades. Lymph node pathology is characteristic of toxoplasmosis.

   b. **Culture** is rarely used.

   c. **Serology** usually establishes the diagnosis. IgM and CF antibodies are useful for the diagnosis of early infection. Titers of both assays decrease after 6 to 12 months. Indirect FA titers are also useful. Sensitive ELISA antibody sandwiches and the use of PCR for *Toxoplasma* DNA have helped differentiate inactive old disease from acute infection.

2. **Management.** Pyrimethamine (a folic acid antagonist) and a sulfa derivative are given in divided doses for 1 month. The development of hematologic toxicity often interrupts treatment.

   a. **Pyrimethamine** is given with a loading dose of 100 to 200 mg PO followed by maintenance of 50 mg/day. Folinic acid, 5 mg/day, is required when 100 mg/day or more is given.

   b. **Sulfadiazine** is given with a loading dose of 50 to 75 mg/kg followed by maintenance of 75 to 100 mg/kg per day (1 g PO four times daily).

   c. **Other combination therapies** for acute disease

     1. Pyrimethamine (100 mg/day PO) plus clindamycin (1.2 g/day IV in divided doses)

     2. 5-Fluorouracil (1.5 mg/kg per day) and clindamycin, (1.8 to 2.4 g/day) for treatment of cerebral toxoplasmosis, which may provide a less toxic option

B. **Pneumocystis.** *P. carinii* causes pneumonia in immunodeficient patients, including those with AIDS. Children (in remission) with acute lymphocytic leukemia and patients in whom corticosteroid therapy is being tapered are particularly susceptible to infection.

Manifestations include dyspnea, fever, nonproductive cough, pulmonary rales, hypoxemia, and hypocapnia. Chest radiographs early in the disease may appear benign, whereas blood gases often demonstrate major hypoxia, and gallium scans light up the entire lung. Chest films more typically show diffuse symmetric, bilateral, perihilar infiltrates that spread rapidly. Nodules or cavities develop infrequently.

1. **Diagnosis.** Methenamine silver and Gram-Weigert stain cyst walls. Giemsa stains sporozoites within the cyst wall but not the wall. Sputum specimens are diagnostic in 10% to 15% of cases, bronchoscopic brushings in 65% to 75%, and open-lung biopsy in 90%. Monoclonal antibody assays for *P. carinii* may speed diagnosis and improve follow-up of this infection. In patients who are critically ill or severely thrombocytopenic, lung biopsy should be deferred. Less invasive procedures or possibly an empiric trial of therapy should be done because the biopsy procedure has high morbidity and mortality rates.
2. **Management.** In patients with any respiratory difficulties associated with their pneumonia, any therapy for active disease should be used in conjunction with a short, rapidly tapering course of corticosteroids. Treatment is given for 14 to 21 days, and options include the following:
   a. TMP-SMZ (Bactrim), 2 double-strength tablets PO or 2 ampules IV every 6 to 8 hours
   b. Pentamidine, 4 mg/kg IM daily
   c. Mepron may be useful in patients who are intolerant of TMP-SMZ.
   d. Trimetrexate in combination with leucovorin appears to be extremely effective even when other regimens have failed.
   e. Clindamycin (450 mg four times daily) and primaquine (15 mg of base per day) have similar efficacy for pneumocystis compared with TMP-SMZ (320 mg/1600 mg four times daily if patient weighs 60 kg or more, or 240 mg/1200 mg four times daily if patient weighs less than 60 kg).
      Clindamycin-primaquine is associated with fewer adverse events, less steroid use, and more rashes than TMP-SMZ.
C. ***Ehrlichia* species** are intraleukocytic rickettsial parasites that are pathogenic for a wide variety of wild and domestic animals. The agent of human ehrlichiosis, *E chaffensis*, has been cultured, can be detected by PCR, and preferentially infects monocytes (HME). A second *Ehrlichia* species capable of causing disease in humans was identified in the United States, is closely related to *E. phagocytophila*, and preferentially infects granulocytes (HGE). Ehrlichiosis can exacerbate marrow suppression in patients with lymphoproliferative disorders.

Patients with ehrlichiosis experience the acute onset of fever, rigors, malaise, headache, and myalgias at a median of 8 or 9 days after tick exposure. Nausea, vomiting, and particularly rash occur less commonly in both forms of this disease than in Rocky Mountain Spotted Fever; rash is reported in 35% of patients with HME and 2% of patients with HGE. Cough occurs in 25% of patients and pulmonary infiltrates are common. Like other rickettsial infections, human ehrlichiosis may be accompanied by aseptic meningitis; confusion is reported in 20% of patients and may have a multifactorial etiology. Serious clinical complications, including renal insufficiency, disseminated intravascular coagulation, and neurologic manifestations, develop in about 15% of patients with HME.

In earlier studies, 50% to 70% of patients with human ehrlichiosis, especially elderly patients, underwent hospitalization; however, most experts believe that many cases of mild or asymptomatic infection remain unidentified. Although ehrlichiosis in humans may persist, as it often does in animals, the median duration of gross clinical manifestations in HME is 23 days. In a human host, coinfection with a combination of *Ehrlichia* species, *Borrelia burgdorferi,* and *Babesia* species may modify the presentation and natural course of disease caused by each of these agents alone.

1. **Diagnosis.** Human ehrlichiosis is accompanied by leukopenia, especially lymphocytopenia, in 50% to 75% of patients and by thrombocytopenia in 70% to 90% of patients. Nadirs in cell counts occur at the end of the first week of illness. Elevated serum aminotransferase levels occur in about 90% of patients at some time during the clinical course. These findings help distinguish human ehrlichiosis from other diseases. About 80% of patients have visible intracytoplasmic inclusion bodies (morulae) on acute-phase peripheral blood smears; these morulae are detected in 1% to 40% of neutrophils (median, 5%). Other laboratory abnormalities, including anemia, are less specific and are not useful in making the diagnosis.
2. **Management.** The drug of choice for both HME and HGE is doxycycline, 0.1 g PO or IV twice daily. Patients who receive doxycycline early in the course of disease have a more rapid recovery and lower mortality rate than do those who do not receive this drug. The necessary duration of therapy is unclear. Most patients have a clinical response to doxycycline within several days, but some experts recommend 14 days of treatment, in part to treat coexistent Lyme disease.
D. **Strongyloidiasis.** Humans are infected by both filariform larvae and adult forms, resulting in self-perpetuating autoinfection. Defective cell-mediated immunity, high-dose corticosteroid therapy, and decreased bowel motility enhance the chance of massive GI tract, pulmonary, or CNS infection. The characteristics of *S. stercoralis* allow it to be harbored within a host for prolonged periods of time, only to disseminate after cell-mediated immunity is suppressed.
   1. **Diagnosis.** A diagnosis of strongyloidiasis should be considered in an immunocompromised patient with a petechial rash. Larvae can be recovered from the stool in 25% to 60% of patients and from duodenal aspirates in 40% to 90%. Peripheral eosinophilia is typical but may be absent in the hyperinfected state.
   2. **Management.** Prompt diagnosis and initiation of thiabendazole therapy, 1.5 g PO twice daily for 2 to 4 days, provides the greatest opportunity for patient survival. Secondary bacterial infections should be aggressively sought. The mortality rate from disseminated strongyloidiasis approaches 80%.
E. **Other parasites**
   1. ***Giardia lamblia*** infection is associated with hypogammaglobulinemia, small bowel lymphoma, and pancreatic carcinoma. Manifestations include diarrhea, nausea, flatulence, and cramps.
   2. **Malaria and babesiosis** may hyperinfect immunosuppressed hosts, especially after splenectomy. Infection results in high fever and hemolysis.
   3. **Cestodes** can disseminate in patients with Hodgkin lymphoma. Invasion of blood vessels and deep organs produces severe symptoms.
      a. **Cysticercosis** is the systemic infection with eggs of *Taenia solium*. It most frequently presents with brain masses (often with calcified rims on radiographic studies). Craniotomy is necessary for both definitive diagnosis and therapy.
      b. **Echinococcosis** can present as a space-occupying lesion in several visceral organs. Diagnosis is established by serologic tests and evidence of the organism by histopathology.
   4. **Proliferation of commensal parasites of the skin.** *Dermodex folliculorum* and *Dermodex brevis* may cause opportunistic infection of the skin in the immunocompromised host. The expected abrogation of cell-mediated immunity secondary to lymphocyte depletion predisposes some children and adults given chemotherapy for leukemia to proliferation of mites.

Suggested Reading

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Chapter 36 Acquired Immunodeficiency Syndrome (AIDS]

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I. Epidemiology and etiology

A. **Epidemiology.** Acquired immunodeficiency syndrome (AIDS) is a worldwide pandemic. Since the initial identification of five cases of AIDS in Los Angeles in 1981, more than 1.25 million cases of AIDS had been reported to the World Health Organization (WHO) by 1995. Data suggest, however, that about 30 million people are infected with human immunodeficiency virus type 1 (HIV-1). About half of all cases of HIV-1 infection are in sub-Saharan Africa. HIV-1 is spreading most rapidly in Asia, with more than 5 million cases estimated. The epidemic continues to expand in South America but appears to have plateaued in North America and Europe.

A related retrovirus, HIV-2, may also cause AIDS, although it is generally less pathogenic than HIV-1. HIV-2 is distributed primarily in West Africa, but a few cases have been identified in the United States.

B. **Transmission**
1. **The efficiency of HIV-1 transmission** varies with the route, the quantity of virus, and certain phenotypic characteristics of the virus. The virus first interacts with CD4 on T cells but requires a coreceptor to penetrate the cell membrane. The CC chemokine receptor-5 (CCR5) that mediates activation of both T cells and macrophages is the major coreceptor for some HIV-1 strains. The natural ligands for CCR5 include RANTES, MIP-1a, and MIP-1b. One percent of whites are homozygous for a defect in this CCR5 receptor and are resistant to HIV infection. The CXC chemokine receptor-4 (CXCR4), which is T-cell specific, appears to be important in late-stage HIV infection. The a-chemokine receptor CCR4, which is also T-cell specific and a receptor for stromal cell-derived factor-1, is involved in infections of late HIV isolates.
2. **Sexual contact** is a relatively inefficient mode of transmission. The estimated risks for sexual transmission of HIV-1 are 1 in 300 for male-to-male transmission; 1 in 500 for male-to-female transmission; and 1 in 1000 for female-to-male transmission; however, these are only average risks. Some infected people appear to be much more efficient than others at transmitting the virus to sexual partners, and some remain uninfected despite extensive exposure to the virus through unprotected sexual contacts. The presence of other sexually transmitted diseases (e.g., chancroid) increases the risk for transmission of HIV.
3. **Casual contact.** At the outset of the epidemic, concerns were raised that HIV-1 might be transmitted by casual contact in the workplace, at schools, and in nosocomial settings. The continued concentration of the virus, however, in people with the same risk behaviors identified at the beginning of the epidemic is strong evidence that HIV-1 is not transmitted by casual contact.
4. **Transmission during pregnancy** can be as high as 27% with HIV-1. This rate can be reduced to 3% to 4% with the use of prophylactic zidovudine and lower yet with nevaripine or combination therapy. HIV-2 is transmitted more frequently than HIV-1 through pregnancy, but it is clinically less expressed in children. Breastfeeding is another major cause of transmission of the virus.

C. **Virology and pathogenesis.** AIDS is caused by HIV-1 or HIV-2.
1. **HIV is a double-stranded RNA lentivirus.** Lentiviruses are retroviruses because they contain a reverse transcriptase, which enables transcription of RNA to DNA. *The remarkable complexity of their viral genomes* distinguishes the lentiviruses from other retroviruses. Most retroviruses that are capable of replication contain only three genes: *gag, env,* and *pol.* The *gag* and *env* genes encode the core nucleocapsid polypeptides and surface-coat proteins of the virus, respectively, whereas the *pol* gene gives rise to the viral reverse transcriptase and other enzymatic activities. HIV-1, however, contains in its 9-kb RNA genome not only these three essential genes but also at least six additional genes: *tat, rev, nef, vif, vpu,* and *vpr.* HIV-2, which is more closely related to simian immunodeficiency viruses than to HIV-1, contains a unique regulatory gene, *vpx.*
2. **Regulating proteins.** HIV produces an early transactivating regulating protein (Tat) as well as an RNA-splicing regulating protein (Rev). Tat increases the level of transcripts derived from the long-terminal repeat (LTR) of HIV-1. Rev interacts with RRE (Rev-responsive element). The Rev-RRE interaction allows unspliced messages to create long RNA transcripts needed for structural proteins. Membrane proteins include gp41 and gp120, and Gag proteins include p17 and p24. Late regulatory proteins include Nef, Vif, Vpu, and an accessory protein, Vpr.
3. **Virus replication.** Although HIV may be clinically inapparent for many years after its acquisition, the virus is always replicating. The clinical course of HIV has no real latent periods but rather clinical plateaus with continued viral activity. Using polymerase chain reactions (PCRs) on either viral RNA or DNA, continuous viral activity has been confirmed.

Early in the asymptomatic period of disease, the virus is less infective and less virulent. Late in the clinically symptomatic period, HIV becomes highly infective and replicative. These two phases appear to correlate with the virus either not inducing syncytia (early) or inducing syncytia (late).

4. **Virus evolution.** HIV appears to evolve as the disease progresses not only from host to host but also within the single host. The viral phenotypic evolution is closely related to changes in the V3 loop of the envelope protein gp120.
5. **HIV is lymphotrophic.** About 10 billion viral particles are produced daily in an infected person. Ninety-nine percent of these viral particles are produced by activated CD4$^+$ T cells, which are killed when the virus enters the lytic stage of infection. This massive amount of viral replication, coupled with the replicative infidelity of HIV-1, results in both a major increase in the turnover of CD4$^+$ T cells and the rapid generation of diverse viral quasispecies. The accelerated rate of CD4$^+$ T-cell turnover gradually results in increasing immunodeficiency.
6. **The chemokine receptors** CCR5 and CXCR4 are coreceptors together with CD4 for HIV-1 entry into target cells. Macrophage-tropic HIV-1 viruses use CCR5 as a coreceptor, whereas T-cell–tropic viruses use CXCR4.
7. **The expression of chemokine receptors in the central nervous system** (CNS) increases during pathologic, especially inflammatory, conditions. The major cofactors for HIV infection (CCR5, CCR3, and CXCR4) have been detected in the human brain in a variety of cell types, including microglia, astrocytes, neurons, and vascular endothelial cells. Antibodies to chemokine receptors can block HIV infectivity in cultured CNS cells. This observation indicates that chemokine receptors are likely to have a functional role in the pathogenesis of HIV encephalitis. CD40 ligand stimulation of dendritic cells suppresses HIV replication and transmission to CD4$^+$ T cells by two potentially different mechanisms:
   a. For the host to recognize HIV and kill infected cells, specific cytotoxic T lymphocytes must be activated through close association with antigen-presenting cells, such as monocytes and macrophages. This interaction requires CD20, CD28, and CD80 receptors.
   b. A superantigen (SAg), also termed *Vß-selective element,* appears to be associated with HIV-1. Such a SAg could activate targeted T cells for optimal viral replication and viral reservoir establishment during the early stages of infection. Alternatively, SAg could participate in the induction of selective cell death (apoptosis) in the T-cell subpopulation targeted by the SAg.
8. **Responses of helper T-cell subtypes** contribute to the immune dysregulation associated with HIV infection. Helper T-cells (CD4$^+$) can be subdivided into TH1 and TH2 cells based on their ability to produce specific cytokines, including interleukins (IL), interferons (IFN), and tumor necrosis factor (TNF). TH1 cells, but not TH2 cells, produce IL-2, IFN- g, and TNF-b. TH2 cells, but not TH1 cells, produce IL-4, IL-5, IL-10, AND IL-13. Many seronegative, HIV-exposed individuals generate strong TH1-type responses to HIV antigens. Resistance to HIV infection or progression to AIDS may depend on maintaining dominance by TH1-type responses.
   a. Asymptomatic patients and those with early disease have increased levels of IL-2 and IFN- g with low expression of IL-4 and IL-10 (TH1-type response).
   b. Progression to AIDS is characterized by loss of production of IL-2 and IFN- g concomitant with increases in levels of IL-4 and IL-10 (TH2-type response).

II. Diagnosis

A. **Clinical presentation**
1. **HIV-1** can present acutely as a primary lymphocytic pneumonia or as a mononucleosis-like syndrome. The infection may also be initially asymptomatic; only many years later do the effects of immune dysfunction emerge. These later clinical scenarios can include night sweats, recurrent sinusitis, progressive skin

lesions, or entities listed in Table 36.1. HIV often becomes evident only when an AIDS-defining event occurs (see Category C in Table 36.1).

Table 36.1 The 1993 classification system for human immunodeficiency virus (HIV) disease

2. **HIV-2.** Clinically, HIV-2 appears to progress more slowly and produces milder immune dysfunction than HIV-1. HIV-2 is particularly associated with CNS disease, such as spastic paraparesis, but is also associated with chronic diarrhea, thrush, and tuberculosis.
B. **Diagnostic tests.** Patients with any significant risk for exposure to HIV should be evaluated for its presence. Screening must remain confidential and be used only for evaluation for therapy and control of further transmission.
   1. **HIV antibody assays.** The most commercially available method of screening for HIV is the enzyme immunoassay systems. The antibody becomes positive 1 to 3 months after exposure to HIV. Rarely, the serum can be antibody negative and antigen positive for as long as 12 to 18 months after the virus is acquired. The false-negative rate is about 3% when only antibody assays are used. The false-positive rate is only 0.2% in high-risk groups but is much higher in low-risk groups.
   2. **Western blot** is the confirmatory test for HIV antibodies. HIV proteins are separated electrophoretically and stained on film, which is then reacted against the test serum.
   3. **HIV-1 PCR for RNA,** and also reasonably for DNA, is the gold standard for measuring disease activity and predicting the future clinical course. RNA PCR measures fragments of virus and quantitates copies per milliliter in plasma. DNA PCR for HIV-1 measures intracellular viral copies and may act as a measurement for chronic reservoirs.
   4. **Staging of HIV infection** should carefully assess the clinical symptoms and signs of HIV-1 infection. Laboratory evaluation should stage the severity of infection and assess the risk for reactivation of opportunistic pathogens.
      a. Certain clinical features, including thrush or prominent systemic symptoms ("B symptoms"), suggest more advanced disease and a propensity for more rapid disease progression.
      b. The CD4$^+$ T-cell count is the most useful indicator of immunologic dysfunction and the immediate risk for opportunistic infections.
      c. The level of HIV-1 RNA in plasma is the best predictor of the rate of clinical and immunologic progression.
C. **Classification.** The 1993 revised Centers for Disease Control and Prevention classification system for syndromes associated with HIV infection (categories A, B, and C) emphasizes the clinical importance of the CD4$^+$ T-lymphocyte count (subcategories 1, 2, and 3). This classification system is shown in Table 36.1. Categories that define the presence of AIDS are A3, B3, C1, C2, and C3. Primarily used for public health practice, this system attempts to reflect the current standards of medical care for HIV-infected patients.

III. Treatment of HIV

A. **Overview.** Early treatment of HIV infection is mandated today. Prophylaxis against opportunistic infections should be provided as immunity reaches crucial levels of decay. The goal is to make HIV infection a chronic disease that permits quality life for decades. Antiretroviral agents have been directed primarily at two viral enzymes: reverse transcriptase and the HIV-1 protease.

The best way to target HIV involves the use of combination therapy: (1) antiretroviral agents, which attack the virus at different assembly sites, and (2) immune modulators, which specifically stimulate host immunity to kill HIV in its cellular home or which downregulate inflammatory chemokines and cytokines (which may be responsible for wasting, lipodystrophy, chronic diarrhea, and CNS dementia). Long-term survivors of HIV-1 disease are now emerging with new problems, such as myocardiopathy, valve disease, chronic diarrhea, atherosclerosis, diabetes, and adrenal insufficiency.

   1. **Factors affecting initiation of antiretroviral chemotherapy.** Clinical latency is not synonymous with viral or immunologic latency. The exact time at which therapy should be initiated depends on several factors:
      a. The degree of immunodeficiency as judged by the CD4$^+$ T-cell count
      b. The risk for disease progression as predicted by the plasma HIV RNA level
      c. The presence or absence of clinical symptoms
      d. The willingness of the patient to commit to a prolonged complex medical regimen
   2. **When to initiate antiretroviral therapy.** Most experienced clinicians recommend antiretroviral therapy for all infected patients with symptoms and all HIV-1–infected patients without symptoms but with a CD4$^+$ T-cell count below 500 cells/μL. The greater risk for disease progression for patients with CD4$^+$ T-cell counts above 500 cells/μL and with 5000 to 10,000 copies/μL of HIV-1 RNA in plasma suggests that antiretroviral chemotherapy should be offered to patients without symptoms who are in this category as well, although prospectively generated clinical data are not yet available to support this recommendation.
   3. **Goal of therapy.** Response to antiretroviral therapy is considered achieved if plasma HIV-1 RNA levels are driven below 50 copies/μL.
   4. **Categories of drugs** used in the treatment of HIV-1 infection include nucleoside analogue reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and adjuvant or immune-modulating agents. The combination of effective agents is termed *Highly Active Antiretroviral Therapy* (HAART).
   5. **Choice of initial drugs.** It is extremely important to emphasize to patients that the initial choice is provisional and that an alternative drug could be selected if side effects limit adherence. In most patients, at least two NRTIs and one potent PI are required to achieve sufficient suppression of viral replication. On the other hand, there is growing acceptance of using either two NRTIs plus an NNRTI or using two *synergistic* NRTIs (e.g., didanosine plus stavudine) plus a drug such as hydroxyurea. Because failure to achieve near-complete suppression of viral replication results in the emergence of resistance to drugs in the chosen regimen, it is not generally in the patient's interest to start antiretroviral chemotherapy with less aggressive regimens. The specific choice of drugs should be determined by the ability of the patient to comply with the regimen prescribed.
      a. **Combinations of NRTIs** should be chosen on the basis of nonoverlapping toxicities and, when possible, of maximizing the number of mutations that the virus must incorporate to replicate in the presence of all the drugs in the regimen. The three most frequently chosen regimens are zidovudine plus lamivudine, stavudine plus lamivudine, and didanosine plus stavudine (the latter pair may have the best efficacy profile). The combination of stavudine and zidovudine should be avoided because of antagonism between these two agents.
      b. **The PI to be combined with the NRTI** should be chosen on considerations of tolerability, toxicity, and potency.
      c. **Evolving combination therapies** include regimens with two PIs and regimens with PIs and NNRTIs. The addition of drugs, such as hydroxyurea or pulsed IL-2, elevates NRTI combinations into HAART, which has as good or better a profile as PIs.
   6. **Evaluation of efficacy.** All patients should be seen 2 to 3 weeks after the initiation of therapy to discuss compliance and to assess the antiviral response. Although the maximal effects of potent regimens is not evident for as long as 20 weeks, a substantial reduction in plasma HIV-1 RNA levels should be evident by the second week of therapy. If side effects are limiting adherence, make changes in the drugs. Responses to changes in plasma HIV-1 RNA levels should be made as follows:
      a. If plasma HIV-1 RNA levels declined by 1.0 log$_{1c}$ or more by this time, reassess the patient 12 to 16 weeks after the initiation of therapy.
      b. If plasma HIV-1 RNA levels declined to less than 50 copies/μL, follow the patient at intervals of 8 to 12 weeks to assess the degree to which suppression of viral replication is maintained.
      c. If plasma HIV-1 RNA levels are several thousand copies or more, it is generally advisable to seek an alternative regimen.
      d. If plasma HIV-1 RNA levels are in an intermediate range of 50 to 1000 copies/μL, recheck plasma HIV-1 RNA levels in 4 weeks. If the plasma HIV-1 RNA level has continued to fall, this sequence can be repeated.
   7. **When to change antiretroviral regimens.** After the initial regimen adequately suppresses viral replication, patients should be followed at intervals of 2 to 3 months to assess for toxicity and for loss of antiretroviral effect.
      a. **Vaccinations and intercurrent infections can transiently raise plasma HIV-1 RNA levels.** Therapeutic decisions should not be made on the basis of a single plasma HIV-1 RNA level.
      b. **The precise level of plasma HIV-1 RNA at which suppression of viral replication should be considered lost has not been established.** It is clear that patients continue to derive substantial clinical and immunologic benefits from therapy, even when low levels of plasma HIV-1 RNA are detected.
         1. Smoldering viral replication, however, in the presence of selective pressure of antiretroviral drugs, may lead to increased drug resistance.
         2. Enumeration of CD4$^+$ T cells is less sensitive than virologic parameters and should no longer be used as a primary indicator of drug failure.
         3. If smoldering viral replication continues while CD4$^+$ cells, cytotoxic T lymphocytes (CTL), and other markers of immune restoration improve, it may be prudent to refrain from any changes in combination therapy.
      c. **When suppression of viral replication is lost,** the clinician should substitute at least two new drugs for components of the previous regimen. The trouble with PIs is that cross-resistance to other PIs develops because mutations in the viral protease gene result when low levels of viral replication

occur in the presence of the initial PI.

