CHAPTER

5

Alterations in Cell Growth and Replication: Neoplasia

Cancer is the second leading cause of death in the United States after cardiovascular disease. The disease affects all age groups, causing more death in children 3 to 15 years of age than any other disease. The American Cancer Society estimates that 1.3 million Americans will develop cancer in 2003, and that one in two males and one in three females will have cancer during their lifetime. It also is estimated that approximately 556,500 Americans will die in the year from neoplastic diseases.[1] As age-adjusted cancer mortality rates increase and heart disease mortality decreases, it is predicted that cancer will become the leading cause of death in a few decades.[2] Trends in cancer survival demonstrate that relative 5-year survival rates have improved since the early 1960s. It is estimated that approximately 59% of people who develop cancer each year will be alive 5 years later.

CONCEPTS OF CELL GROWTH

Cancers result from a process of altered cell differentiation and growth. The resulting tissue is called *neoplasia*. The term *neoplasm* comes from a Greek word meaning *new formation*. Unlike the tissue growth that occurs with hypertrophy and hyperplasia, the growth of a neoplasm is uncoordinated and relatively autonomous in that it lacks normal regulatory controls over cell growth and division. Neoplasms tend to increase in size and continue to grow after the stimulus has ceased or the needs of the organism have been met.

Cancer is not a single disease. The term describes almost all forms of malignant neoplasia. Cancer can originate in almost any organ, with the prostate being the most common site in men and