8. **During the late stages of AIDS,** antiretroviral drug therapy is complicated by increases in drug intolerance, virus resistance, and probability of drug–drug interactions. Even then, however, most patients derive measurable clinical benefit if the plasma HIV-1 RNA level is at least 0.3 to 0.5 log $_{1c}$ lower than it would be without therapy. Therapy should be stopped if no drugs can be tolerated or if no evidence of antiretroviral activity can be demonstrated. Drugs such as hydroxyurea may be important in salvage therapy because they can potentially enhance the activity of NRTIs and reestablish their efficacy against HIV-1, in addition to providing other benefits (see later).

B. **NRTIs** have proved to be a useful although relatively weak class of HIV-1 replication inhibitors. In general, a reduction in plasma HIV-1 RNA levels of less than one log $_{1c}$ is observed when these drugs are initiated as monotherapy in previously untreated patients.

1. **Zidovudine** (AZT, ZDV, Retrovir) is an analogue of thymidine.
   a. **Dosage.** 300 mg given twice daily.
   b. **Toxicity**
      1. **Hematosuppression** without thrombocytopenia is the major dose-limiting toxicity. Macrocytosis develops with such regularity over the first 6 to 12 weeks of therapy that increases in the mean corpuscular volume can be taken as a direct indicator of compliance. The development of anemia and granulocytopenia is usually related to dosage and disease stage.
      2. **Anorexia or headache** develops in about 15% of patients. In about half of affected patients, these adverse effects resolve within 2 weeks after initiation of therapy.
      3. **Liver failure,** although extremely rare, is the most serious toxicity and appears to occur more frequently in patients with preexisting liver disease or obesity.
   c. **Clinical utility.** Zidovudine has modest antiviral activity when used singly, and zidovudine-resistant viral quasispecies emerge during ongoing treatment. Zidovudine monotherapy delays clinical evidence of disease progression in previously untreated patients with CD4 $^+$ T-cell counts below 500 cells/mm^3. Zidovudine also prevents or reverses HIV encephalopathy. Combinations of zidovudine and didanosine, lamivudine, or zalcitabine are associated with significantly better outcomes than zidovudine monotherapy.

2. **Didanosine** (ddI, Videx) is an analogue of deoxyadenosine.
   a. **Dosage.** 200 mg given twice daily for patients weighing 60 kg or more and 125 mg twice daily for those weighing less than 60 kg (can be administered in a single daily dose); should be taken on an empty stomach. Didanosine is formulated as a chewable tablet that is not acceptable to all patients.
   b. **Toxicity.** The major toxicities associated with didanosine are pancreatitis and peripheral neuropathy, which are dose related and are more often seen in patients with advanced disease.
      1. **Peripheral neuropathy** is generally reversible if the patient stops taking the drug. Many patients tolerate resumption of the drug at a reduced dose. Patients who have experienced neuropathy with didanosine are at a greater risk for the development of this complication in association with zalcitabine or stavudine.
      2. **Pancreatitis** is potentially life-threatening. Pancreatitis occurs more often in patients with late-stage disease, diabetes, or previous bouts of pancreatitis. Pancreatitis may occur at any time after initiation of the drug and with such rapid onset that regular monitoring of the serum amylase or lipase level is not useful in preventing this complication.
   c. **Clinical utility.** Didanosine is superior to zidovudine in antiviral and immunomodulatory effects and provides additional clinical benefits to patients who have used zidovudine. The combination of didanosine with hydroxyurea is synergistic.

3. **Zalcitabine** (dideoxycytosine, ddC, Hivid) is an analogue of cytidine.
   a. **Dosage.** 0.75 mg three times daily. Dose escalation is limited by neuropathy and is therefore used only in combination regimens or for the treatment of patients who are intolerant of or unresponsive to other NRTIs. Bioavailability of the drug is not significantly affected by food.
   b. **Toxicity.** Peripheral neuropathy is the major dose-limiting toxicity, and other side effects are rare. This complication, which is related to dose and disease stage, occurs at doses below those that exhibit maximal antiretroviral activity *in vivo.* When the drug is stopped promptly, neuropathy is usually reversible. After resolution of symptoms, many patients tolerate reintroduction of the drug in reduced doses.
   c. **Clinical utility.** Because of its convenient formulation and dosing schedule, zalcitabine has been used extensively in combination regimens for patients with advanced AIDS who are intolerant of or unresponsive to other antiretroviral agents.

4. **Stavudine** (d4T, Zerit) is an analogue of thymidine.
   a. **Dosage.** 40 mg given twice daily for patients weighing 60 kg or more and 30 mg twice daily for patients weighing less than 60 kg. The drug achieves cerebrospinal fluid levels that are in the range of 25% to 50% of serum levels.
   b. **Toxicity.** Stavudine causes macrocytosis of red blood cells but is seldom associated with anemia.
      1. **Peripheral neuropathy** is the major side effect (about 15% of patients). This toxicity is dose related and is more frequently observed in patients with advanced HIV-1 infection and in patients who have experienced previous NRTI-associated peripheral neuropathy. The neuropathy is reversible if the drug is discontinued promptly; about half of patients tolerate resumption of the drug at half the original dose.
      2. **Hepatitis** develops in about 15% of patients and is almost always reversible with discontinuance of the drug. Hepatitis is seldom life-threatening if the drug is stopped when significant elevations in serum hepatocellular enzymes occur.
   c. **Clinical utility.** Stavudine is useful in combination with didanosine or lamivudine and for HAART combinations.

5. **Lamivudine** (3TC, Epivir) is an analogue of cytidine. A single mutation in reverse transcriptase at position 184 results in a 100-fold to 1000-fold decrease in susceptibility to lamivudine. Any measurable degree of viral replication in the presence of the drug results in the rapid emergence of resistant mutations.
   a. **Dosage.** 150 mg given twice daily; single daily dosing is a feasible option.
   b. **Toxicity. Hematosuppression:** lamivudine is occasionally associated with suppression of the erythroid and myeloid elements of the bone marrow. This complication, however, is related to dose and disease stage and is less frequently observed than with zidovudine.
   c. **Clinical utility.** Although lamivudine rapidly selects for resistant viral isolates with a mutation at position 184 of the reverse transcriptase, this mutation compromises the ability of the virus to make mutations simultaneously that are associated with resistance to zidovudine. Mutations that antagonize the simultaneous development of resistance to two or more antiretroviral agents are termed *suppressor mutations* and have also been observed with didanosine and zidovudine. Because of these suppressor mutations, combination therapy with lamivudine and zidovudine results in an increase in CD4 $^+$ T-cell counts and a much more pronounced and prolonged reduction in viral load than does therapy with zidovudine alone. Lamivudine can also be combined with stavudine, with excellent antiviral effects *in vivo.* The addition of lamivudine to regimens with NRTIs has been shown to have a profound effect on disease progression and to decrease morbidity and mortality rates by 50%.

6. **Abacavir** (Ziagen) is the first guanosine analogue NRTI to be used clinically.
   a. **Dosage.** 300 mg given twice daily
   b. **Toxicities.** Nausea or a mild headache occurs in a minority of patients. A dramatic **shocklike syndrome** occurs in some patients who are given the drug after experiencing a febrile rash during the early period of dosing. The mechanism of this syndrome is unknown. Thus, patients experiencing a rash and systemic symptoms associated with abacavir should never be rechallenged with the drug.
   c. **Clinical utility.** Appropriate clinical settings for abacavir are being investigated. Because the activity of the drug is compromised by mutations at positions 65, 74, and 184, prior treatment with didanosine or lamivudine may decrease the utility of abacavir.

C. **NNRTIs** are a class of structurally diverse HIV-1 replication inhibitors that were developed from drug screening for activity against the HIV-1 reverse transcriptase. The propensity for the virus to develop high-level resistance to NNRTIs, if it is allowed to replicate in the presence of selective pressure, necessitates that use of these agents be restricted to combination therapy.

1. **Nevirapine** (Viramune) acutely suppresses plasma HIV-1 RNA levels by as much as 2.0 log $_{1c}$. When nevirapine is given as monotherapy, however, the virus rapidly becomes resistant to the drug by the incorporation of a single mutation at position 188 or 190 of the reverse transcriptase enzyme, with complete loss of activity of the drug resulting within 2 to 4 weeks.
   a. **Dosage.** 200 mg given twice daily
   b. **Toxicity.** A maculopapular eruption occurs in 10% to 15% of patients within the first 2 weeks of treatment; the rash usually resolves without the need to discontinue therapy. The drug should be stopped immediately if it induces a Stevens-Johnson–like syndrome and never given again.
   c. **Clinical utility.** Nevirapine has modest and transient effects when part of a combination regimen that incompletely suppresses viral replication but can enhance regimens that drive plasma HIV-1 RNA levels to 50 copies/mm^3 or less. Nevirapine induces the hepatic cytochrome P-450 system, thereby enhancing the metabolism of most HIV-1 PIs; thus, the dosage of such drugs should be adjusted when used in combination with nevirapine.

2. **Delavirdine** (Rescriptor) is a potent inhibitor of HIV-1 replication *in vivo,* but like nevirapine, high-level resistance to the drug is encountered within the first several weeks of dosing if it is administered in regimens that do not completely suppress viral replication.
   a. **Dosage.** 400 mg given three times daily, taken at least 1 hour apart from didanosine and from antacids
   b. **Toxicity.** Delavirdine is also associated with a rash in 10% to 15% of patients. Management of patients who develop a rash with delavirdine is identical to that with nevirapine. It is not clear whether the prior occurrence of a rash with nevirapine increases the likelihood of a rash with delavirdine.
   c. **Clinical utility** of delavirdine is similar to that of nevirapine. Although responses are impressive, combination regimens with NRTIs and delavirdine have not been compared with similar regimens with PIs. Unlike nevirapine, delavirdine is a modest inhibitor of protease metabolism; it has been suggested that it be used in combinations to convert dosing of PIs from three times daily to twice daily.

3. **Efavirenz** (Sustiva) is in the late stages of clinical development.

a. **Dosage.** 600 mg once daily at bedtime; avoid fatty meals.
b. **Toxicity.** Unlike the other NNRTIs, efavirenz is seldom associated with a rash. The drug may be associated with confusion or light-headedness, which are related to drug levels and are generally rapidly reversible.
c. **Clinical utility.** Although it appears that high-level resistance to efavirenz requires more than a single mutation, the optimal strategy for use of efavirenz entails complete suppression of plasma HIV-1 RNA. Efavirenz is similar to nevirapine with respect to its induction of PI metabolism.

D. **HIV-1 protease inhibitors** (PIs). HIV-1 encodes an aspartyl protease that cleaves the initially synthesized polyproteins of HIV-1 into functional subcomponents. In the absence of this proteolysis, noninfectious viral particles are synthesized, and the replicative cycle is broken. Acute declines in plasma HIV-1 RNA levels by 1.5 to 2.0 $\log_{1c}$ have been demonstrated after initiation of therapy with the PIs.

A rebound phenomena has been seen with these agents associated with excess dysregulated cytokines, which increase with rapid improvement in CD4$^+$ T cells. This phenomenon has been associated with worsening of wasting, diarrhea, shingles, cytomegalovirus (CMV) retinitis, lipodystrophy, and progressive multifocal leukoencephalopathy (PML). The excess of cytokines may act as a "friendly fire" to the host, causing autoimmune-like disease and exacerbating reactions to infections or injuries. It may be important to use downregulating agents to stabilize this type of dysregulation.

1. **Saquinavir** (Fortovase, Invirase) is one of the most active inhibitors of HIV-1 replication in this class. The major challenge to the development of saquinavir is a severe limitation on bioavailability imposed by extensive first-pass hepatic metabolism and an extremely difficult synthesis process of the drug.
   a. **Dosage:** 600 mg three times daily for Invirase and 1200 mg three times daily for Fortovase; taken within 2 hours of a full meal
   b. **Toxicity.** Mild gastroenteritis, occasional liver inflammation, rash
   c. **Clinical utility.** Saquinavir increases and prolongs the antiviral and immune-enhancing effects of zidovudine and zalcitabine. The addition of saquinavir to regimens with NRTIs appears to have a significant effect on morbidity and mortality in both treated and treatment-naive patient populations. Saquinavir bioavailability is dramatically enhanced by the coadministration of ritonavir. This strategy results in substantial and durable antiretroviral activity, but drawbacks are the unpalatability of ritonavir, hepatotoxicity (especially in patients who have preexisting liver abnormalities), and the cost of two protease inhibitors.

2. **Indinavir** (Crixivan) is much more bioavailable than saquinavir.
   a. **Dosage:** 800 mg three times daily. The bioavailability of indinavir is greatly compromised if taken with food. Administer on an empty stomach (1 hour before and 2 hours after a meal); encourage the intake of at least 3 pints of liquid per day.
   b. **Toxicity**
      1. **Formation of renal stones** containing indinavir is the major dose-limiting toxicity. Assiduous attention to hydration has greatly decreased the incidence of nephrolithiasis. In most situations, the occurrence of a stone does not necessitate discontinuance of indinavir.
      2. **Transient hyperbilirubinemia** develops in many patients. It superficially resembles Gilbert's syndrome, is reversible, and is not dose limiting.
   c. **Clinical utility.** Indinavir is synergistic *in vitrc* with NRTIs. The combination of indinavir, zidovudine, and lamivudine is particularly potent. In a recently completed clinical trial of patients who had previously received only zidovudine, the three drug combination reduced plasma HIV-1 RNA levels to less than detectable in 90% of the participants and produced substantial clinical benefit in patients with advanced disease.

3. **Ritonavir** (Norvir) is a potent HIV-1 PI that is highly bioavailable and has significant antiretroviral activity, but it is difficult to administer because of subjective toxicities.
   a. **Dosage.** Start at 300 mg twice daily and increase in 100 mg increments up to 600 mg twice daily; take with meals.
   b. **Toxicity** includes circumoral paresthesias, nausea, vomiting, and liver toxicity.
   c. **Clinical utility.** Ritonavir was the first PI to demonstrate clinical benefit with decreased mortality and disease progression in patients with advanced HIV-1 infection. The drug's effects on the hepatic metabolism of a variety of other chemotherapeutic agents and its unpalatability has limited its clinical usefulness.

4. **Nelfinavir** (Viracept) may be slightly less potent *in vivc* than ritonavir and indinavir, but its superior tolerability has made it a popular agent.
   a. **Dosage.** 750 mg given three times daily; taken with meals
   b. **Toxicity.** The drug has few adverse effects other than diarrhea, which is usually controlled with over-the-counter medications.
   c. **Clinical utility.** Nelfinavir is additive with reverse transcriptase inhibitors.

5. **Amprenavir** (Agenerase) is a potent HIV-1 PI. This drug is well tolerated, has no significant food interactions, and results in viral load reductions of roughly 2.0 $\log_{10}$.
   a. **Dosage**. 1200 mg given twice daily
   b. **Toxicity** includes perioral dysesthesia and mild gastrointestinal complaints. It may have a lower association with the development of lipodystrophy than other PIs.
   c. **Clinical utility.** It may be used for its unique mutational changes, which differ from other PIs, and it may produce less lipodystrophy.

E. **Intensification therapies**
   1. **Hydroxyurea** (Hydrea) is a ribonucleotide reductase inhibitor that blocks viral replication through depletion of substrate (purine nucleotide triphosphates) in infected cells. Hydroxyurea also competitively improves the phosphorylation of NRTIs to increase their antiviral activity (especially with didanosine), induces quiet lymphocytes (which tend to remain nonreplicative), and downregulates proinflammatory cytokines. A secondary effect of therapy with the combination of hydroxyurea, didanosine, and stavudine is to improve naive memory cell presence and CTL.

   Although hydroxyurea can have mild hematosuppressive effects and thus lower absolute CD4$^+$ T-cell numbers slightly, its overall effect is to diminish viral load, suppress viral replication, help restore immune integrity, and improve CD4$^+$ percentages. Hydroxyurea has good documentation in trial data to make it an important adjunct in new clinical trials. It should have a primary role as a first-line drug in combination with NRTIs, NNRTIs, and other agents. It can also reverse resistance in combination with drugs such as didanosine and therefore can play a role as a salvage agent as part of combination therapy.

   2. **IL-2** given for HIV-1 by continuous intravenous infusion at low dosage for 5 days per month leads to sustained increase of CD4$^+$ T cells. Naive and memory CD4$^+$ T cells, CD28 expression on CD4$^+$ and CD8$^+$ T cells, *in vitrc* proliferative response to mitogens, and recall antigens increased using IL-2 in combination HAART therapy. This method of administration is, however, inconvenient and has limiting toxic effects.
   3. **Acyclic nucleoside phosphonates** include HPMPC (cidofovir), PMEA (adefovir), and PMPA. They are effective *in vitro* and *in vivc* against a wide variety of DNA virus and retrovirus infections. PMPA is active against both hepadnavirus and retrovirus infections. NRTIs such as these do not need to be phosphorylated *in vivc* and thus can compete more actively with HIV-1. Using combinations such as PMPA with didanosine and stavudine with a synergistic agent, such as hydroxyurea, should have HAART potential clinically.
   4. **T20-cell fusion inhibitor.** HIV-1 envelope protein gp41 mediates viral fusion with human host cells. The peptide segment T20/DP178, located in the C terminus of the ectodomain of gp41, interacts with the N-terminal leucine zipper-like domain on gp41 to establish the fusogenic conformation of the virus. Synthetic T20/DP178 peptide (T20) is highly efficacious in inhibiting HIV-1 infection *in vitrc* at low concentrations by disrupting the transformation of fusogenic status of viral gp41. Short-term intravenous administration of T20 appears to be safe and has been shown to provide potent inhibition of HIV replication comparable to approved antiretroviral regimens.
   5. **Integrase inhibitors.** Retroviruses, including HIV-1, integrate a DNA copy of their RNA genome into the cellular DNA of the infected cell. This reaction, essential and unique to replication of retroviruses, is mediated by the viral enzyme, integrase. Retroviral integrase catalyzes the integration of double-stranded viral DNA into the host cell genome. The reaction can be divided in two steps: 3' end processing and DNA strand transfer. Preferential recognition of viral DNA by HIV integrase is achieved only in the presence of metal cofactor and requires a free, wild-type viral DNA end. An HIV integrase inhibitor, L-chicoric acid, has been shown to be at least additive in combination *in vitrc* with existing multidrug regimens (e.g., zidovudine and a PI).

F. **Summary: Strategy For HIV-1 Therapy (or, *Rules of retroviral poker*)**
   1. **Play to strength, treat early.** Do not wait for symptoms to begin therapy if you already have a diagnosis. Do not wait for a little disease to become a big disease.
   2. **Take your best shot.** Early aggressive therapy has the best chance to control HIV-1 disease, maintain or help restore immunity, and limit the development of long-term virus reservoirs.
   3. **Three or more of different kinds always beats three or more of the same kind.** Attacking HIV-1 through different targets such as using two NRTIs (such as didanosine and stavudine) plus one NNRTI (such as efavirenz) plus one PI or "wild-card" immune modulator or facilitator (e.g., hydroxyurea; see later) is better than three or four of any one kind (*the reverse poker rule*).
   4. **Two pairs may beat three of a kind or three different kinds.** Two PIs (such as ritonavir and saquinavir) may be synergistic and allow lower dosage of both and be combined with two NRTIs or two NNRTIs. Adding or pulsing with an immune modulator as a wild card may strengthen the hand further.
   5. **Play two or more cards at a time.** If the patient's virus is resistant to a regimen, change at least two or three members of the cocktail. Changing a single member runs a high risk for rapid resistance to the new member (*rule of passing the worst two to three cards*).
   6. **Reasonable bids beget best results.** Using fewer drugs at less frequent intervals is associated with fewer therapeutic failures.
   7. **Single time points do not count**. CD4$^+$ absolute numbers are less important than percentage of CD4$^+$ T cells and are affected by clinical events other than

progressive disease. Viral loads may bounce around or stay slightly above undetectable levels in the most sensitive new assays, even if the patient is doing well. Use at least two measurements over time to judge success or failure of a regimen.

8. **Gestalt holistic therapy.** Look at the whole patient when judging a therapeutic outcome. A patient who begins treatment with low CD4 counts and high viral load may show clinical stability without reaching the end points defined to be satisfactory for patients who begin therapy with near-normal CD4$^+$ counts and only modestly elevated viral loads. The effectiveness of therapy is relational to the stability or improvement in immunity parameters, laboratory data, and clinical status of the patient.
9. **Salvage therapy.** Certain drugs may be recycled in new combinations over time. Phenotyping is more likely to help in defining salvage therapy than genotyping if evaluated for synergy in therapeutic cocktails rather than as single-drug activities (*rule of evaluating the power of the combination of all cards, not one card at a time*).
10. **Wild cards** for use in salvage therapy include cell-fusion inhibitors, integrase inhibitors, pulsed therapy with interleukins, or hydroxyurea-like agents.
11. **Playing partners.** The complexity of therapy and the lengthy convolutions of illnesses inherent in HIV-1 disease require the total skills of the health care practitioner in maintaining vigilance over not only the body but also the spirit of the patient.
12. **The author's end-game vision for eradication of HIV-1 in the future.** Begin with aggressive combination therapy at the earliest opportunity in the disease. Pulse with drugs such as IL-2 or IL-15 when the patient is virologically stable; cycle these agents to set up and kill virus. These drugs and others may also help restore immune integrity and leech the chronic reservoirs of HIV-1 from the body. Mop up with ribozyme or antisense therapy or newer gene therapy constructs, which improve CTL and other immune parameters. At this point, new vaccines become therapeutic as well as preventative.

IV. Management of opportunistic infections

A. **Parasites**
1. *Pneumocystis carinii* **pneumonia** (PCP). See Chapter 35, section VII.B for diagnosis and treatment of PCP.
2. **Microsporidiosis and cryptosporidiosis** may produce high mortality rates in HIV patients with severe immune deficiency who develop severe diarrhea, electrolyte imbalances, and wasting. *Enterocytozoon bieneusi* (microsporidia), one of the most common causes of chronic diarrhea in HIV disease, often occurs with CMV. Affected patients can present with cholangitis, cholecystitis, or kidney dysfunction. Diagnosis of microsporidia requires either electron microscopy or Warthin-Starry stain of punch biopsies of the middle duodenum obtained at endoscopy. Treatment is usually ineffective.
3. **Toxoplasmosis.** Cerebral toxoplasmosis possibly represents the most common CNS opportunistic infection associated with AIDS. Neither the highly variable clinical presentation nor the neuroradiologic imaging (see section V.C.3) is pathognomonic. In patients with AIDS, toxoplasmic encephalitis is almost always a reactivation of a preexisting latent infection, most often occurring when the total CD4 count falls below 100 cells/µL. Toxoplasmosis causes pneumonia, lymphadenopathy, and chorioretinitis outside of the CNS. Because of its prevalence in the HIV population, many clinicians believe prophylaxis for toxoplasmosis is appropriate. See section E.3 for dosage recommendations for prophylaxis. See Chapter 35, section VII.A for diagnosis and treatment of systemic and CNS disease.
B. **Bacteria**
1. **Mycobacteria.** *Mycobacterium avium* complex (MAC) causes disseminated disease in 15% to 40% of patients with HIV infection in the United States. Disseminated MAC typically occurs in patients with advanced disease and peripheral blood CD4$^+$ T-lymphocyte counts below 100/µL. Acute disseminated disease is often associated with profound weight loss, anemia, diarrhea, abdominal pain, night sweats, rising serum levels of alkaline phosphatase, intraabdominal lymphadenopathy, and hepatosplenomegaly. Compared with MAC, patients infected with *Mycobacterium tuberculosis* present with more lung involvement and less blood and lymph node dissemination. See section E.5 for prophylaxis recommendations for MAC. See Chapter 35, section V.A for diagnosis and treatment of mycobacterial infections.
2. **Pyomyositis** (solitary or multiple pyogenic muscle abscesses) is common in the tropics but rare in temperate climates, where it is associated with recent travel to tropical areas, trauma, diabetes mellitus, neutropenia, and drug use. Nontropical pyomyositis, usually caused by *Staphylococcus aureus,* has been described repeatedly in patients infected with HIV. Pyomyositis is clinically characterized by fever and painful muscle swelling, most commonly affecting the quadriceps, gluteal, paraspinal, psoas, pectoral, and deltoid muscles. Elevation of skeletal muscle enzyme levels is uncommon.

   Early diagnosis of pyomyositis may be difficult because the inflamed muscle is usually deep, and classic signs of inflammation may be absent. Ultrasound and computed tomography (CT) scanning are useful in diagnosis, and needle aspiration may yield pus for microbiologic investigations. Failure to institute appropriate treatment for pyomyositis promptly may result in septicemia with metastatic abscesses.

3. **Bacillary angiomatosis** presents as a folliculitis or pustular skin disease. *Rochalimaea henselae* is a causative agent of bacillary angiomatosis, peliosis hepatis, and cat-scratch disease. Erythromycin or tetracycline are the drugs of choice. Zithromycin and clarithromycin also appear to be active.
4. **Bacterial infections.** Pneumonias and focal abscesses with gram-positive and gram-negative bacteria are markedly increased in HIV patients. Therapy is the same as for immunocompromised patients without AIDS.
C. **Fungi**
1. **Candidiasis** is the most common fungal infection seen in association with HIV infection. The severity of oropharyngeal candidiasis and the frequency of relapses increase with worsening immunodeficiency. Women with mildly reduced CD4 counts tend to have vaginal candidiasis, often as their first HIV-related illness. Oral candidiasis develops with more severe immunodeficiency (CD4 counts below 300/µL), progressing to candidal esophagitis at counts below 100/µL. Although treatment with systemic antifungals is usually successful at first, relapses are so frequent that maintenance therapy is nearly always needed (section E.1). See Chapter 35, section VI.B for diagnosis and treatment of candidiasis.
2. **Cryptococcosis.** *Cryptococcus neoformans* is the most common systemic fungal infection associated with HIV infection. Extrapulmonary infection has been reported in up to 13% of patients with AIDS. Cryptococcal meningitis can be insidious or acute. Up to 35% of patients with cryptococcal meningitis die during induction therapy, and only 20% to 30% survive for longer than 12 months. See Chapter 35, section VI.A for diagnosis and treatment.
D. **Viruses**
1. **CMV** is the most common viral opportunistic infection in patients with AIDS. More than 90% of homosexual men have serologic evidence of CMV exposure, and up to 90% of patients with HIV-1 show signs of CMV infection at autopsy. Retinitis, the most common disease manifestation of CMV, affects about 20% of patients with AIDS. CMV is also estimated to be responsible for about 30% of gastrointestinal disease in AIDS patients, manifesting as colitis, cholecystitis, pancreatitis, and esophagitis. CMV can also present as severe pneumonia and central or peripheral nervous system disease. See Chapter 35, section IV.B for diagnosis and treatment of CMV.
2. **Human papillomavirus** (HPV) is closely associated with dysplasia and carcinoma of the uterine cervix and anus in both HIV-infected patients and normal hosts. The severity of these lesions, however, often parallels increasing immune deficiency. HPV DNA has also been found in cervicovaginal fluids from HIV-1–seropositive female prostitutes with cervical intraepithelial neoplasia. HPV types 16, 18, 31, 33, and 56 and ME180-HPV have been associated with development of neoplasm. Among HIV-infected men, immunosuppression has been correlated with the development of anal squamous intraepithelial lesions, the detection of specific anal HPV types, and the detection of high levels of anal HPV DNA.
3. **Oral hairy leukoplakia** (OHL), a benign lesion caused by Epstein-Barr virus, is characterized by an asymptomatic thready white pattern seen along the tongue and buccal mucosa of HIV patients. OHL is highly predictive of the development of AIDS. Ultrastructural examination or *in situ* hybridization of exfoliative cytologic specimens may confirm the diagnosis of OHL. Anecdotal experience suggests that high-dose acyclovir improves OHL.
4. **Lichen planus** causes mucocutaneous lesions that often appear thrushlike. These lesions may respond to ganciclovir.
5. **Herpesviruses.** Diagnosis and therapy are described in Chapter 35, section IV.D.
E. **Recommendations for antimicrobial prophylaxis**
1. **Candidiasis.** Fluconazole, 50 mg PO every other day to 200 mg/day, depending on the number of episodes, response to therapy, and severity of immunosuppression, is effective.
2. **Recurrent herpes simplex.** Acyclovir, 200 mg to 800 mg PO daily. The lowest dosage that inhibits recurrent outbreaks is used.
3. **Toxoplasmosis.** Trimethoprim-sulfamethoxazole (Bactrim-DS), 1 tablet PO daily or twice daily for 2 days per week. Dapsone plus pyrimethamine also has merit for prophylaxis.
4. **PCP.** Trimethoprim-sulfamethoxazole (Bactrim-DS, 1 tablet every other day) is the drug of first choice. Dapsone (25 mg PO daily) is a reasonable alternative. Pentamidine, either IV or as an aerosol via nebulizer, is expensive and associated with higher failure rates and toxicity than oral prophylaxis. Prophylaxis for PCP is given to patients who have recovered from the illness or who have less than 200 CD4 cells/µL.
5. **MAC.** Rifabutin, 300 mg/day PO, or biaxin, 500 mg PO twice daily, is given. Prophylactic treatment to prevent the onset of MAC is indicated in patients who have less than 200 CD4 cells/µL.

V. Management of specific syndromes in AIDS

A. **HIV wasting syndrome** affects fat more severely in women and muscle initially in men. High serum levels of triglycerides with low levels of cholesterol are a hallmark of the syndrome.

1. **Pathogenesis.** The underlying causes behind weight loss and negative nitrogen balance in HIV are incompletely understood. Synergy between cytokines (such as IL-1, IFN-a, IFN-g, tumor necrosis factor, and transforming growth factor) is probably required for significant wasting, which is also magnified by gastrointestinal disease and malabsorption. Secondary infection appears to trigger the initiation of wasting.
2. **Treatment** involves controlling HIV progression and secondary infection. Megestrol acetate (Megace) and oral marijuana (Marinol) increase appetite, decrease nausea, and can temporize weight loss, if not true wasting. Total parenteral nutrition for more than 6 weeks probably does not alter the clinical course. Therapy with cytokine inhibitors theoretically may block wasting.

B. **Lipodystrophy associated with therapy.** A syndrome of peripheral fat wasting (lipodystrophy), central adiposity, hyperlipidemia, and insulin resistance has been described in patients receiving PIs. Some homology of the catalytic region of the HIV-1 protease enzyme to regions within two proteins that regulate lipid metabolism has led to the hypothesis that the syndrome is caused by inhibition of these enzymes by protease inhibitors.

Some of the abnormalities being described, however, may not be due to PI therapy. Hypertriglyceridemia, loss of body cell mass and fat, and increased abdominal fat content were reported in patients with HIV-1 and AIDS long before combination therapy was introduced. Second, any combination therapy that raises CD4 cell numbers and improves cell function may lead to an amplification of disordered cytokines and chemokines. These proinflammatory changes may work through effects on inhibiting growth hormone, regulating pituitary cortisol, and affecting the insulin resistance.

C. **CNS demyelinating syndromes**
1. **PML** is a rare demyelinating disease of the CNS seen in immunocompromised adults. PML is caused by the JC virus (JCV), which belongs to the papovavirus family. Most cases of PML are due to reactivation of latent JCV infection. PML does not appear to be contagious. An estimated 4% of AIDS patients develop PML; in 25% of these cases, it is the AIDS-defining diagnosis.
   a. Symptoms and signs are diverse and include limb weakness, altered mental status, speech difficulties, and gait disturbance. Paresis, personality changes, dysarthria, dysphasia, tremor, headache, cranial nerve palsies, nystagmus, and visual-field defects can also develop. Clinical evolution is typically rapidly fatal. Patients usually die 3 to 4 months after presenting with their first neurologic symptom. Rare cases of remission and prolonged survival have been reported.
   b. There is no approved treatment for PML; however, observational data using intravenous peptide T suggests good efficacy in stopping PML clinical progression and reversing much of the neurologic damage that is attributed to proinflammatory cytokine and chemokine injury. A pivotal study of this drug for treatment of PML is required.
2. **AIDS dementia complex** (ADC), manifested by encephalitis with neuropsychiatric symptoms, can follow HIV-1 replication within the CNS. Although HIV-1 may have a direct role in demyelination, the pathogenesis of ADC is complex. Furthermore, HIV-1 Tat protein secreted by infected microglial cells can penetrate neighboring oligodendrocytes that are latently infected by JCV and then reactivate JCV and result in PML. CMV coinfection in the same brain cells can increase HIV-1 viral load in the CNS by transactivating HIV-1 LTR-driven gene expression. Cytokines and HIV-1–specific CTLs are also involved in increasing viral load and in disease progression.
3. **Diagnosis of HIV-related CNS disease.** Brain biopsy is the gold standard for diagnosis of PML; two thirds of biopsies lead to treatable diagnoses. Magnetic resonance imaging (MRI) and CT radiographic findings are as follows:
   a. **Toxoplasmosis.** Multiple ring-enhancing lesions with discrete margins, mass effect, and edema are commonly seen. Most patients have bilateral lesions with basal ganglia involvement. Gray and white matter may be involved.
   b. **CNS lymphoma.** Lesions are often single and hyperdense, although multiple lesions have been seen in up to half of cases. Mass effect and edema are frequent. Ring enhancement is variable. A solitary lesion on MRI is most likely to be lymphoma.
   c. **HIV encephalopathy and PML** may be indistinguishable. Atrophy may be apparent on CT or MRI. MRI often shows subcortical white-matter abnormalities with increased T2-signal multifocally. These lesions tend to be large, bilateral, patchy to confluent areas with ill-defined and irregular margins.
D. **Hematologic and oncologic problems in AIDS**
1. **AIDS-associated hematosuppression.** Pancytopenia inevitably occurs during the course of AIDS. Contributing factors to the significant depression of bone marrow function include HIV infection of macrophages, lymphocytes, and stromal cells; drugs commonly used in AIDS patients (zidovudine, ganciclovir, trimethoprim-sulfamethoxazole); intercurrent hematosuppressive infections (CMV, parvovirus, hepatitis virus, mycobacteria); autoimmune destruction of hematopoietic cells; marrow involvement with lymphoma; and anemia of chronic inflammation.
2. **Treatment of anemia and neutropenia**
   a. **Erythropoietin** (EPO). Spontaneous anemia in AIDS is successfully treated with 100 to 200 IU/kg EPO IV or SC three times weekly. Worsening anemia in association with zidovudine therapy can also be abrogated with decreased transfusion requirement using the same dose of EPO if the endogenous EPO level is less than 500 mU/mL, particularly if the MCV is high.
   b. **Hematinics.** Iron and folic acid should be administered to those patients in whom stores of these nutrients may be marginal.
   c. **Granulocyte colony-stimulating factor** (filgastrim), 2 to 5 μg/kg SC daily, can improve the neutrophil count in patients who developed neutropenia spontaneously or received hematosuppressive agents, such as zidovudine.
   d. **Granulocyte-macrophage colony-stimulating factor** can also improve neutropenia associated with AIDS or its treatment but may stimulate HIV replication.
   e. **Hyperimmune gamma globulin** may be effective for red blood cell aplasia associated with parvovirus B19 infection in AIDS patients.
3. **HIV-associated thrombocytopenia.** Thrombocytopenia is the most common hematologic manifestation of early HIV infection. Only 1% to 2% of patients suffer moderate or severe thrombocytopenia (less than 50,000/μL). Patients with hemophilia and HIV-associated thrombocytopenia may develop spontaneous bleeding when the platelet count is less than 50,000/μL. Other patients with HIV rarely experience symptoms until the platelet count is less than 20,000/μL.
   a. **Pathophysiology.** Impaired thrombocytopoiesis is found almost universally in patients with HIV-associated thrombocytopenia, in contrast to patients with idiopathic thrombocytopenic purpura (ITP). Qualitative and quantitative abnormalities of megakaryocyte colony growth have been demonstrated. Anti-HIV antibodies found on the platelet surface appear to cross-react with platelet membrane glycoprotein IIb-IIIa.
   b. **Treatment.** Spontaneous resolution of thrombocytopenia occurs in 50% of patients, particularly in those with platelet counts below 50,000/μL.
      1. Zidovudine in doses as low as 600 mg/day is the treatment of choice. At least in part, the drug stimulates platelet production, independent of its antiviral effect. Responses are seen in half of patients within 2 to 4 weeks, are sustained for 18 to 24 months, and cease when the drug is stopped. Continuous therapy is required.
      2. Prednisone is effective in 50% to 75% of patients, but almost all patients relapse when the dose is tapered.
      3. Splenectomy can be safely performed and should be considered in patients with persistent severe thrombocytopenia. It is helpful in 90% of patients. Sustained satisfactory platelet counts (more than 50,000/μL) are achieved in most patients.
4. **Opportunistic malignancies** (see Chapter 37).

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Chapter 37 AIDS-Related Malignancies

Alexandra M. Levine

I. Introduction. More than 40% of all patients with human immunodeficiency virus (HIV) infection develop malignant disease at some time during the course of infection. Further, as survival rates in HIV disease are increased, greater numbers of patients with neoplastic disease may be diagnosed.

The cancers that occur in acquired immunodeficiency syndrome (AIDS) are similar to the tumors that are known to develop in organ transplant recipients who receive immunosuppressive drugs to prevent graft rejection. The most frequent cancers in this setting are Kaposi's sarcoma, lymphoma, and anogenital carcinomas. Other disorders of immune dysregulation are also associated with an increased risk for lymphoma, as documented in various autoimmune and congenital immune deficiency diseases.

II. AIDS-related lymphoma

A. **Incidence**
  1. Lymphoma accounts for about 3% of all new cases of AIDS. All age groups and all risk groups for acquisition of HIV infection are equally likely to develop lymphoma.
  2. Lymphoma is a late manifestation of HIV disease and is more likely to occur after an earlier AIDS-defining illness. The risk for lymphoma developing after another clinical AIDS illness is about 650-fold greater than expected. Further, about 15% of patients eventually die from AIDS-related lymphoma, even though non-Hodgkin lymphoma (NHL) was the initial AIDS-defining illness in only 3% or 4%.
  3. With the advent of highly active antiretroviral therapy (HAART), the clinical outcome of AIDS has changed substantially in the United States and other resource-rich countries. Although a few studies have shown a slight decrease in the occurrence of AIDS-related lymphoma, most studies have demonstrated no substantive change in the incidence of lymphomatous disease.
B. **Pathology.** Most AIDS-related lymphomas are B-cell tumors of high-grade pathologic type. About 70% of patients are diagnosed with immunoblastic lymphoma or small noncleaved lymphoma; the latter may be Burkitt or non-Burkitt subtypes. In contrast, only 10% to 15% of patients with *de novo* lymphoma are diagnosed with one of these rather unusual forms of lymphoma. Intermediate-grade, diffuse large cell lymphomas have been reported in 30%.

A newly recognized entity, termed *body cavity–based lymphoma* (BCBL), has been identified among HIV-infected patients, who are also infected with human herpesvirus type 8 (HHV-8). BCBL is a B-cell neoplasm with the morphologic appearance of an anaplastic or immunoblastic lymphoma. Patients present with malignant serous effusions, usually in the absence of specific mass lesions. Median survival time is in the range of 2 months, despite therapy.

C. **Clinical features**
  1. About 80% to 90% of patients with newly diagnosed AIDS-related lymphoma present with systemic B symptoms, consisting of fever, drenching night sweats, or weight loss.
  2. About 60% to 90% of patients have far-advanced disease presenting in extranodal sites. This occurrence is in sharp distinction to patients with *de novo* lymphoma, of whom about 40% present with extranodal disease.
     a. The more common sites of initial extranodal disease include the central nervous system (CNS; about 30% prevalence at diagnosis), gastrointestinal (GI) tract (25%), bone marrow (20% to 33%), and liver (10%).
     b. Any anatomic site may be involved, with lymphoma reported in the myocardium, ear lobe, gallbladder, rectum, gingiva, and elsewhere.
D. **Diagnosis and staging evaluation**
  1. **Biopsy.** Immunophenotypic or genotypic studies are often helpful to confirm the monoclonality (and thus the malignant nature) of the process.
  2. **Computed tomography** (CT) **scans.** Staging evaluation should begin with a CT scan of the chest, abdomen, and pelvis. Nearly two thirds of patients with AIDS-related lymphoma have evidence of intra-abdominal lymphomatous disease, which most commonly involves the lymph nodes, GI tract, liver, kidney, and adrenal gland. Isolated hepatic or splenic enlargement is not usually seen in the absence of other intraabdominal findings.
  3. **[67]Ga scanning** is an important staging tool that may be particularly useful in evaluating residual stable masses after the completion of systemic chemotherapy (see Chapter 2, section II.D).
  4. **Bone marrow** aspiration and biopsy should be performed, usually from two sites.
  5. **Lumbar puncture** (LP). Although not required in most patients with *de novo* lymphoma, LP should be performed routinely as part of the staging evaluation of patients with AIDS-related lymphoma. About 20% of HIV-infected patients are found to have leptomeningeal involvement even when they have no CNS symptoms. Because prophylactic intrathecal chemotherapy has become an integral part of initial therapy, it is now common practice to inject the first dose of methotrexate or cytosine arabinoside at the time of this initial staging LP in an attempt to prevent isolated CNS relapse.
E. **Prognostic factors.** No strong evidence has been documented to suggest that patients with intermediate-grade large cell lymphoma fare any differently from those with high-grade disease.
  1. **Decreased survival** in AIDS-related lymphoma is associated with the following factors:
     a. CD4 cells less than 100/dL
     b. Karnofsky performance status less than 70%
     c. Age older than 35 years
     d. Stage III or IV
     e. Elevated lactate dehydrogenase in serum
     f. History of injection drug use
  2. **Lymphoma primary to the CNS** (P-CNS). Patients with P-CNS disease fare significantly worse than patients with AIDS-related systemic lymphoma. The median survival is only 2 to 3 months despite therapy, probably because of the far-advanced degree of HIV disease (see section G.1).
  3. **Leptomeningeal involvement** in patients with AIDS-related systemic lymphoma is *not* a poor prognostic indicator. Long-term survival is possible in these patients provided that specific therapy is given.
F. **Management**
  1. **High-dose regimens.** Several dose-intensive regimens were found to be ineffective and associated with high rates (60% to 80%) of complicating opportunistic infections, often leading to early patient demise. Patients with good prognostic indicators (such as excellent performance status and no history of AIDS before the lymphoma), however, may be able to tolerate the dose-intensive regimens that appear overly toxic in patients with poor prognostic features.
  2. **Low-dose regimens.** The AIDS Clinical Trials Group, sponsored by the National Institutes of Allergy and Infectious Disease, studied a low-dose modification of the m-BACOD regimen in patients with AIDS-related lymphoma, in an attempt to evaluate the hypothesis that "less might be better." Intrathecal cytosine arabinoside was administered weekly four times during the first cycle of therapy, in an attempt to prevent isolated CNS relapse. In addition, prophylactic therapy for *Pneumocystis carini* pneumonia was mandated. After two cycles, a restaging evaluation was performed. With complete remission, the patient received two additional cycles, at which time all chemotherapy was discontinued, and zidovudine (AZT) was begun.
     a. **The low dose m-BACOD regimen** is given at 28-day intervals for four to six cycles, as follows:

        Bleomycin, 4 mg/m^2 IV, day 1
        Doxorubicin, 25 mg/m^2 IV, day 1
        Cyclophosphamide, 300 mg/m^2 IV, day 1
        Vincristine sulfate, 1.4 mg/m^2 IV (not to exceed 2 mg), day 1
        Dexamethasone, 3 mg/m^2 PO, days 1 to 5

Methotrexate (MTX), 200 mg/m^2 IV day 15, with folinic acid rescue, 25 mg PO every 6 hours for 4 days, beginning 6 hours after completion of MTX

Cytosine arabinoside, 50 mg intrathecally, days 1, 8, 21, and 28 of first cycle

Helmet-field radiation therapy (RT), 2400 cGy with marrow involvement; 4000 cGy with known CNS involvement

    b. **Results.** This low-dose m-BACOD regimen was compared with standard-dose m-BACOD (see Appendix A-2), given with hematopoietic growth factor support (granulocyte-macrophage colony-stimulating factor [GM-CSF]). A total of 192 patients were entered onto this phase III study, after stratification for prognostic factors. There was no statistical difference in response rate (complete remission is about 50%), duration of response, or duration of survival between the groups. Significantly more hematologic toxicity occurred with standard-dose m-BACOD, however, despite use of GM-CSF. This study indicated that low-dose chemotherapy might be used effectively in patients with AIDS-related NHL. Median survival time, however, is only in the range of 6 to 8 months, indicating that alternative strategies must be explored.

    c. **Antiretroviral therapy** may be used simultaneously with m-BACOD or may be discontinued until chemotherapy has been completed. If used simultaneously with chemotherapy, AZT should not be incorporated into the antiretroviral regimen because this drug is myelosuppressive on its own. With this exception, however, pharmacokinetic studies have indicated no clinically significant interactions between HAART (including protease inhibitors) and multiagent chemotherapy. Accepted practice now includes the combined use of chemotherapy with HAART.

    d. **Results of CHOP chemotherapy.** Although CHOP chemotherapy (see Appendix A-2) appears equivalent to other, more dose-intensive regimens in patients with *de novo* lymphoma, initial results in patients with AIDS-related lymphoma appear inferior to those reported with the other regimens discussed previously, although direct, prospective comparisons have not been accomplished.

    e. **Use of infusional chemotherapy regimens.** A dose-adjusted EPOCH regimen has been used in a limited number of patients studied at the National Cancer Institute, with excellent preliminary results. Further study of this regimen is warranted to validate initial results. Another infusional regimen, CDE (cyclophosphamide, doxorubicin, and etoposide), has resulted in a complete remission rate of about 50% when studied in a large national trial.

G. **Primary CNS lymphoma** (see also Chapter 21, section VI.B)

  1. **Clinical features.** Patients with P-CNS lymphoma present with far-advanced HIV disease, with a median of CD4 cells of less than 50/μL and history of AIDS before the lymphoma in about 75% of cases. Initial symptoms and signs are variable and include seizures, headache, or focal neurologic dysfunction. Isolated subtle changes in personality or behavior may also be seen.

  2. **Diagnosis.** Radiographic scanning reveals mass lesions in the brain, occurring at any site. These masses are likely to be relatively large (2 to 4 cm) and relatively few in number (one to three). Ring enhancement may be seen. No specific radiographic findings on CT scans are characteristic of P-CNS lymphoma. Positron-emission tomography (PET) scans or thallium single-photon emission computed tomography (SPECT) scans may provide more specific information in terms of the differentiation of P-CNS lymphoma from other space-occupying lesions within the brain of HIV-infected patients. Further, because AIDS-related P-CNS lymphoma is essentially always associated with infection by Epstein-Barr virus (EBV), determination of latent EBV proteins within the cerebrospinal fluid may also be used to diagnose P-CNS lymphoma. In the case of equivocal results, definitive diagnosis requires brain biopsy.

  3. **Management.** RT is associated with complete remission in 20% to 50% of cases, but the median survival time has been only 2 to 3 months, with death often due to opportunistic infection. Although RT may not improve the duration of survival, the quality of life does improve, often dramatically, in about 75% of patients. Combined use of chemotherapy and radiation improves survival in P-CNS lymphoma unrelated to AIDS, but such information is lacking in AIDS-related disease.

III. Hodgkin lymphoma (HL)

A. **Incidence.** HL is not considered an AIDS-defining condition, although the incidence of HL has increased significantly in HIV-infected patients. All groups at risk for HIV infection appear equally at risk for HL.

B. **Biology.** An association of HL with EBV has been suggested for years based on epidemiologic data. About half of patients with HL tissues have been shown to contain clonally integrated EBV within the diagnostic Reed-Sternberg cells. No data indicate that EBV is actively replicating within HL tissues. Thus, the use of acyclovir or other agents would not be expected to be efficacious.

C. **Clinical features.** Patients with underlying HIV infection have different clinical and pathologic manifestations of HL than expected in patients without HIV disease.

  1. **Sites of disease.** Most HIV-infected patients with HL have widespread extranodal disease at diagnosis, with about 80% to 90% presenting with stage III or IV disease. Systemic B symptoms (e.g., fever, drenching night sweats, weight loss) are seen in about 80% to 90% of patients.

  Unusual extranodal sites of disease may be seen, including the anus and rectum and CNS. Bone marrow is commonly involved and may be the only site of disease in patients with B symptoms, either with or without various peripheral cytopenias.

  2. **Pathology.** Mixed cellularity and lymphocyte depletion subtypes are prominent. Nodular sclerosis and lymphocyte predominant subtypes are relatively decreased in incidence in the setting of HIV infection.

D. **Prognostic factors.** The median survival after definitive therapy is about 1 to 2 years, as opposed to uninfected patients with HL. About 80% to 90% of the latter patients may be cured.

E. **Management.** The ABVD regimen (see Appendix A-1) is used most frequently, along with hematopoietic growth factors.

IV. Kaposi's sarcoma (KS)

A. **Incidence and epidemiology.** AIDS-related KS is seen primarily in homosexual or bisexual men, for reasons that are not understood. With the advent of effective antiretroviral therapy (HAART), the incidence of KS has fallen dramatically in the United States and other resource-rich areas. This dramatic change in the incidence of disease, coincident with the marked decrease in HIV viral load and improvement in immune function associated with HAART, serves to emphasize the crucial role of immunity in the development of KS.

B. **Pathogenesis: HHV-8.** A new human herpesvirus has recently been identified as HHV-8. It is associated with all types of KS, including that associated with HIV, with organ transplantation, and with the classic KS seen in elderly men of Mediterranean descent. HHV-8 infection occurs before the development of KS and is associated with a history of greater numbers of sexual partners. The specific mechanisms of HHV-8 transmission have not yet been elucidated. A growing body of evidence suggests that HHV-8 infection is clearly required for development of KS, although the virus itself may not be sufficient for KS outcome. Thus, about 2% to 10% of normal, healthy people in the United States have evidence of antibody to HHV-8, without clinical illness. HHV-8 may infect endothelial cells and B lymphocytes and has also been detected in saliva, nasal secretions, and semen.

C. **Pathogenesis: inflammatory cytokines and angiogenic factors.** HIV infection induces an inflammatory cytokine response, with secretion of interleukin-6 (IL-6), IL-1, tumor necrosis factor-α and others. These cytokines serve as growth factors for HHV-8–infected endothelial cells and may also be operative in changing the morphology of these cells to the typical spindle cell, which characterizes the KS lesion. Further, secretion of angiogenic factors, such as basic fibroblast growth factor, vascular-endothelial growth factor, and others, by HIV-1–infected mononuclear cells serves to induce the prominent profusion of vascular tissue which characterizes the KS lesion. HHV8 itself has genes that encode a viral IL-6 and other proteins that further contribute to the growth and dissemination of the tumor.

D. **Clinical features**

  1. **Natural history of disease.** Some patients experience a slowly progressive disease over many years, whereas others have fulminant rapidly advancing KS that rapidly leads to death.

  2. **Sites of involvement.** The patient with KS usually presents with disease on the skin that may consist of nodular, hyperpigmented lesions or irregular lesions. The lesions are often remarkably symmetric. Lymphedema may be profound, occasionally in the absence of visible skin lesions. Lymphadenopathy, sometimes in the absence of KS lesions on the skin, is often seen. Another common site of involvement is the oral cavity, which is associated with KS lower in the GI tract about 50% of the time. Literally any visceral organ may be involved. KS in the lung is associated with a poor prognosis and mandates immediate chemotherapy.

E. **Diagnosis and staging evaluation.** An initial biopsy with pathologic confirmation should be obtained. Routine staging is not necessary in the patient with KS. Assessment of visible disease on the skin and oral cavity, a baseline chest radiograph, and determination of the number of CD4 cells in blood should be performed. If the patient has symptoms suggestive of GI involvement (e.g., abdominal pain, weight loss, or diarrhea), endoscopy should be performed. With unexplained abnormalities on chest radiograph, bronchoscopy should be performed; the diagnosis of KS is usually made by visualization and not by biopsy, which may be associated with hemorrhage.

F. **Prognostic factors.** Factors associated with poor prognosis include (1) history or presence of opportunistic infection; (2) presence of systemic B symptoms, consisting of fever, drenching night sweats, or weight loss in excess of 10% of the normal body weight; and (3) CD4 cells less than 300/μL. In the absence of all such factors, the median survival is about 3 years. A history of opportunistic infection is the most significant poor prognostic factor, with a median survival time of only 7 months.

G. **Management**

1. **HAART.** The widespread use of HAART has been associated with a marked decrease in the incidence of KS in the United States. Further, multiple case reports have documented significant regression of KS after HAART therapy alone. The initial treatment of patients with KS is an effective antiretroviral regimen. If the KS does not regress despite a reduction in HIV viral load and an increase in CD4 cells, alternative treatment for KS may be considered.

2. **Antiherpetic therapy.** *In vitro,* HHV-8 may be suppressed by ganciclovir, cidofovir, and foscarnet, whereas acyclovir is ineffective. A prospective trial in patients with CMV retinitis randomized patients in maintenance phase to receive either a ganciclovir ocular implant alone or the implant together with systemic ganciclovir. Of great interest, the patients treated with systemic ganciclovir (either intravenous or oral) had a significant reduction in the development of KS over time. This study is an extremely important one, suggesting that effective treatment of HHV-8 may be associated with antitumor efficacy. Additional studies are underway to evaluate this concept more carefully.

3. **Local therapy.** Topical 9-*cis*-retinoic acid (Panretin) is associated with a 30% to 50% response rate and has been licensed for use in cutaneous KS. Individual lesions may be injected with vincristine (0.1 mg) or vinblastine (0.1 mg), or with interferon- a (1 million U). Local lesions may be treated effectively with cryotherapy, laser, or surgical excision. Local radiation may be helpful; however, care must be taken to avoid undue toxicity, as has been reported in HIV-infected patients after receipt of standard doses and dose schedules of radiation.

4. **Immune response modifiers, including anti-angiogenesis compounds, and those which inhibit inflammatory cytokines.** Oral retinoic 9-*cis*-retinoic acid may be useful in the therapy of KS, working by means of its ability to downregulate IL-6, which is a growth factor for KS. Interferon- a (1 to 2 million U/day) is also effective, especially when combined with antiretroviral agents. Of great interest, interferon- a in low doses is known to function as an anti-angiogenic factor, which may explain its efficacy in AIDS-related KS. Numerous other biologic agents, which aim to decrease either inflammatory cytokines or angiogenic factors, are currently under study. The optimal therapy of AIDS-related KS is expected to change considerably over the next several years.

5. **Chemotherapy** is indicated for (a) rapidly progressive disease; (b) severe lymphoedema; (c) pulmonary involvement; and (d) symptomatic visceral disease. Low doses of doxorubicin (10 mg/m^2 IV), bleomycin (10 mg/m^2 IV), and vincristine (2 mg IV), given every 2 weeks, may result in response rates of 25% to 50%. More recently, liposomal preparations of anthracyclines (Doxil and DaunoXome) have shown greater efficacy with lesser degrees of toxicity and have been licensed for use in KS. Taxol (100 mg/m^2 or 135 mg/m^2 given IV every 2 to 3 weeks) is also highly effective and has been licensed for this purpose.

V. Cervical cancer

A. **Incidence.** Cervical cancer is now an AIDS-defining diagnosis. Women constitute the fastest rising group of new AIDS cases in the United States. The primary risk factor for HIV infection in these patients is heterosexual transmission, usually from a partner who was not known to be infected by the woman in question. The precise incidence of cervical carcinoma or *in situ* carcinoma (cervical intraepithelial neoplasia, CIN) is unknown but is expected to increase significantly over the next several years.

B. **Biologic factors.** Cervical cancer is associated with prior infection by human papillomavirus (HPV), usually involving serotypes 16, 18, 31, 33, or 35. Immunosuppression may allow more rapid development of *in situ* or invasive disease in the setting of such HPV infection. Preliminary data indicates that infection by more than one serotype may increase the risk for cervical cancer or CIN.

C. **Clinical features** of cervical cancer in the HIV-infected woman are not different from those in uninfected people (see Chapter 11). Preliminary evidence suggests that HIV-infected women are more likely to have advanced-stage disease, high-grade pathologic type, and relapse after definitive therapy.

D. **Management.** Because of the aggressive nature of cervical carcinoma in HIV-infected women, it becomes extremely important to diagnose such patients early, at the time of *"in situ'* abnormalities on the Papanicolaou's (Pap) smear. It is recommended that HIV-infected patients undergo routine Pap testing every 6 to 12 months with evaluation of HPV status, although this is not yet well established. Colposcopy and biopsy should be performed in the presence of positive HPV status or any questionable Pap smear results. After definitive therapy for CIN II or III, about half of patients relapse within 1 to 2 years. Topical 5-fluorouracil may reduce the short-term recurrence rate of CIN II or III. Invasive cervical cancer is treated in the "usual" manner.

VI. Anal carcinoma.
Although not considered part of the AIDS epidemic, the incidence of HPV-related anal carcinoma is known to be increased in homosexual men. Large cohort studies are being conducted to determine the natural history of anal cancer in HIV-infected patients and its response to therapy.

Suggested Reading

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Appendix A. Combination Chemotherapy Regimens for Lymphomas

Appendix A. Combination Chemotherapy Regimens for Lymphomas

Appendix A-1. Chemotherapy Regimens for Hodgkin lymphoma

Appendix A. Combination Chemotherapy Regimens for Lymphomas

Appendix A-2. Chemotherapy regimens for non-Hodgkin lymphoma (NHL)

Appendix A. Combination Chemotherapy Regimens for Lymphomas

Appendix A-3. Salvage regimens for Hodgkin and non-Hodgkin lymphoma

Appendix B. Toxicity of Chemotherapy

Appendix B. Toxicity of Chemotherapy

Appendix B-1. Major toxicities and dose modifications for chemotherapeutic agents

Appendix B. Toxicity of Chemotherapy

Appendix C. Tumor Identifiers

Dennis A. Casciato[*]

Appendix C. Tumor Identifiers

Appendix C-1. Microscopic clues of tumor origin

Appendix C. Tumor Identifiers

Appendix C-2. Selected immunohistochemical tumor markers

Appendix C. Tumor Identifiers

Appendix C-3. Expected immunophenotypes on biopsies

Appendix C. Tumor Identifiers

Appendix C-4. Discriminatory immunophenotypes for lymphocytic neoplasms

Appendix C. Tumor Identifiers

The antibody **clusters of differentiation (CD)** are designated at international workshops. The designations are derived from the first through the sixth workshops (Paris 1982 through Kobe 1996). "Related functions or proteins" represented here are highly selected and very incomplete. **Useful CDs for hematopoietic malignancies are highlighted in bold type.**

Appendix C-5. Leukocyte differentiation antigens (CDs)

Appendix D. Glossary of Cytogenetic Nomenclature

Symbol	Definition	Example[a]
p	Short arm of a chromosome [arm above the centromere]; a prefix number gives the number of the chromosome, and a suffix number refers to a particular band on the chromosome	22p5 is the 5th band from the centromere on the short arm of chromosome 22
q	Long arm of a chromosome [arm below the centromere]; numbering is the same as for p	22q5 is the 5th band from the centromere on the long arm of chromosome 22
t	Translocation of part of one chromosome to another. The first set of parentheses indicates the chromosomes involved, and the second set indicates the bands affected by the breakpoints on the respective chromosomes	t(3;21)(q26;q22) is the translocation of material between the long arms of chromosomes 3 and 21 with breakpoints at band q26 for chromosome 3 and band q22 for chromosome 21
ins	Insertion of extra material [e.g., portions of a chromosome] within a chromosome	ins(3;3)(q26;q21q26) is the insertion of band 26 to a position between bands 21 and 26 in the long arms of chromosome 3 [for different chromosomes being involved, the conventions for t are followed]
inv	Inversion [or turn in the opposite direction] of a portion of the chromosome	inv(3)(q21q26) is inversion of bands of 21 through 26 on the long arm of chromosome 3
+ or −	Before a chromosome: Addition [+] or loss [−] of a whole chromosome	+8 or −7 is an extra chromosome 8 or a missing chromosome 7 [see del]
+ or −	After an arm: Additional material [+] or loss of material [−] in the designated arm of the specified chromosome	7q⁻ is missing material in the long arm of chromosome 7 [see del]
del	Deletion of all or part of a chromosome	del (7q) or del (7)(q22) is deletion of the long arm or of band 22 in the long arm of chromosome 7, respectively [see "+ or −"]
der	Derivative chromosome: an abnormal chromosome resulting from structural rearrangement, generally of a balanced nature, involving 2 or more chromosomes	der(1;7)(q10;p10)
i	Isochromosome: a symmetric chromosome composed of duplicated long or short arm with associated centromere	[see t, ins, inv]
idic	Isocentric: symmetric abnormal chromosome composed of the duplication of a total arm and its centromere with part of the adjacent other arm	i(17q) is chromosome 17 with duplicated long arms
dic	Dicentric: a chromosome with 2 centromeres	idic(X)(q13)

[a]All examples presented have been observed in myelodysplastic syndromes.

Type of cancer	Male		Female	
	Proportion of cancers (%)	Proportion of cancer deaths (%)	Proportion of cancers (%)	Proportion of cancer deaths (%)
Prostate	29	13	—	—
Breast	—	—	29	16
Endometrium	—	—	6	2
Ovary	—	—	4	5
Lung	15	31	13	25
Colon and rectum	10	10	11	11
Pancreas	2	5	2	5
Urinary bladder	6	3	3	1
Melanoma	4	2	3	1
Lymphomas	5	5	4	5
Leukemias	3	4	2	4
Other sites	26	27	23	25

Adapted from Landis SH, et al. Cancer statistics, *CA* 1999;49:16, with permission.

Marker	Upper limit	Serum half-life	Application in cancer
α-FP	25 μ/L	3–6 d	Testis, hepatoma
β-HCG	<1 ng/mL	18–24 h	Testis, trophoblastic neoplasia
β₂-microglobulin	2 μg/mL	?	Myeloma, lymphoma
Calcitonin	0.1 ng/mL[a]	12 min	Thyroid (medullary carcinoma)
CA 15-3	25 U/mL	<2 weeks	Breast
CA 19-9	37 U/mL	?	Pancreas
CA 125	35 U/L	4–5 d	Ovary
Carcinoembryonic antigen (CEA)	5 ng/mL	Weeks	Colorectal, breasts, lung (small cell)
Prostate-specific antigen (PSA)	2.5–4 ng/mL	2–3 d	Prostate
Thyroglobulin	10 ng/mL	Weeks	Thyroid

[a] Without calcium infusion, 0.10 ng/mL; with calcium infusion, 0.55 ng/mL.
Abbreviations are defined in text.
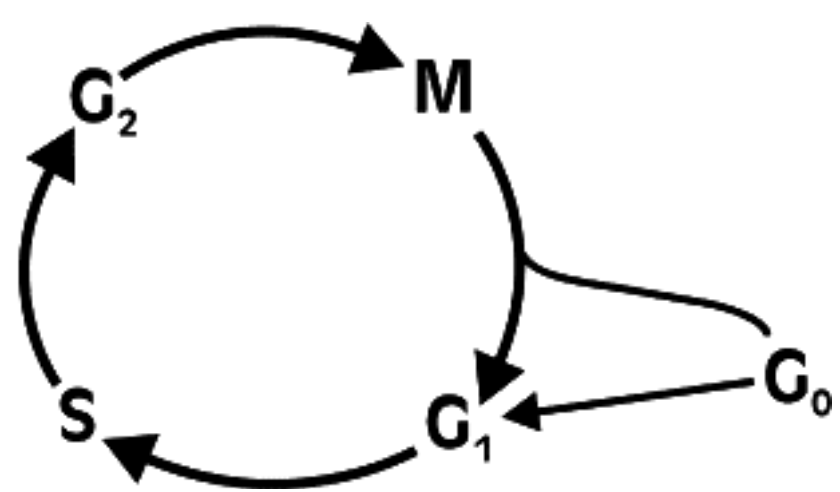
Nuclide	Pharmaceutical	Pharmacology	Dosage	Patient preparation	Use
^{18}F	FDG	Glycolysis	10 mCi	Fasting	Tumor viability
^{67}Ga	Citrate	Transferrin receptor	10 mCi	Laxatives	Lymphoma, inflammation
^{123}I	MIBG	Catecholamine uptake	0.5 mCi	Off α-, β-blockers	Neuroendocrine tumor
^{131}I	Sodium iodide	Thyroid hormone	25 μCi	Off thyroid hormone, iodides	Thyroid dysfunction
^{111}In	Leukocytes	Target inflammation	5 mCi	None	Phlegmon
^{111}In	Pentetreotide	Somatastatin receptors	5 mCi	Off steroids and octreotide; laxatives	Endocrine malignancy
^{111}In	Oncoscint	Anti-TAG-72 MoAb	5 mCi	Laxatives	Colorectal and ovarian cancer
^{111}In	Prostascint	Anti-PSMA MoAb	6 mCi	Laxatives enema	Prostate cancer recurrence
^{99m}Tc	Phosphonates	Bone mineralization	25 mCi	None	Bone disease
^{99m}Tc	Sulfur colloid	Lymphatic clearance	0.2–0.5 mCi	None	Identify sentinel node
^{99m}Tc	Albumen	Lymphatic clearance	1 mCi	None	Lymphatic drainage
^{99m}Tc	Aggregated albumin	Capillary blockade	5 mCi	None	Pulmonary emboli
^{99m}Tc	Erythrocytes	Vascular marker	30 mCi	Off β-blockers	Measure LVEF
^{99m}Tc	Pertechnetate	Thyroid iodine trap	10 mCi	Off thyroxine, iodide	Thyroid nodule
^{99m}Tc	MIBI	Lipophilicity and intracellular binding	20 mCi	Fasting; stop xanthines	Tumor viability, cardiac perfusion
^{99m}Tc	CEAScan	Anti-CEA MoAb	20–30 mCi	Laxatives	Colorectal cancer
^{201}Tl	Chloride	Na$^+$, K$^+$ pump	5 mCi	None	Tumor viability

Key: CEA, carcinoembryonic antigen; FDG, fluorodeoxyglucose; LVEF, left ventricular ejection fraction; MIBG, metaiodobenzylguanidine; MIBI, methoxyisobutyl isonitrile; MoAb, monoclonal antibody; PSMA, prostate-specific membrane antigen.

Proportion of marrow (%)	Site	Approximate proportion in combined sites (%)
13	Head	
4	Cervical vertebrae	15
10	Sternum and ribs	
8	Scapulae, clavicles, and humeri	30
15	Thoracic vertebrae	25
10	Lumbar vertebrae	
15	Sacrum	50
25	Pelvis, femoral head, and neck	40
100		

Lethal number of cells

12

LOG CELL NUMBER →

9 Tumor clinically detectable

50% volume reduction

6

3

0

TIME →

Pyrimidine bases   Purine bases

Cytosine   Guanine ----- 6-TC
Thymine   Adenine ----- 6-MP
Uracil   5-Aza   2-Cda
                                     Dcf

Deoxyuridylate   Other
                        ribonucleotides
               CH₃   CH₃
5-FU → 5-fluoro-   Thymidylate   FH₄   FH₂
      deoxyuridylate   synthetase
               Folinic   Reductase
               acid
                        MTX
Thymidylate

HU -------------------------

Deoxyribonucleotides

Ara C ---- Polymerase
Flud

DNA   RNA

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1–T4	Classification defined under specific site

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm
N2b	Metastasis in a multiple ipsilateral lymph nodes, none >6 cm
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm
N3	Metastasis in a lymph node >6 cm

Distant metastases (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Histopathologic grades

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Stage groupings

0	Tis N0 M0
I	T1 N0 M0
II	T2 N0 M0
III	T1–3 N1 M0, T3 N0 M0
IVA	T4 N0–1 M0, any T N2 M0
IVB	Any T N3 M0
IVC	Any T any N M1

* Includes carcinomas of the lip, oral cavity, oropharynx, hypopharynx, nasopharynx, and larynx (supraglottic, glottic, and subglottic). Cancers of the nasopharynx, nasal cavity, paranasal sinuses, and salivary glands have staging variations that are defined in the text. Adapted from the *AJCC Cancer Staging Manual*, 5th edition. Philadelphia: Lippincott-Raven, 1997.

Primary tumor	Most common site	Relative occurrence (%)	Cervical lymph node metastases at time of presentation (%)
Lip[a]	Lower lip (90%)	15	5
Oral cavity[a]	Tongue (lateral border)	20	40
Oropharynx[a]	Tonsillar region	10	80 for tonsillar fossa and base of tongue 40 for other sites
Hypopharynx[a]	Pyriform sinus	5	80
Larynx[a]	True vocal cord	25	<5 for early glottic 35 for other sites
Nasopharynx[a]	Roof	3	80
Nasal cavity and paranasal sinuses	Maxillary antrum	4	15
Salivary glands	Parotid (80%)	15	25

[a] At least 97% are squamous cell carcinomas.

Characteristic	Benign	Malignant
Growth rate	Slow, steady	Usually rapid
Pain	Rare	Often present
Tenderness	Occasional	Frequent
7th Nerve palsy	Absent	Often present (nearly pathognomonic)
Consistency	Cystic to rubbery	Very hard
Attachment	Mobile	Fixed to muscle or skin
Trismus	Absent	Present when deeply invasive
Lymph nodes	Absent unless infected	Occasionally present

Regimen	Dose (mg/m^2)[a]	Day of administration	Cycle length (d)
Cisplatin	100	1	28
Vinorelbine	25	1, 8, 15	
Carboplatin	AUC = 6	1	21
Paclitaxel	225	1	
Cisplatin	100	1	28
Gemcitabine	1000	1, 8, 15	
Vinorelbine alone	30	1, 8	21
Docetaxel alone	75	1	21

[a] Except for carboplatin, which is administered using area under the curve (AUC) dosing, based on calculated renal function.

Regimen	Dose (mg/m^2)[a]	Day of administration	Cycle length (d)
Cisplatin	100	1	28
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Docetaxel alone	75	1	21

[a] Except for carboplatin, which is administered using area under the curve (AUC) dosing, based on calculated renal function.

Regimens and investigators	Trial phase	Response rate (%)	Median survival (mos)	1-year survival (%)
Carboplatin and paclitaxel				
Langer 1995	I–II	62	12	54
Vafai 1995	I–II	61	11	43
Belani 1998	III	23	8	32
Cisplatin and gemcitabine				
Abratt 1997	II	48	13	61
Crino 1997	II	54	15	60
Sandler 1998	III	32	9	39
Crino 1998	III	38	9	33
Cisplatin and vinorelbine				
Gebbia 1994	II	46	11	—
Le Chevalier 1994	III	30	9	35
Wozniak 1992	III	26	8	36

Regimen	Dose(mg/m^2)	Day of administration	Cycle length (d)
Cisplatin	100	1	21
Etoposide	100	1, 2, 3	
Cyclophosphamide	1000	1	21
Doxorubicin	45	1	
Vincristine	1.5[a]	1	
Cisplatin	60	1	21 (total of 4 cycles)
Etoposide	120	1, 2, 3	
Chest RT	4.5 Gy	Twice daily	For 5 weeks[b]
PCI	2.0 Gy	Daily	For 3 weeks (after completion of other therapy)[b]

RT = radiation therapy

[a] Many would use a maximum dose of 2 mg.

[b] PCI (prophylactic cranial irradiation) is indicated in patients with limited disease who have obtained a good partial response or a complete response after the completion of other therapy. Chest RT and PCI are given Monday through Friday.

Primary site	Proportion of digestive tract cancers		
	Frequency of new cases (%)	Frequency of cancer death (%)	Male-to-female ratio
Esophagus	6	9	3:1
Stomach	10	10	5:3
Small bowel	2	1	1:1
Colon	42	36	5:6
Rectum	15	7	5:4
Liver and biliary tract[a]	10	13	7:5[b]
Pancreas	13	22	1:1
Other digestive	2	1	1:2
TOTAL	100	100	1:1

[a] About 20% are primary liver cancers, 35% bile duct cancers, and 45% gallbladder cancers.
[b] The male-to-female ratio is 2:1 for liver and bile duct cancers and 1:5 for gallbladder cancer.
Note: Gastrointestinal tract malignancies account for about 226,300 new cancers and 131,000 cancer deaths annually.

Disease	Histology	Distribution of polyps	Malignant potential	Associated manifestations	Age for first FOB test	Age for first colonoscopy	Surgery
Discrete polyps and CC	Few AP	Colon	High	None	≥45 yr	≥45 yr	Same as for general population
Hereditary discrete common polyps and CC	AP	Proximal colon	High	Lynch I[a]	30–35 yr	35 yr	Same as for general population
HNPCC	AP → Ac	Proximal colon	High	Lynch II[a]	None (ES)[a]	20 yr	Subtotal colectomy[a]
Familial CC	AP	Proximal colon; may be distal	High	None	30–35 yr	35 yr	Same as for general population
FAP and Turcot's syndrome	Scattered AP → Ac	Colon	High	Central nervous system tumors	None (ES)[a]	Teens	Prophylactic subtotal colectomy[d]
FAP and Oldfield's syndrome	Scattered AP → Ac	Colon	High	Skin tumors	None (ES)[a]	Teens	Prophylactic subtotal colectomy[d]
FAP and Gardner's syndrome	Scattered AP → Ac	Usually colon, also stomach and SB	High	See footnote[c]	None (ES)[a]	Teens	Prophylactic subtotal colectomy[d,e]
Peutz-Jeghers syndrome	Hamartomas	Stomach, SB, colon, ovary	Low	Buccal and cutaneous pigmentation	≥45 yr	≥45 yr	None
Generalized GI juvenile polyposis	JP	Stomach, SB, colon	Low	None	None	≥45 yr	None
Juvenile polyposis coli of infancy	JP	Stomach, SB, colon	None	Protein-losing enteropathy	None	No special indications	None
Cronkhite-Canada syndrome	JP	Stomach, SB, colon	None	Protein-losing enteropathy[c]	None	No special indications	None

AP, adenomatous polyps; Ac, adenocarcinoma; CC, colorectal cancer; ES, endoscopic surveillance; FAP, familial adenomatous polyposis; FOB, fecal occult blood; GI, gastrointestinal; HNPCC, hereditary nonpolyposis colorectal cancer ("cancer family syndrome"); JP, juvenile (retention) polyps; SB, small bowel.

[a] **Lynch syndrome I:** autosomal dominant inheritance with susceptibility to early onset of colorectal cancer proximal to the splenic flexure in the absence of diffuse polyps. **Lynch syndrome II:** contains most of the features of Lynch I with excess incidence of carcinoma of the endometrium, ovary, kidney, ureter, bladder, bile duct, and small bowel and of lymphoma (Lynch II). The surgeon and colorectal cancer genetics. *Arch Surg* 1990;125:699).

[c] Epidermoid cysts, fibromas, desmoids, dental and osseous abnormalities, intraperitoneal and retroperitoneal fibrosis, ampullary carcinoma, and tumors in other glandular structures. Follow with ophthalmoscopy for associated congenital hypertrophy of the retinal pigment epithelium.

[c] And hyperpigmentation, alopecia, and nail dystrophy.

[d] Prophylactic colectomy should be considered if 5 to 10 adenomatous polyps are present or if polyps recur.

[e] Or, total colectomy with pouch reconstruction. Nonsteroidal anti-inflammatory drugs decrease the number and size of polyps (see section V B 3).

Characteristics	HCC	Adenocarcinoma[a]
Clinical features		
Sex predilection	Male	None
Presence of cirrhosis	Common	Exceptional
Preferential spread	Venous	Lymphatics
Pathologic features		
Gross features	Soft and hemorrhagic	Hard and whitish
Main growth pattern	Trabecular	Glandular
Growth at tumor margin	Replacement	Often sinusoidal
Fibrous stroma	Minimal[b]	Often prominent
Microscopic features		
Tumor cell nucleus		
Intranuclear inclusions	Common	Uncommon
Prominent nucleolus	Typical	Often
Tumor cell cytoplasm	Often abundant	Variable
Hyaline globules	Occ present	Rare
Mallory bodies	Occ present	Absent
Bile	Occ present	Absent
Mucin	Absent	Often present
Hepatocyte dysplasia	May be present	Absent
Immunohistochemistry		
α-Fetoprotein	Often present	Occ present (metastases)
β-Antitrypsin	Often present	Absent
Villin	Often present	Absent
HB,Ag	Often present	Absent
Polyclonal CEA (canalicular)	Often present	Absent
Monoclonal CEA (cytoplasmic)	Rarely present	Often present
Erythropoiesis associated	Often present	Absent

Occ, occasionally; CEA, carcinoembryonic antigen.
[a] Adenocarcinoma = cholangiocarcinoma and metastatic adenocarcinoma.
[b] The fibrolamellar and sclerosing variants of HCC are exceptions because they contain prominently fibrous stroma.
Adapted from Sternberg SS, eds. *Diagnostic Surgical Pathology*. 2nd ed. New York: Raven Press, 1994:1543, and other sources.

Type of discharge	Frequency (%)	Approximate chance of cancer (%)
Milky	1	Negligible
Purulent	5	Negligible
Multicolored and sticky	10	Negligible
Serous	35	5
Serosanguineous	30	15
Bloody	25	20
Watery	5	50

Primary tumor (T)[a]

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ or Paget's disease of the nipple with no tumor
T0	No demonstrable tumor in breast
T1	Size: ≤ 2 cm
T1mic	Microinvasion < 0.1 cm
T1a	> 0.1 cm and ≤ 0.5 cm
T1b	> 0.5 cm and ≤ 1.0 cm
T1c	> 1.0 cm and ≤ 2.0 cm
T2	Size: > 2 cm and ≤ 5 cm
T3	Size: > 5 cm
T4	Any size with
T4a	Extension to chest wall
T4b	Skin ulceration, edema, or satellite nodules
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma[c]

Lymph nodes (N)[a]

NX	IAN cannot be assessed (e.g., nodes previously removed or not removed)
N0	IAN without metastases
N1a	IAN with micrometastasis (≤ 0.2 cm)
N1b	IAN with metastasis, any > 0.2 cm
N1bi	1 to 3 nodes positive (any > 0.2 cm, all < 2 cm)
N1bii	4 or more nodes positive (any > 0.2 cm, all < 2 cm)
N1biii	Extension of tumor beyond capsule of a lymph node < 2 cm
N1biv	Any node ≥ 2 cm
N2	IAN with metastasis, fixed to one another or to other structures
N3	Ipsilateral internal mammary lymph node metastases (in the interrupted spaces along the sternal edge)

Distant metastases (M)

M0	Absent
M1	Present

Stage grouping and survival

Stage	TNM classification[d]	5-yr Survival rate (%)[e]
0	Tis N0 M0	92
I	T1 N0 M0	87
IIA	T0 N1 M0	78
	T1 N1 M0, T2 N0 M0	
IIB	T2 N1 M0, T3 N0 M0	68
IIIA	T0 N2 M0	51
	T1 N2 M0, T2 N2 M0	
	T3 N1 M0, T3 N2 M0	
IIIB	T4 Any N M0, Any T N3 M0	42
IV	Any T Any N M1	13

Indicated sizes are greatest dimensions. IAN, ipsilateral axillary nodes (subsummary nodes are coded as IAN).

[a] For multiple or simultaneous ipsilateral carcinomas, use the largest primary carcinoma to classify T. For bilateral breast carcinomas, each is staged as a separate primary in a separate organ.

[c] The prognosis of patients with N1a is similar to that of patients with N0 disease.

[c] Inflammatory carcinoma of the breast is characterized by diffuse, brawny induration of the skin of the breast with an erysipeloid edge, usually with no underlying palpable mass, because of tumor embolization of dermal lymphatics. Skin dimpling and nipple retraction do not affect staging classification.

[e] Observed survival rate (i.e., deaths from any cause) are extracted from data obtained from more than 50,000 patients in the National Cancer Data Base for 1989.

Adapted from the American Joint Committee on Cancer Staging Manual, 5th ed. Philadelphia: Lippincott-Raven, 1997.

LIFE-THREATENING DISEASE
- Lymphangitic lung metastases
- Liver metastases
- Rapidly growing tumor at any site

NO → Estrogen-binding protein receptor

YES → Cytotoxic agent chemotherapy

Estrogen-binding protein receptor:
- Unknown or positive → Tamoxifen → Failure → Aromatase inhibitor → Failure → Cytotoxic agent chemotherapy
- Negative → Cytotoxic agent chemotherapy
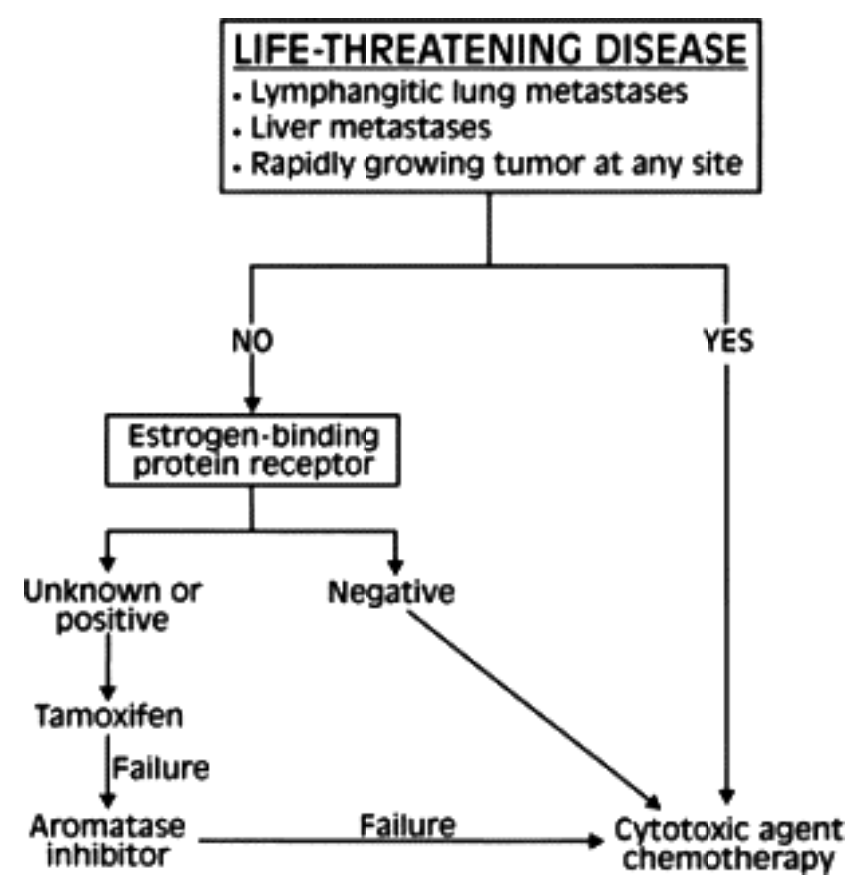
ER	PgR	Response rate (%)
Negative	Negative	5–10
Positive	Negative	35
Negative	Positive	35
Positive	Positive	70
Unknown	Unknown	30

Drug	Regimens[a]			
	Classic CMF	CMF	CA	FAC
Cyclophosphamide (C)	100 PO (days 1 to 14)	600 IV	600 IV (day 1)	400–500 IV (day 1)
Methotrexate (M)	40 IV (days 1 & 8)	40 IV (day 1)		
5-Fluorouracil (F)	600 IV (days 1 & 8)	600 IV (day 1)		400–500 IV (days 1 & 8)
Doxorubicin (A) (Adriamycin)			60 IV (day 1)	40–50 IV (day 1)
Cycle frequency	4 wk	3 wk	3 wk	4 wk

[a] Drug doses in mg/m² body surface area; days on which drugs are given in each cycle.

Age or ER or node status	10-yr Survival rate (%)		Reduction in mortality from any cause[a]	
	Patients treated	Controls	Improvement in survival (%)	Decrease in death rate (%)
Tamoxifen for 5 yr[b]				
ER+ or ? / node+	61.4	50.5	10.9[a1]	26[c]
ER+ or ? / node–	78.9	73.3	5.6[a1]	
Chemotherapy[d]				
< 50 yr; node+	53	42	11.0[a1]	27[e]
< 50 yr; node–	78	71	7.1[a2]	
50–69 yr; node+	49	46	3.2[a3]	11[e]
50–69 yr; node–	70	67	2.4[a3]	
≥ 70 yr			Insufficient data	

ER, estrogen receptor activity; +, positive; –, negative; ?, unknown.

[a] Highly statistically significant: [a1] $2p < 0.00001$; [a2] $2p = 0.02$; [a3] $2p \leq 0.005$.

[b] Data from Early Breast Cancer Trialists Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998;351:1451–1467 (analysis of about 37,000 women in 55 randomized trials that were begun before 1990).

[c] Proportional decreases in mortality: ER–, 6%; ER+, 28%; ER + strongly, 36%.

[d] Data from Early Breast Cancer Trialists Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998;352:930–942 (analysis of about 30,000 women in 62 randomized trials that were begun before 1990).

[e] Proportional decreases in mortality for age: < 50 yr, 27%; 50–59 yr, 16%; 60–69 yr, 8%.

Primary site	Proportion of female genital tract malignancies (%)	
	New cases	Deaths from cancer
Cervix (invasive carcinoma)	16	18
Endometrium	46	23
Ovary	31	53
Other sites	7	6
TOTAL	100	100

Note: Cancers of the female genital tract accounted for about 81,000 new cancer cases and 27,200 cancer deaths in 1999.

Stage	Extent	5-yr Survival rate (%)
0	Carcinoma *in situ* (no stromal invasion)	100
I	Strictly confined to cervix (disregard extension to the corpus)	80
Ia	Preclinical carcinoma (diagnosed only by microscopy)	
Ia1	Lesions with ≤3 mm depth of stromal invasion	
Ia2	Lesions detected microscopically that can be measured (>3–5 mm in depth of invasion from the originating epithelial base *and* ≤7 mm in horizontal spread)	
Ib	Lesions with greater dimensions than Ia2, whether seen clinically or not	
Ib1	Lesion ≤4 cm in greatest dimension	
Ib2	Lesion >4 cm in greatest dimension	
II	Tumor extends beyond the cervix but not onto the pelvic side wall	60
IIa	Lesion involves the proximal vagina (upper two thirds)	
IIb	Obvious parametrial involvement	
III	Tumor extends to the pelvic side wall or to the lower one third of vagina, or causes hydronephrosis or a nonfunctioning kidney	30
IV	Tumor extends beyond true pelvis, or biopsy-proved involvement of bladder or rectal mucosa	5
IVa	Spread to adjacent organs	
IVb	Distant metastases	

**Squamous intraepithelial lesion on Pap smear:
Colposcopic examination**

Lesion entirely visible (90%)

Biopsy with ECC

CIN or CIS

ECC Result

Invasive Cancer

Negative

Positive → Conization*

Radical hysterectomy
or
Radiotherapy

Fertility
not wanted

Fertility
wanted

Conization or
Hysterectomy

Cryotherapy, or
Laser therapy, or
Conization

Lesion not entirely visible (10%)

Invasive Cancer Suspected

No

Yes

Biopsy

Invasive Cancer present

No

Yes

Radical hysterectomy
or
Radiotherapy

Stage	Typical treatment options
Ia1 with ≤3 mm invasion but without lymph–vascular space invasion	Therapeutic cone or type I hysterectomy
Ia1 with 1–3 mm invasion and with lymph–vascular space invasion	Type I or II hysterectomy with (?) pelvic lymph node dissection
Ia2 with >3–5 mm invasion	Type II hysterectomy and bilateral pelvic lymphadenectomy or radiation therapy for inoperable patients
Ib and IIa	Type III hysterectomy with bilateral pelvic lymphadenectomy with paraaortic lymph node evaluation or radiation therapy for inoperable patients

Stage	Extent	Percentage of cases	5-yr Survival rate (%)
I	Cancer confined to the corpus	75	85
Ia	Tumor limited to endometrium		
Ib	Invasion to less than one half the myometrium		
Ic	Invasion to more than one half the myometrium		
	G1*: Well differentiated (≤5% of a nonsquamous or nonmorular solid growth pattern)		95
	G2*: Moderately differentiated (6%–50%)		80
	G3*: Predominantly solid or undifferentiated		70
II	Cancer involves corpus and cervix but does not extend outside the uterus	11	60
IIa	Endocervical glandular involvement only		
IIb	Cervical stromal invasion		
III	Cancer extends outside the uterus but not outside the true pelvis	11	30
IIIa	Tumor invades serosa and/or adnexa or positive peritoneal cytology		
IIIb	Vaginal metastases		
IIIc	Positive pelvic and/or paraaortic nodes		
IV	Cancer extends outside true pelvis or invades bladder or rectal mucosa	3	10
IVa	Tumor invasion of bladder and/or bowel mucosa		
IVb	Distant metastases including intra-abdominal and/or inguinal lymph nodes		

* Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component. In serous adenocarcinomas, clear cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence. Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or 2 tumor by one.

A. Epithelial tumors (approximate frequency)
    Serous cystadenocarcinoma (75%–80%)
    Mucinous cystadenocarcinoma (10%)
    Endometrioid carcinoma (10%)
    Clear cell (mesonephroma) (<1%)
    Undifferentiated carcinoma (<1%)
    Brenner's tumor (<1%)
    Mixed epithelial tumor
    Unclassified

B. Germ cell tumors
    Dysgerminoma
    Endodermal sinus tumor
    Embryonal carcinoma
    Polyembryoma
    Choriocarcinoma
    Teratoma
    Mixed

C. Sex cord stromal tumors
    Sertoli-Leydig cell tumor
    Granulosa–stromal cell tumor
    Gynandroblastoma
    Androblastoma
    Unclassified

D. Other tumors
    Lipid cell tumors
    Gonadoblastoma
    Nonspecific soft tissue tumors
    Unclassified

Stage	Extent (proportion of cases)	5-yr Survival rate (%)
I	Cancer limited to ovaries (15%)	80
Ia	Limited to one ovary, no ascites	
Ib	Both ovaries involved, no ascites	
Ic	Ia or Ib with ascites or positive peritoneal washings	
II	Cancer of one or both ovaries with extension limited to pelvic tissue (15%)	60
IIa	Extension to uterus or tubes	
IIb	Extension to other pelvic tissues	
IIc	IIa or IIb with ascites or positive peritoneal washings	
III	Cancer involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Tumor is limited to the true pelvis but with histologically proved extension to small bowel or omentum (65%).	30
IIIa	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces	60
IIIb	Same as IIIa, but abdominal peritoneal implants do not exceed 2 cm in diameter.	30
IIIc	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal lymph nodes	5–10
IV	Distant metastases present (including cytology-positive pleural effusions, metastasis to liver parenchyma or peripheral superficial lymph nodes [5%].)	5

NORMAL EMBRYONIC DEVELOPMENT	MALIGNANT COUNTERPART	TUMOR MARKERS
Spermatocyte	→ Seminoma	None
Early cleavage embryo		
—Inner cell mass	→ Embryonal cell carcinoma	α-FP
—Blastocoel		
—Amnion		
—Embryo	→ Teratoma	β-HCG + α-FP
—Yolk sac	→ Yolk sac tumor of childhood	α-FP
—Chorionic villus	→ Choriocarcinoma	β-HCG
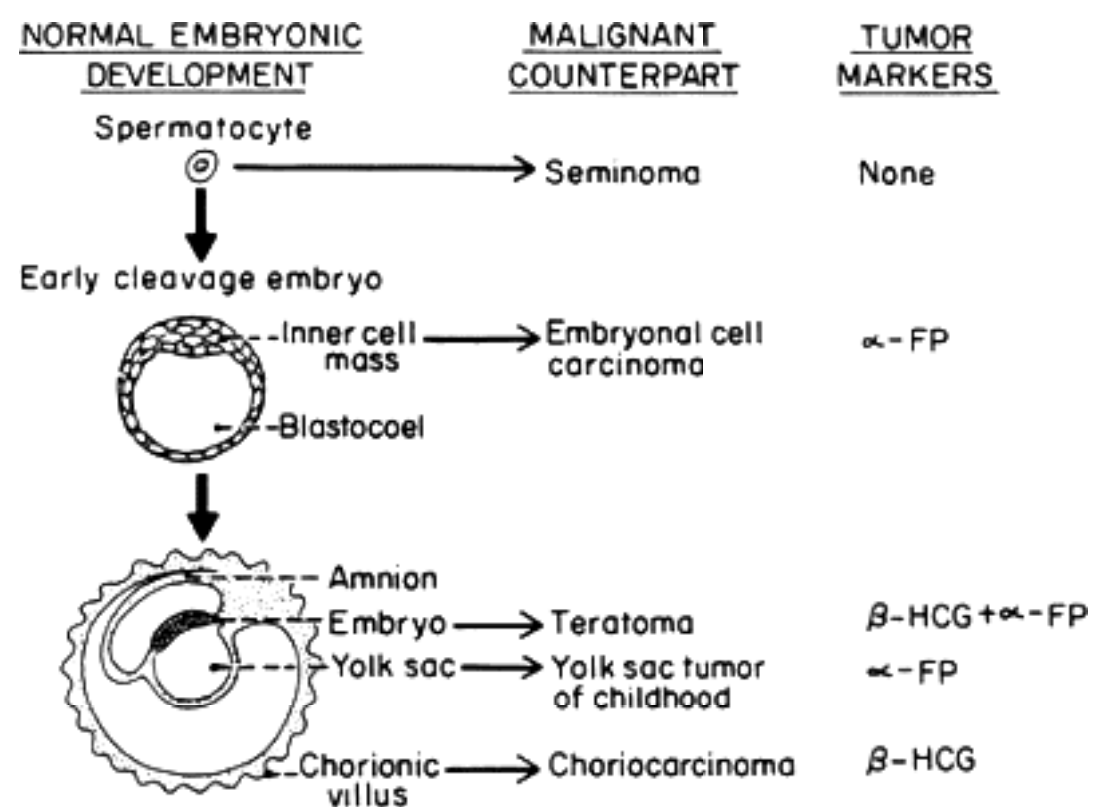
Neoplasm	Proportion of cases (%)	
	β-HCG[a]	α-Fetoprotein[b]
Seminoma	10	<1
Embryonal carcinomas with or without teratomas	65	>70
Choriocarcinoma	100	<1

β-HCG, β-human chorionic gonadotropin.
[a] Normal levels of β-HCG = 0 ng/mL.
[b] Normal levels of α-fetoprotein = <40 μg/mL.

Primary site		Incidence, 1996[a]	Mortality, 1996[a]	Organ-confined disease, 1989–1995
Kidney and renal pelvis cancer	All	9.4	3.5	
	Men	12.9	5.1	48%
	Women	6.5	2.3	
Urinary bladder cancer	All	16.2	3.2	
	Men	27.7	5.5	73%
	Women	7.4	1.7	
Prostate cancer		135.7	24.1	79%

[a] Cases per 100,000 population.
Data from the National Cancer Institute website for clinical trials (http://cancernet.nci.nih.gov/prot/dismenue.html).

| Tumor type	Age	Common location	Clinical features	Survival	RT	Chemotherapy
Astrocytoma	Adult > child	Supratentorial	Slow growing, may be present for years	5 yr MS	Yes	At recurrence
Anaplastic astrocytoma	Adult	Supratentorial	Rapidly growing	2.5 yr MS	Yes	Yes
Glioblastoma multiforme	Adult, elderly	Supratentorial	Rapidly growing, highly malignant	1 yr MS	Yes	At recurrence
Oligodendroglioma	Any	Supratentorial, often frontal	Seizures more common	5 yr MS	Yes	Yes
Brain-stem glioma	Child > adult	Brain stem, especially pons	Marked morbidity from cranial nerve deficits	1 yr MS	Yes	Seldom
Pilocytic astrocytoma	Child > adult	Cerebellum and hypothalamus	Cure with total resection	80% 10 yr	Yes	Seldom
Ependymoma	Child, adult	Fourth ventricle, cauda equina	Cure with total resection, can disseminate in CSF	70% 5 yr	Yes	Seldom
Medulloblastoma	Child > adult	Cerebellum	Likely to disseminate in CSF	55% 5 yr	Yes	Yes
Meningioma	Adult	Convexity, clival, thoracic	More common in women, cure with total resection	Long term	Yes	Rare
Primary CNS lymphoma	Adult	Multifocal, peri-ventricular	CSF/ocular dissemination common	2 yr MS	Yes	Yes
Germinoma	Second and third decades	Pineal and suprasellar	Highly sensitive to chemotherapy and RT	80% 5 yr	Yes	Yes
Nongerminoma germ cell tumor	Second and third decades	Pineal	Mixed histologies, often marker positive	20% 5 yr	Yes	Yes

MS, median survival; CSF, cerebrospinal fluid; CNS, central nervous system; RT, radiation therapy.

TRYPTOPHAN —— *Normal pathway* ——→ Nicotinic Acid

Hydroxylase

5-HYDROXYTRYPTOPHAN

Decarboxylase

5-HYDROXYTRYPTAMINE (Serotonin)

Monamine oxidase *
+ Aldehyde dehydrogenase

Peripheral conversion
in patients with gastric
carcinoids

5-HIAA
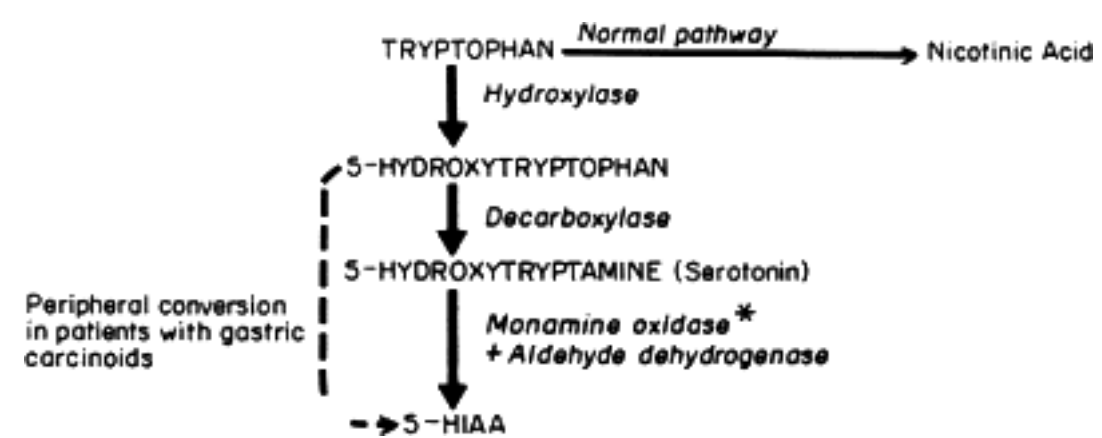
Etiology	Pituitary Cushing's syndrome	Ectopic ACTH secretion	Adrenal carcinoma	Adrenal adenoma
Serum potassium	N or ↓	↓ ↓	N or ↓	N or ↓
Urine 17-ketosteroids	↑	↑	↑ or ↑ ↑	↑ or ↑ ↑
Plasma ACTH	N or ↑	↑ ↑	↓	↓
Adrenal enlargement[a]	Bilateral	Bilateral	Unilateral	Unilateral
Suppression of plasma cortisol with dexamethasone	Yes	No	No	No

ACTH, adrenocorticotropic hormone; ↓, decreased; ↓ ↓, markedly decreased; ↑, increased; ↑ ↑, markedly increased; N, normal.
[a] Adrenal gland enlargement is determined by CT scan.

I	II	III	IV	V	]–Clark's level
					–Epidermis
					–Basal lamina
					–Papillary dermis
					–Reticular dermis
					–Subcutaneous fat
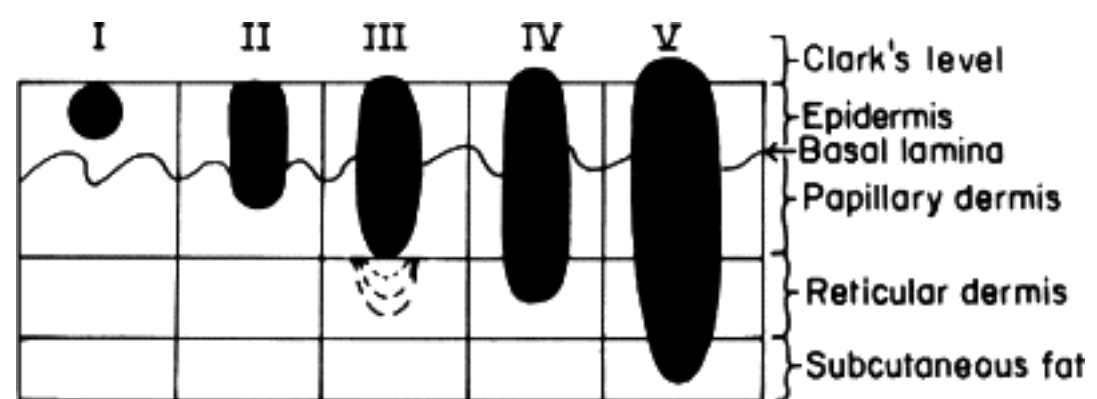
Stage grouping[a]	G-TNM stage				2-yr Survival rate (%)	5-yr Survival rate (%)
I	G1	T1–2	N0	M0	90	80
II	G2	T1–2	N0	M0	80	70
III	G3	T1–2	N0	M0	65	45
IV	G1–3	T1–2	N1	M0; or	25	10
	G1–3	T1–2	N0–1	M1		

[a] Stage groups I, II, and III can be further separated into substage A (for T1 lesions) and substage B (for T2 lesions).

Regimen (cycle: 21–28 days)	Drug	Daily dose (mg/m²)	Days given in cycle (route)
MAID	Mesna	1500–2500	1, 2, and 3 (CIV)
	Doxorubicin	15–20	1, 2, and 3 (CIV)
	Ifosfamide	1500–2500	1, 2, and 3 (CIV)
	Dacarbazine	250	1, 2, 3, and 4 (CIV)
CyVADic	Cyclophosphamide	500	1 (IV)
	Vincristine	1.4ª	1 and 5 (IV)
	Doxorubicin	50	1 (IV)
	Dacarbazine	250	1 through 5 (IV)
Ifosfamide	Ifosfamide	Age ≥ 50 yr: 2000	For 7 days (CIV)
		Age < 50 yr: 2250	For 8 days (CIV)
	Mesna	Age ≥ 50 yr: 2000	For 7 days (CIV)
		Age < 50 yr: 2250	For 8 days (CIV)
Doxorubicin plus cisplatin	Cisplatin	90–120	1 (IV)
	Doxorubicin	75–100	Over 48–96 hr (CIV)

CIV, continuous intravenous infusion; IV, intravenously.
ª Maximum, 2 mg.

Lymph nodes	Histopathology: relative frequencies (%)			
	Squamous cell carcinoma	Undifferentiated carcinoma	Adenocarcinoma	Other [a]
Upper to middle cervical	60	25	10	5
Lower cervical	45	40	5	10
Supraclavicular	20	45	35	

[a] Malignant melanoma accounts for most cases with other histologies.

Presentation	Probable site of origin
Lymph nodes	
Upper and middle cervical	Head and neck tissues
Lower cervical and supraclavicular	
Right side	Lung, breast
Left side	GI, lung (upper lobe), breast
Axillary	Breast, upper extremity, stomach (very rarely)
Inguinal	Lower extremity, vulva, anus/rectum, bladder, prostate
Skin	Lung, breast, kidney, ovary, melanoma
Lower extremity	Kidney
Abdomen and upper extremity	Colon, bladder
Umbilicus	Stomach, pancreas, colon
Brain	Lung, breast, melanoma
Lung	Lung, breast, GI, GU
Pleura	Lung, breast, stomach, pancreas, liver
Pericardium	Lung, breast, melanoma
Liver	Pancreas, stomach, colon, lung, breast
Ascites	Ovary, pancreas, stomach, colon
Bone marrow	Breast, lung (small cell), prostate, thyroid
Bone	
Osteolytic lesions	Myeloma, breast, lung (non-small cell), thyroid
Osteoblastic lesions	Prostate, sarcoma, carcinoid, lung (small cell)
Mixed lesions	Breast
Spinal cord compression	Lung, breast, prostate, kidney, GI, sarcoma, myeloma
High thoracic	Breast, lung
Lumbar	Prostate
Migratory thrombophlebitis	Pancreas, lung, GI

GI, gastrointestinal tract; GU, genitourinary tract.

| | | Metastatic site involved (% of cases) | |
Type of carcinoma	Metastatic site	With primary site known	With MUO
Lung	Bone	30–50	5
Pancreas	Bone	5–10	30
Prostate	Liver or lung	15	>50

MUO, metastases of unknown origin.

Involved field (local)

Total Nodal

Extended Field

Mantle

Paraaortic/
splenic

Inverted-Y

Pelvic
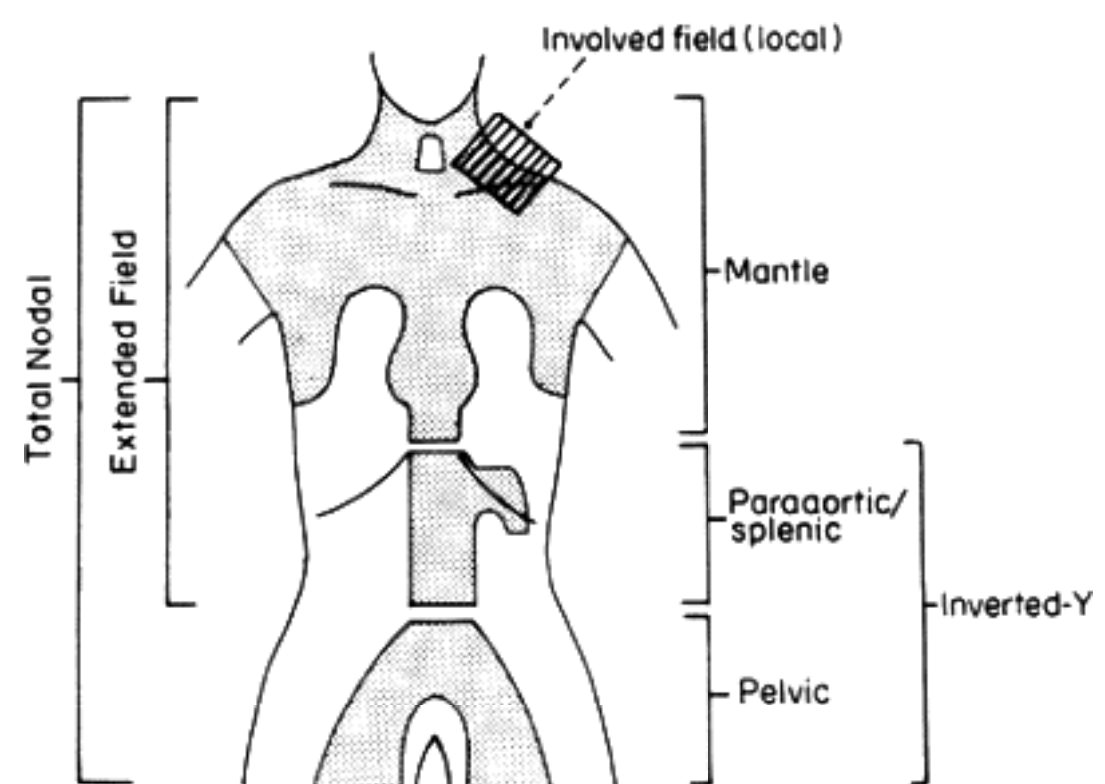
| Characteristic | In Hodgkin lymphoma | In non-Hodgkin lymphomas | |
		Low-grade	Others
Site of origin	Nodal	Extranodal (~10%)	Extranodal (~35%)
Nodal distribution	Centripetal (axial)	Centrifugal	Centrifugal
Nodal spread	Contiguous	Noncontiguous	Noncontiguous
CNS involvement	Rare (<1%)	Rare (<1%)	Uncommon (<10%)
Hepatic involvement	Uncommon	Common (>50%)	Uncommon
Bone marrow involvement	Uncommon (<10%)	Common (>50%)	Uncommon (<20%)
Marrow involvement adversely affects prognosis	Yes	No	Yes
Curable by chemotherapy	Yes	No	Yes

| Histologic subtype	Frequency (%)	Pathology	Age (yr)	Characteristics	Common stage
Lymphocyte predominant	5	L & H cells (large polypoid cells). Difficult pathologic diagnosis. Nodular form is a B-NHL (see section II.A.4).	20–40	Males; often localized disease. Late relapse; transformation to high-grade B-NHL.	I–IIA
Nodular sclerosis	65–80	"Lacunar cells." Birefringent bands of collagen.	15–40	Females; mediastinal, supraclavicular lymphadenopathy	I–IIIA or B
Mixed cellularity	20–35	R-S cells more frequent; necrosis, partial nodal involvement. Heterogeneous cellularity.	30–50	Frequently retroperitoneal; often symptomatic	II–IVA or B
Lymphocyte depletion	<5	Very rare. Diffuse fibrosis	40–80	Febrile, wasting syndrome. Liver, bone marrow involvement.	III–IVB

B-NHL, B-cell non-Hodgkin lymphoma.

Presentation	Recommended treatment
Early stages: IA–IIA	
Very early disease	RT alone
High solitary cervical node, or	
Female with nonbulky NS	
mediastinal nodes, or	
LP cervical or epitrochlear nodes	
with absence of adverse factors[a]	
Adverse factors	
Absence of adverse factors[a]	Combined modality with 2 to 4 cycles of first-line regimen (ABVD), or less intense regimen and IF RT
Presence of adverse factors[a] indicating intermediate risk	Combined modality with 3 to 4 cycles of first-line regimen (e.g., ABVD) and IF RT
Advanced stages	Full course chemotherapy plus RT to bulky site
Bulky disease of any stage	
Clinical stage III–IV	
Presence of B symptoms	

[a] "Adverse factors" include bulky disease, anemia, elevation of erythrocyte sedimentation rate, and inflammatory signs.
IF, involved field; RT, radiation therapy; HL, Hodgkin lymphoma; LP = Lymphocyte predominant; NS = Nodular sclerosing

Grade	Malignant lymphoma type	Frequency (%)	Median age (yr)	Stage III or IV (%)	Bone marrow involvement (%)	Survival rate Median (yr)	Survival rate 5-yr (%)
Low-grade	A. Small lymphocytic (CLL-type) Plasmacytoid	3.6	60	89	71	6.0	59
	B. Follicular, small cleaved cell	22.5	54	82	51	7.2	70
	C. Follicular, mixed (small cleaved and large cell)	7.7	56	71	30	5.1	50
Intermediate-grade	D. Follicular, large cell	3.8	55	73	34	3.0	45
	E. Diffuse, small cleaved cell	6.9	58	72	32	3.4	33
	F. Diffuse, mixed cell (small and large cell)	6.7	58	55	14	2.7	38
	G. Diffuse, large cell	19.7	57	64	10	1.5	35
High-grade	H. Immunoblastic (large cell)	7.9	51	49	12	1.3	32
	I. Lymphoblastic	4.2	17	73	50	2.0	26
	J. Small, non-cleaved Burkett Non-Burkett	5.0	30	66	14	0.7	23
	TOTAL = 88.0%						

The Working Formulation was based on a study of 1,014 patients. It does not include cutaneous T-cell lymphomas, adult T-cell leukemia lymphoma, diffuse—intermediately differentiated lymphocytic lymphoma, and malignant histiocytoma, which constitute 12% of cases.

From Rosenberg SA, Berard CW, Braun HW Jr, et al. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. Cancer 1982;49:2112.
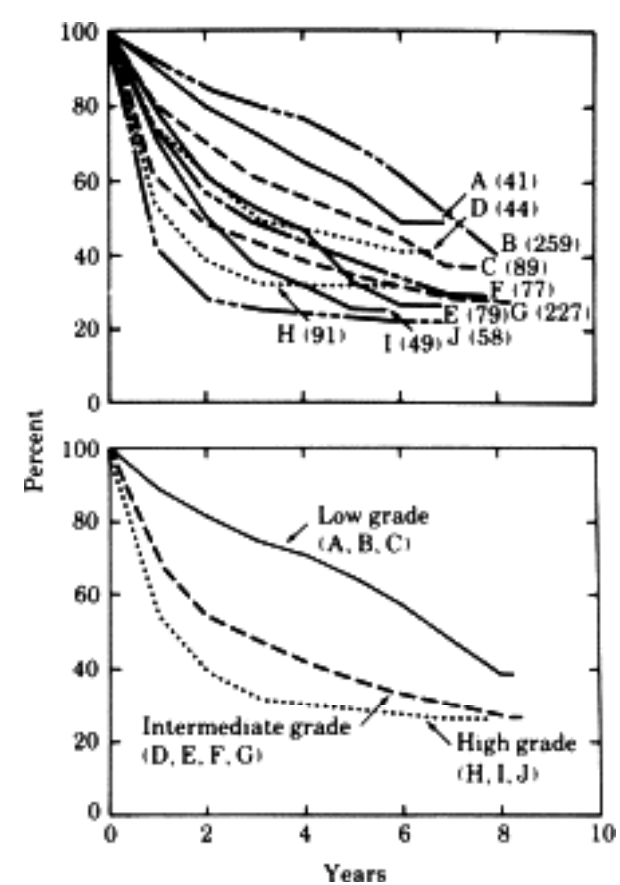
Lymphoma type	Translocation	Genes at breakpoint
B-cell lymphoma		
Small lymphocytic	t(14;19)(q32;q13)	Heavy chain; *BCL-3*
Plasmacytoid	t(9;14)(p13;q32)	Heavy chain; —
Mantle cell	t(11;14)(q13;q32)	*BCL-1*; heavy chain
Follicular	t(14;18)(q32;q21)	Heavy chain; *BCL-2*
Small noncleaved	t(8;14)(q24;q32)	*MYC*; heavy chain
(including Burkitt)	t(2;8)(p12;q24)	kappa; *MYC*
	t(8;22)(q24;q11)	*MYC*; lambda
Large cell	t(3;14)(q27;q32)	*BCL-6*
	t(3;22)(q27;q11)	
	t(2;3)(p12;q27)	
T-cell lymphoma		
Lymphoblastic	Variable involvement of T-cell receptor genes	—
Anaplastic large cell (Ki-1)	t(2;5)(p23;q35)	—

Key: CD5 = Leu-1 or T-101; CD10 = common acute lymphocytic leukemia antigen (CALLA); SIg = surface immunoglobulin; CIg = cytoplasmic immunoglobulin; TdT = terminal deoxynucleotidyl transferase.
* See Appendix C5 for leukocyte differentiation antigens and Appendix D for glossary of cytogenetic nomenclature.

	Endemic (Africa)	Sporadic
Association with Epstein-Barr virus	Yes	Rarely
Chromosomal translocation	t(8;14), Common	t(8;14), Common
Sites of involvement	Jaw, orbit	Abdomen, gastrointestinal tract, marrow
Lymph node involvement	Rarely	Not infrequently
Therapy	50% Prolonged survival rate with cyclophosphamide	Requires multiple agents
Relapse	Survival possible	Poor prognosis

Ig (heavy chain)	MW (×1000)	$T_{1/2}$ (days)	Portion of Igs (%)	IV (%)
IgG[a] (γ)	150	20	75	52
IgA (α)	160	6	15	55
IgM (μ)	900	5	10	75
IgD (δ)	180	3	0.2	75
IgE (ε)	190	3	0.005	40

Ig, immunoglobulin; IV, proportion of Ig distributed intravascularly; MW, molecular weight; $T_{1/2}$, half-life.

[a] IgG comprises four subclasses. About 70% of IgG is IgG₁, 17% is IgG₂, 8% is IgG₃, and 5% is IgG₄. The data shown apply to all subtypes except IgG₃. IgG₃ differs from the other subclasses in that 65% is distributed intravascularly, its serum half-life is 7 days and is not affected by high serum concentrations, it most avidly binds complement (other subclasses do so weakly, if at all), and it is most likely to produce hyperviscosity.

SERUM   URINE

Albumin
Origin
  γ ↓ β ━━
Normal   Polyclonal   Normal (concentrated)
              Hypergammaglobulinemia

IgG Myeloma   Benign IgG Gammopathy   Myeloma

IgA Myeloma   Pseudoparaproteinemia   Nephrotic syndrome
                                         (unconcentrated)

Macroglobulinemia   IgD Myeloma   Benign IgG Gammopathy
                                         (concentrated)
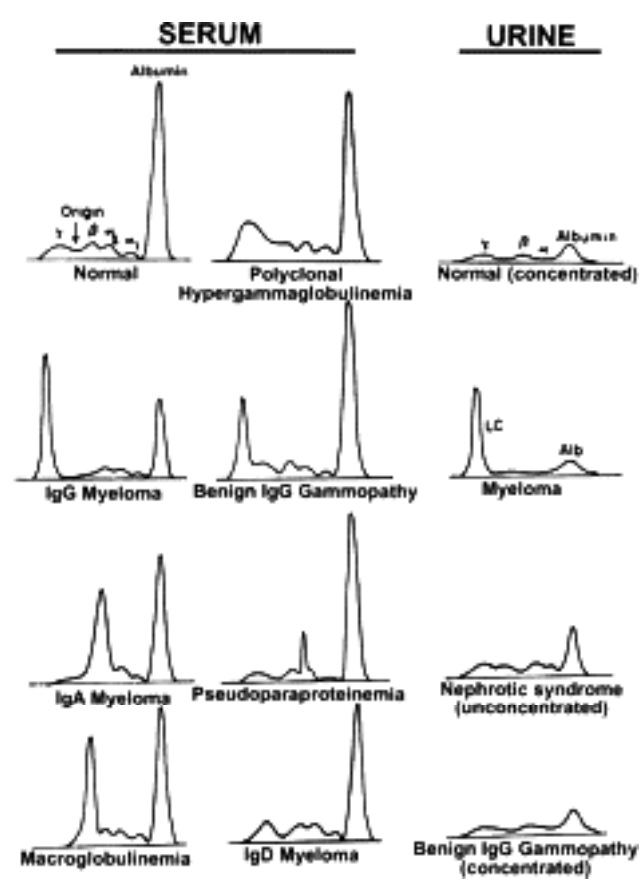
Variable	Monoclonal gammopathy of undetermined significance (MGUS)	Malignant monoclonal gammopathy (PCM, WM, B-lymphocyte neoplasms)
Serum paraprotein concentration		
IgG	<2.0 g/dL	>2.0 g/dL
IgM	<2.0 g/dL	>2.0 g/dL
IgA	<1.0 g/dL	>1.0 g/dL
Other serum immunoglobulins	Normal or decreased	Decreased
Change in paraprotein concentration over time	Stable or transient	Increases
Serum albumin	Normal	Decreased
Urine light chains	Absent or normal κ/λ ratio and less than 300 mg/day	Present and abnormal κ/λ ratio (>30 mg/dL or 300 mg/day)

PCM, plasma cell myeloma; WM, Waldenström's macroglobulinemia.

Stage	Extent of disease	Risk	Median survival (yr)
0	Lymphocytosis of bone marrow (≥40% lymphocytes) and blood (>5,000/μL)	Low	10
I	Stage 0 plus lymphadenopathy	Intermediate	7
II	Stage 0 or I plus splenomegaly and/or hepatomegaly	Intermediate	7
III	Stage 0, I, or II plus anemia (hemoglobin < 11.0g/dL)[a]	High	2
IV	Stage 0, I, or II plus thrombocytopenia (platelets < 100,000/μL)[a]	High	2

[a] Excluding anemia or thrombocytopenia caused by immunologic destruction of cells.

Feature	PV	ET	MMM	U-MPD	CML
Degree of cellular proliferation[*]					
Erythrocytes	2+	N	N or D	N	N
Megakaryocytes	1+ → 2+	4+	2+ → 4+	1+	1+ → 2+
Granulocytes	1+ → 2+	N → 2+	D → 2+	1+ → 2+	4+
Fibroblasts, fibrosis	1+	N → 1+	2+ → 4+	N → 1+	N → 1+
Extramedullary hematopoiesis	Late	A → 1+	2+ → 4+	A → 1+	N → 1+
Proportion of patients with:					
Splenomegaly	75%	75%	95%	Variable	95%
Hepatomegaly	40%	<15%	70%	A	50%
Special assays					
NAP score	N or I	N or I	N, I, or D	N or I	D or A
B_{12} and UBBC	I	N	I	N or I	2–4 × N
Ph' chromosome	A	A	A	A	90%
Abnormal karyotypes	30%	A	30%	Unknown	Ph' deviant
Preeminent clinical features	Hyperviscosity	Thrombosis, hemorrhage	Poikilocytosis, splenomegaly	Leukoerythroblastosis	Leukemic infiltration
Transition to acute leukemia	5%–25%	Rare	5%–10%	Unknown	80%

PV, polycythemia vera; ET, essential thrombocythemia; MMM, myelofibrosis with myeloid metaplasia; U-MPD, unclassified myeloproliferative disorder; CML, chronic myelogenous leukemia. NAP, neutrophil alkaline phosphatase; UBBC, unsaturated B_{12} binding capacity.
N, normal; D, decreased; A, absent.
* The designations 1+ → 4+ indicate relative degrees of prominence.

Abnormality	RA	RA-S	RAEB	RAEB-T
Dyserythropoiesis	+	+ +	+	+
Ringed sideroblasts	–	+ +	+	+
Dysmegakaryocytopoiesis	–	–	+ +	+ +
Dysgranulocytopoiesis	–	–	+ +	+ +
Auer rods	– –	– –	– –	+
Proportion of blasts in bone marrow[a]	<5%	<5%	5–20%	20–30%

+, may be present; + +, prominent; –, usually absent; – –, always absent; RA, refractory anemia and/or cytopenia; RA-S, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; RAEB-T, RAEB in transformation.
[a] The diagnosis of acute myelogenous leukemia is established with more than 30% blasts in the bone marrow.

Characteristics of immature cells

Subtype	Morphology	Incidence in adults (%)	Cell size	Cytoplasmic nuclear ratio	Nucleoli	Cytoplasmic granules	Auer rods	Comments
M0	Myeloblastic leukemia without maturation	<5	Small or intermediate	Equal to most	Usually distinct	Absent	Absent	Confused with ALL; requires immune markers CD13 and CD33 to confirm
M1	Myeloblastic leukemia with minimal maturation	15	Small to large	About equal	Distinct	Scarce	Occasional	Confused with M2 or L2 without spot of nuclear smolt; associated with thrombocytopenia
M2	Myeloblastic leukemia with maturation	25	Large	About equal	Distinct	Present	Occasional	Predominant cells are blasts and early promyelocytes; extramedullary involvement and splenomegaly
M3	Promyelocytic leukemia	10	Large	Increased	Distinct	Large, abundant, and azurophil	Common	Associated with high incidence of DIC; treated with all-trans retinoic acid; Sfbr lactic acidosis and may be mistaken for M4
M4	Myelomonocytic leukemia[*]	25	Large with indented nucleus	Increased	Distinct	Present	Occasional	Both monocytic and granulocytic differentiation; extramedullary involvement
M5	Monocytic leukemia, poorly differentiated or well differentiated	10	Large, monocyte lineage	About equal	Large	Present	Rare	See Table 25-4 for distinguishing characteristics; extramedullary involvement is common; gingiva, skin, CNS+
M6	Erythroleukemia	<5						Floral erythroid bizarre nuclei with bizarre multinucleate and erythroblasts
M7	Megakaryoblastic leukemia	<5	Small to large	Heterogeneous	Distinct	Scarce		Platelet peroxidase reaction by electron microscopy or monoclonal antibodies against platelet glycoproteins; prominent marrow fibrosis
L1	Lymphocytic leukemia, childhood form	30	Small	Round	Indistinct	Absent	Absent	Homogeneous cell population
L2	Lymphocytic leukemia, adult form	65	Intermediate to large	Heterogeneous	Distinct	Absent	Absent	Heterogeneous cell population
L3	Burkitt-type leukemia	5						Absent	See Chapter 21, Non-Hodgkin lymphoma, section VI D

ALL, acute lymphoblastic leukemia; DIC, disseminated intravascular coagulation.
[*] M4Eo is a subtype of M4 that is characterized by bone marrow that contains abnormal eosinophils. These eosinophils have large basophilic granules, stain strongly positive for periodic acid–Schiff (PAS) and chloroacetate esterase staining (normal eosinophils stain negatively). M4 eosinophilic involvement occurs frequently, and this subtype may have a better prognosis.

Subtype	Common phenotype*	Comments and variations	Potentially associated chromosome abnormalities*
M0	DR, CD13, CD33, CD34, CD7 +/-, TdT +/-	Blasts > 90% Lymphoid markers	Complex changes often involve 5 or 7; t(9;22) is possible
M1	Similar to M0 except CD15 +/-	Blasts > 90%	None consistent
M2	DR, CD13, CD33 more CD15 and less CD34 than M1	Blasts < 90%, isolated CD19	t(8;21) more likely
M3	DR-, CD13, CD15, CD33, CD34 -/+, CD2 -/+	Strong SSC except M3v Consider M3 diagnosis in maturing AML if CD2 positive and DR negative	t(11;17); Consider M3 variants if t(15;17) is negative cytogenetically and RAR rearrangement is positive molecularly
M4, M5	DR, CD15, CD14 +/-, CD4 weak, CD33 > CD13, CD 34 -/+	Consider M4Eo if CD2 positive	11q23 rearrangement in 35%+; inv(16) or t(16;16) in most M4Eo
M6	DR, CD13 -/+, CD33 +/-, CD34, CD45 weak	Frequent in dysplastic background, mature forms express glycophorin	-7 or del(7q) and/or -5 or del (5q)
M7	DR -/+, CD33 +/-, CD34, CD41, CD61	Phenotyping critical; beware of platelet adhesion to blasts	t(1;22) in 20%-25%; frequently hyperdiploid Most frequent subtype in children with trisomy 21
T-ALL (L1, L2)	DR -/+, CD1, CD2, cCD3, CD5, CD7 dual CD4/CD8, CD10 +/-, CD34 -/+, CD45 weak, TdT	CD10 negative may have poor prognosis; frequently lose T-cell antigens	15%-25% are t(1;14)
B-precursor ALL (L1, L2)	DR, CD10, CD19, CD20 -/+, CD24, CD34, TdT	Multiple myeloid antigens Infants with CD10 -, CD15, CD65	t(9;22), 11q23 rearrangements
Pre-B ALL (L1, L2)	DR, CD9, CD10, CD19, CD20 +/-, CD24, CD34-, TdT +/-, cIgM	CD9, CD10, CD19, CD20 +/-, CD34-	t(1;19)
B-ALL (L3)	DR, CD10 +/-, CD19, CD20, CD22, CD24, CD34-, TdT -, SIg	Bright clonal SIg (usually IgM)	t(8;14); t(2;8); t(8;22)

-, negative; +/-, variable (more often positive); -/+, variable (more often negative); AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; DR, HLA-DR; Ig, immunoglobulin (SIg, surface Ig; cIg, cytoplasmic Ig); M3v, microgranular variant; RAR, retinoic acid receptor; SSC, side scatter; TdT, terminal deoxytransferase.
* See Appendices C4, C5, and D1.
Note: CD10 = CALLA; t(9;22) = Philadelphia (Ph+) chromosome.

Reaction	Degree of reaction		
	Absent or weak	Moderate	Strong
Nonspecific esterase[a]	M0, M1, L	M2, M3	M4, M5
Nonspecific esterase with fluoride inhibitor[b]	M0, M1, M5, L	M2, M3, M4	—
Peroxidase or Sudan black	M0, M5, M7, L	M1, M4	M2, M3
Lysozyme (muramidase)[c]	M0, M1, M2, M3, L	M4	M5
Period acid–Schiff stain	M0, M1, M2, M3, L	M4, M5, L	L

[a] M0 through M7 types of myelogenous leukemia are described in Table 25.2. M6 is excluded. The three types of lymphocytic leukemia (L) are not distinguished by these studies.
[b] Sodium fluoride is a potent inhibitor of the predominant esterase in precursors of monocytes but not in precursors of granulocytes or lymphocytes; it is most useful to identify type M5 leukemia.
[c] Increased lysozyme levels are measured in the serum and characterize mixed (M4) or pure (M5) monocytic leukemia.

| Subtype | Blasts (%) | | Nonerythroid cells (%) | | Erythroblasts (%) (ANC) |
	ANC	NEC	Granulocytes[b] (NEC)	Monocytes (NEC)	
M1		>90	<10	<10	
M2	>30	30–89	>10	<20	<50
M4[c]	>30	>30	>20	>20	<50
M5		>80[d]	<20	>80[c]	
M6	< or > 30	>30	Variable	Variable	>50

ANC, % of all nucleated cells; NEC, % of nonerythroid cells.

[a] M3 and M7 subtypes are classified by other criteria.

[b] Promyelocytes, myelocytes, metamyelocytes, and neutrophils.

[c] Also requires absolute monocyte count in peripheral blood greater than 5000/µL and/or lysozyme concentration greater than three times normal in serum or urine.

[d] Monoblasts in M5a; predominantly promonocytes and monocytes in M5b.

| Condition | BUN | Osmolality | | Urine Na concentration |
		S	U	
SIADH	D,(N)	D	I	N,I
Edematous states	D,N,I	D	I	D
Myxedema	N	D	N,I	(D),N,I
Salt-wasting states				
Mineralocorticoid deficiency	I	D	I	I
Glucocorticoid deficiency	N	D	(N),I	N,I
Diuretics	N	D	I	(D),N,I
Chronic renal failure	I	D	D,N,I	D,N,I
GI loss with hypotonic replacement	N,I	D	D	D
Compulsive water drinking	N,D	D	D	N
Hypothalamic osmoregulatory defect	N	D	N	D,N,I
Pseudohyponatremia				
Hyperglycemia	N,I	I	D,N,I	N
Mannitol	N,I	N	D,N	D,N
Marked hyperlipidemia or				
paraproteinemia	N	N	N	N

BUN, blood urea nitrogen; S, serum; U, urine; SIADH, syndrome of inappropriate antidiuretic hormone; GI, gastrointestinal; D, decreased; N, normal; I, increased; ( ), slight or occasional.

Drug	Dosage
Bleomycin	1 U/kg (40 U maximum in the elderly)
Cisplatin	100 mg/m² (pleural)
Cytarabine	1200 mg (pleural)
Doxorubicin	30 mg
Doxycycline	500 mg (may be repeated)
5-Fluorouracil	750–1000 mg
Thiotepa	30–45 mg
Talc, dry powder or 50-mL suspensions	1–2 g (pericardial), 2–6 g (pleural)

Drug[a]	Incidence (%)	Dose dependent	Onset after therapy	Reaction type[b]	Reversibility (steroids[c])	Risk factors[d]
Bleomycin	1–10	Yes	Immediate to months	A, BO, F, H	Possible (0)	Age >70, RT, CT, O₂, renal insufficiency
Busulfan	1–10	Yes	At least 1 yr	F	Occasional (+)	RT, CT
Carmustine (BCNU)	2–30	Yes	2 mo to 17 yr	A, F	Rare (0)	Preexisting lung disease, younger age, RT, CT
Cytarabine	20	Yes	2 to 21 days (usually <6 days)	E	— (?)	Total dose
Mitomycin C	3–10	Possible	2 to 6 wk	A, F	50% recover partially (++)	RT, CT, FA, O₂
Methotrexate	Occasional	No	10 days to 5 yr	E, F, H, P	Common (+++)	CT, FA, steroid tapering, previous adrenalectomy
Chlorambucil	Rare	Possible	6 to 9 mo	A, F	Occasional (+)	CT
Cyclophosphamide	Rare	Possible	2 wk to 3 yr	E, F, H	Common (++)	CT, RT (?)
Procarbazine	Rare	No	2 to 6 mo	H	Possible (0)	

[a] Cases of chemotherapy lung have also been rarely associated with azathioprine, lomustine (CCNU), melphalan, mercaptopurine, nitrogen mustard, teniposide (VM-26), vinblastine, vindesine, and zinostatin. This complication occurs more frequently when vinblastine or vindesine is given with mitomycin C.

[b] A, acute pneumonitis; B, bronchospasm; BO, bronchiolitis obliterans; E, pulmonary edema; F, pulmonary fibrosis; H, hypersensitivity pneumonitis; P, pleuritis.

[c] Corticosteroid therapy. 0, no or questionable value; +, occasionally helpful; ++, may be helpful.

[d] CT, combination chemotherapy regimens; RT, radiation therapy; FA, frequency of administration; O₂, oxygen administration.

Characteristic	Prerenal	Renal
Fractional sodium excretion $[FE_{Na} = (U_{Na} \times S_{creat}) \div (S_{Na} \times U_{creat}) \times 100]$	≤ 1	≥ 2
U_{Na}	<15 mEq/L	>30 mEq/L
$U_{creat} : S_{creat}$ ratio	>40	<20
BUN : S_{creat} ratio	>20	<20
Response to fluid or loop diuretics	Positive	Negative

U, concentration in urine; S, concentration in serum; Na, sodium; creat, creatinine.

General cause	Predisposing factors in patients with malignancies
Hypovolemia	
Decreased intake	Anorexia from malignancy or chemotherapy, intercurrent illness, obtundation, neglect
Increased loss	
Vomiting	Intestinal obstruction, chemotherapy
Diarrhea	Enteral hyperalimentation, carcinoid, VIPoma, chemotherapy, antibiotic-associated
Renal	
Diabetes insipidus (DI)	Primary pineal tumor, craniopharyngioma, metastasis (breast)
Nephrogenic DI	Chronic renal insufficiency, myeloma kidney, lithium, demeclocycline, nephrocalcinosis
Osmotic diuresis	Hypercalcemia, hyperglycemia
Blood loss	Tumor- or chemotherapy-related
Hypoalbuminemia	Poor nutrition, severe liver disease, nephrotic syndrome
Intravascular shifts	
Congestive heart failure, low cardiac output	Malignant pericardial effusion, radiation-induced pericarditis or myocarditis
Sepsis, shock	Lymphoma, leukemia, myeloma; neutropenia due to chemotherapy
Renal artery obstruction	Tumor (rare)

	Minimal change (%)	Membranous nephropathy (%)	Membranoproliferative glomerulonephritis (%)
Carcinoma	4–6	80	4–6
Hodgkin lymphoma	50–67	8–12	—
Non-Hodgkin lymphoma	33	33	33

Characteristic	Erythrocytes	Platelets	Neutrophils	Lymphocytes
Bone marrow				
Storage cell	Reticulocyte	Megakaryocyte (32n ploidy); platelets	Metamyelocyte	Lymphocyte
From blast to storage cell	3 days	5 days	5 days	Unknown
Storage time	2 days	<1 day	3–4 days	Unknown
Circulation				
Cells replaced daily	1%	10%	300%–400%	25%–40%
Half-life	60 days	5 days	7 hr	Days to years
Onset of cytopenia[a]	5 days[b]	3–30 days	5 days	2–3 weeks

[a] The type, severity, and duration of cytopenia depends on the etiology of the injury, its dose and exposure time, and other factors.
[b] Reticulocytopenia; anemia requires prolonged and repeated arrests of erythropoiesis.

Feature	Acute DIC	Primary fibrinolysis
Incidence	Common	Very rare
Platelets[a]	Decreased	Usually normal
Paracoagulation test (fibrin monomers)[a]	Positive	Negative
Clot lysis or euglobulin lysis time[a]	Normal or long	Rapid
Fibrinogen	Decreased	Decreased
Fibrin degradation products	Variable	Large amounts

[a] Discriminatory assays.

Category A consists of one or more of the following conditions
    Asymptomatic HIV infection
    Acute retroviral syndrome
    Persistent generalized lymphadenopathy
Category B consists of conditions formerly classified as acquired immunodeficiency
    syndrome–AIDS-related complex (ARC):
    Bacillary angiomatosis
    Candidiasis, oropharyngeal or recurrent vulvovaginal
    Cervical dysplasia
    Constitutional symptoms for longer than 1 month (e.g., fever or diarrhea)
    Hairy leukoplakia, oral
    Herpes zoster involving more than one dermatome
    Idiopathic thrombocytopenic purpura
    Listeriosis
    Pelvic inflammatory disease
    Peripheral neuropathy
Category C consists of AIDS-defining conditions
    CD4 count less than 200/μL
    Candidiasis, esophageal or pulmonary
    Cervical cancer
    Coccidioidomycosis
    Cryptococcosis, extrapulmonary
    Cryptosporidiosis
    Cytomegalovirus disease, active
    Encephalopathy
    Herpes simplex: chronic ulcers > 1 month's duration; or bronchitis, pneumonitis,
      or esophagitis
    Histoplasmosis
    Isosporiasis, chronic intestinal
    Kaposi's sarcoma
    Lymphoma: Burkitt, immunoblastic, or primary brain (or equivalent)
    Mycobacterium avium-intracellulare complex, *M. kansasii*, or other
      Mycobacterium species disseminated or extrapulmonary
    Mycobacterium tuberculosis, any site
    Pneumocystis carinii pneumonia
    Pneumonia, recurrent
    Progressive multifocal leukoencephalopathy
    Salmonella septicemia, recurrent
    Toxoplasmosis of brain
    Wasting syndrome due to HIV

	Categories[*]		
Subcategories based on CD4+ T-lymphocyte counts	**A**	**B**	**C**
1: > 500 cells/μL	A1	B1	C1
2: 200–400 cells/μL	A2	B2	C2
3: < 200 cells/μL	A3	B3	C3

[*] Shaded categories define the presence of AIDS

I. Traditional First-Line Regimens for HL

Regimen (Cycle frequency)	Alkylating Agent	Plant Alkaloid	Anthracycline or Antibiotic	Antimetabolite	Corticosteroid	Other
MOPP (28 d)	Mechl 6 [d 1 + 8]	Vcr 1.4 [d 1 + 8]			Pred 40 PO [d 1 → 14]	Pcz 100 PO [d 1 → 14]
ABVD (28 d)		Vbl 6 [d 1 + 15]	Doxo 25 [d 1 + 15] Bleo 10 [d 1 + 15]			DTIC 375 [d 1 + 15]
MOPP/ABVD (alternate cycles of MOPP & ABVD)						
MOPP/ABV Hybrid (28 d)	Mechl 6 [d 1]	Vcr 1.4 [d 1] Vbl 6 [d 8]	Doxo 35 [d 8] Bleo 10 [d 8]		Pred 40 PO [d 1 → 14]	Pcz 100 PO [d 1 → 7]
COPP (21 d)	Cyclo 400–650 [d 1 + 8]	Vcr 1.4 [d 1 + 8]			Pred 40 PO [d 1 → 14]	Pcz 100 PO [d 1 + 14]
Chl-VPP (28 d)	Chl 6 [d 1 → 14] (max. 10 mg)	Vbl 6 [d 1 + 8] (max. 10 mg)			Pred 40 PO [d 1 → 14]	Pcz 100 PO [d 1 → 14] (max. 150 mg)

II. Regimens Combined with Radiation Therapy for Early-Stage and Favorable-Prognosis HL

Regimen (Cycle frequency)	Alkylating Agent	Plant Alkaloid	Anthracycline or Antibiotic	Antimetabolite	Corticosteroid	Other
VBM (28 d)		Vbl 6 [d 1 + 8]	Bleo 10 [d 1 + 8] (Reduced to 2.5 after RT)	Mtx 30 [d 1 + 8]		
EBVP (28 d)		Vbl 6 [d 1]	Epir 70 [d 1] Bleo 10 [d 1]		Pred 40 PO [d 1 → 5]	

III. Dose-Intense Regimens for HL

Regimen (Cycle frequency)	Alkylating Agent	Plant Alkaloid	Anthracycline or Antibiotic	Antimetabolite	Corticosteroid	Other
Stanford V (28 d)	Mechl 6 [d 1 + 15]	Vbl 6 [d 1 + 15] Vcr 1.4 [d 8 + 22] Etop 60 [d 15]	Doxo 25 [d 1 + 15] Bleo 5 [d 8 + 22]		Pred 40 PO (q.o.d. for 3 cycles)	
BEACOPP (21 d)	Cyclo 650 [d 1]	Etop 100 [d 1 → 3] Vcr 1.4 [d 8]	Doxo 25 [d 1] Bleo 10 [d 8]		Pred 40 PO [d 1 → 14]	Pcz 100 PO [d 1 → 7]
BEACOPP escalated (21 d)	Cyclo 1250 [d 1]	Etop 200 [d 1 → 3] Vcr 1.4 [d 8]	Doxo 35 [d 1] Bleo 10 [d 8]		Pred 40 PO [d 1 → 14]	Pcz 100 PO [d 1 → 7]

Bleo, bleomycin [dose in IU/m²]; Chl, chlorambucil; Cyclo, cyclophosphamide; Doxo, doxorubicin (Adriamycin); DTIC, dacarbazine; Epir, epirubicin; Etop, etoposide; Mechl, mechlorethamine (nitrogen mustard); Mtx, methotrexate; Pcz, procarbazine; Pred, prednisone; Vbl, vinblastine; Vcr, vincristine; RT, radiation therapy.
ᵃ All doses are given intravenously except when they are PO (oral), where indicated
ᵇ Maximum 2 mg dose

I. Low grade lymphomas, relapsing NHL.

Regimen (Cycle frequency)	Drugs & Dosage in mg/m² (days given in cycle)[a]					
	Alkylating Agent	Plant Alkaloid	Anthracycline or Antibiotic	Antimetabolite	Corticosteroid	Other
Chl & P (q4 d)	Chl 16 PO (d 1 or d 1 → 5)				Pred 40 PO (d 1 → 5)	
CVP (q2 d)	Cyclo 750 – 1000 (d 1)	Vcr 1.4[b] (d 1)			Pred 100 PO (d 1 → 5)	
CVP (q4 d)	Cyclo 400 PO (d 1 → 5)	Vcr 1.4[b] (d 1)			Pred 100 PO (d 1 → 5)	
FMD (q4 d)			Mitox 10 (d 1)	Flud 25 (d 1 → 3)	Dexa 8 20 PO (d 1 → 4)	

II. Intermediate-high grade NHL.

Regimen (Cycle frequency)	Alkylating Agent	Plant Alkaloid	Anthracycline or Antibiotic	Antimetabolite	Corticosteroid	Other
CHOP (q3 d)	Cyclo 750 (d 1)	Vcr 1.4[b] (d 1)	Doxo 50 (d 1)		Pred 100 PO (d 1 → 5)	
M-BACOD (q3 d)	Cyclo 600 (d 1)	Vcr 1.0 (d 1)	Doxo 45 (d 1) Bleo 4 (d 1)	Mtx 3000 (d 14) (rescue Mtx levels)	Dexa 6 PO (d 1 → 5)	Leucovorin[c]
m-BACOD (q4 d)	Cyclo 600 (d 1)	Vcr 1.0 (d 1)	Doxo 45 (d 1) Bleo 4 (d 1)	Mtx 200 (d 8 + 15)	Dexa 6 PO (d 1 → 5)	Leucovorin[d]
ProMACE-CytaBOM (q3 d)	Cyclo 650 (d 1)	Vcr 1.4 (d 8) Etop 120 (d 1)	Doxo 25 (d 1) Bleo 5 (d 8)	Mtx 120 (d 8) Cytar 300 (d 8)	Pred 60 PO (d 1 → 14)	Leucovorin[c]
MACOP-B (q8 d for 3 cycles)	Cyclo 350 (d 1 + 15)	Vcr 1.4 (d 8 + 22)	Doxo 50 (d 1 + 15) Bleo 10 (d 22)	Mtx 400 (d 8)	Pred 75 PO (12 wk, tapered over last 16 d)	Leucovorin[e] Ambulatory basis[f]

III. High grade small noncleaved cell NHL ("CODOX-M/IVAC")

Regimen (Cycle frequency)	Drugs & Dosage in mg/m² (days given in cycle)[a]					
	Alkylating Agent	Plant Alkaloid	Anthracycline or Antibiotic	Antimetabolite	IT Therapy	Other
Regimen A: Codox-M (2 cycles alternating with Regimen B)	Cyclo 800 (d 1) Cyclo 200 (d 2 → 5)	Vcr 1.5 (d 1 + 8)	Doxo 40 (d 1)	Mtx 1200 over 1 hr, then 240/hr × 23 hr (d 10)	IT Cytar 70 (d 1 + 3) IT Mtx 12 (d 15)	CSF q d (d 13 until ANC > 1000) Leucovorin[g]
Regimen B: IVAC (2 cycles alternating with Regimen A)	Ifos[b] 1500 over 1-2 hr (d 1 → 5)	Etop 60 (d 1 → 5)		Cytar 2000 over 1-2 hr q 12 hr (d 1 & 2)	IT Mtx 12 (d 5)	CSF q d (d 7 until ANC > 1000)

1 = with Mesna 360 mg/m² over 1 hr q 3 hr (d 1 → 5)
2 = Leucovorin 10 mg/m² q 6 hr × 6 doses beginning at 24 hr after Mtx is started
3 = Leucovorin 10 mg/m² q 6 hr × 8 doses beginning at 24 hr after Mtx is started
4 = Leucovorin 15 mg/m² q 6 hr × 6 doses beginning at 24 hr after Mtx is started
5 = Leucovorin 15 mg/m² q 6 hr × 6 doses beginning at 24 hr after Mtx is started
6 = Aprinocrbrals PO daily for (d wk) co-trimoxazole 2 b.i.d. and ketoconazole 200 mg q.d.
7 = Leucovorin 192 mg/m² given at 36 hr after Mtx started, and then 12 mg/m² q 6 hr until serum Mtx level < 10⁻⁸ M

Bleo bleomycin (dose in U/m²), Chl chlorambucil, CSF colony stimulating factor, Cyclo cyclophosphamide, Cytar cytarabine, Dexa dexamethasone, Doxo doxorubicin (Adriamycin), DTIC dacarbazine, Etop etoposide, Flud fludarabine, Ifos ifosfamide, Mitox mitoxantrone (Novantrone), Mtx methotrexate, Pred prednisone, Vcr vincristine

[a] All doses are given intravenously except when they are PO (oral) or IT (intrathecal) — where indicated.
[b] Minimum 2 mg dose
[c] Total dose (not per m²)

	Drugs & Dosage in mg/m² [days given in cycle]ᵃ					
Regimen (Cycle frequency)	Alkylating Agent	Plant Alkaloid	Anthracycline or Antibiotic	Antimetabolite	Corticosteroid	Other
CEP (28 d)	CCNU 80 PO [d 1]	Etop 100 PO [d 1 → 5]				Procarbazine 60 PO [d 1 → 5]
CEPP-B (28 d)	Cyclo 600 [d 1 + 8]	Etop 70 [d 1 → 3]	Bleo 15 [d 1 + 15]		Pred 60 PO [d 1 → 10]	Procarbazine 60 [d 1 → 10]
DHAP (21–28 d)	Cispl 100 by 24 hr CIV [d 1]			Cytar 2000 over 2 hr q 12 hr [d 2 × 2 doses]	Dexa 40ᵇ [d 1 → 4]	
ESHAP (21–28 d)	Cispl 25 per day by 24 hr CIV [d 1 → 4]	Etop 40 [d 1 → 4]		Cytar 2000 over 2 hr [d 5, one dose]	Mepr 500ᵇ [d 1 → 4]	
EVA (28 d)		Etop 100 [d 1 → 3] Vbl 6 [d 1]	Doxo 50 [d 1]			
miniBEAM (28 d)	BCNU 60 [d 1]	Etop 75 [d 2 → 5]		Cytar 100 b.i.d. [d 2 → 5]		Melphalan 20–30 PO [d 6]
VAPEC-B (28 d for total of 3 cycles)	Cyclo 350 [d 1]	Vcr 1.4 [d 8 + 22] Etop 100 [d 15 → 19]	Doxo 35 [d 1 + 15] Bleo 10 [d 8]		Pred 50ᵇ PO q.d. × 6 wk, then 25ᵇ PO q.d. × 6 wk	Cotrimoxazole 2 tablets b.i.d.
MINE (21–28 d)	Ifos 1330 over 1 hr [d 1 → 3]	Etop 65 [d 1 → 3]	Mitox 8 [d 1]			Mesna 1330 mg/m² IV over 1 hr with Ifos and 500 mg PO 4 hr after completion of Ifos [d 1 → 3]

Bleo, bleomycin (dose in U/m²); BCNU, carmustine; CCNU, lomustine; CIV, continuous intravenous infusion; Cispl, cisplatin; Cyclo, cyclophosphamide; Cytar, cytarabine; Dexa, dexamethasone; Doxo, doxorubicin (Adriamycin); Etop, etoposide; Ifos, ifosfamide; Mepr, methyl prednisolone (Solu-Medrol); Mitox, mitoxantrone (Novantrone); Pred, prednisone; RT, radiation therapy; Vbl, vinblastine; Vcr, vincristine; Vsa, vinorelbine.

ᵃ All doses are given intravenously except when they are PO (oral), where indicated.

ᵇ Total dose (not per m²)

Potentially Helpful Findings	Primary Site or Tumor Type
HISTOPATHOLOGY	
Signet-ring cells	Gastrointestinal tract, pancreas, ovary, breast (tubular carcinoma), prostate
Psammoma bodies	Ovary, thyroid, breast, meningioma
Papillary	Thyroid, ovary, breast, parotous, (and Schiller)
Indian file tumor cells	Breast (especially lobular), pancreas, neuroblastoma, small cell carcinoma, carcinoid
Sustentacular cells	Carcinoid, melanoma, paraganglioma
Intranuclear inclusions	Breast (especially lobular), papillary thyroid, melanoma
Rosettes	Neuroblastoma, retinoblastoma, pineal, small cell tumors, neuroendocrine carcinoma
	Retinoblastoma, Ewing's, carcinoid, rhabdomyosarcoma
Neural-type tumors	Primitive neuroectoderm tumors (PNET), Ewing's sarcoma, paraganglioma, neuroblastoma, ganglioneuroblastoma
Clear cell neoplasms	See Chapter 28, section II.F.4
Poorly differentiated small cell neoplasms	See Chapter 28, section II.F.3
HISTOCHEMISTRY	
Mucin stains (e.g. mucicarmine)	Adenocarcinoma (absent in renal cell carcinoma)
Chromatin stains (positive precede and Schiff (PAS) stain removed by diastase)	Abundant in renal cell carcinoma, germ cell cancer, and some adrenocortical carcinoma
	Sometimes melanoma, rhabdomyosarcoma
	Sometimes alveolar soft parts, Ewing's, clear cell, leiomyosarcoma, rhabdomyosarcoma
Silver impregnation (e.g. Fontana-Masson, Grimelius, Bodian-Masson)	Neurosecretory polypeptide-forming neuroendocrine cells, melanin-forming cells, melanoma
ELECTRON MICROSCOPY	
Lamellar surfactant bodies	Alveolar carcinoma (lung)
Cells united by well-developed cell junctions (desmosomes) intercellular bridges, tonofilaments	Squamous cell carcinoma
Premelanosomes, melanosomes, tubular arrays	Melanoma
Abundant polyribosomes, absence of cytoskeletal structures	Lymphoma, leukemia
Myofibrils, intracellular actinin-dense rough endoplasmic reticulum	Sarcoma
Long surface microvilli	Mesothelioma (tumor)
Cytoplasmic "neurosecretory" membrane granules	Neuroendocrine tumors, including carcinoid
Apical terminal webs	Gut epithelial cells
Acinar spaces, zonular complex, tight junctions, microvilli, desmosomes	Adenocarcinoma
Microvilli, glycocalyceal bodies, terminal webs, apical reserve granules	Colon
Extracellular secretion, prominent intrafilaments	Breast
Stigiform materials	Ovary
Tubuloreticular structures of cytoplasm	Kidney

Detectable Antigen	Tumor Type
α-Fetoprotein (AFP)	Germ cell and trophoblastic tumors, hepatocellular carcinoma
β-Antitrypsin	Hepatocellular carcinoma
Carcinoembryonic antigen (CEA)	Gut, pancreas, cervix, uterus, lung, ovary, breast, urinary tract
Chromogranin	NET
Collagen, type IV, laminin	Sarcomas (nonorganic, smooth muscle)
Cytokeratin	Nonspecific, broad range of carcinomas and sarcomas
Desmin	Sarcomas (smooth or skeletal muscle, glomus tumors; corpus uteri (connective tissue part)
Factor VIII; CD31, CD34	Sarcomas (vascular)
Gross cystic disease fluid protein (GCDFP-15)	Breast
Hormones, specific	Endocrine gland, gut, or pancreatic tumors
Human chorionic gonadotropin (hCG)	Trophoblastic, breast, and other tumors
Human placental lactogen	Trophoblastic tumors
Immunoglobulin molecules	Lymphomas/leukemias
Involucrin	Squamous epithelia
Leukocyte common antigen (LCA)	Lymphomas/leukemias, leukocytic tumors
Lymphoid cell epitopes and activation markers	Lymphomas/leukemias
Milk fat globulin	Breast (nonspecific)
Muramidase (lysozyme); CD68	Histiocytic tumors, myelogenous leukemia
Myelin basic protein	Sarcomas (neurogenic)
Myoglobin	Sarcomas (neurogenic, skeletal muscle, corpus uteri)
Muscle-specific actin	Sarcomas (leiomyosarcoma, MFH)
Neurofilaments	NET; lung (small cell carcinoma)
Neuron-specific enolase	NET; lung (small cell carcinoma (breast carcinoma tester)
NKI/C3 or MB-5	Melanoma
Pancreatic carcinoma antigen	Pancreas, gut
Prostate-specific acid phosphatase, prostate antigen (PAP, PSA)	Prostate
S100 protein	Melanoma; sarcomas (neurogenic, cartilage); histiocytic tumors
Thyroglobulin	Thyroid
Vimentin	Sarcomas (muscle, cartilage, vessels, bone, synovia); epithelioid, MFH); renal cell carcinoma; lymphomas/leukemia; melanoma

MFH, malignant fibrous histiocytoma; NET, neuroendocrine tumor (neuroblastic, Merkel's cell, and carcinoid tumors; paragangliomas; pheochromocytoma, oat cell carcinoma)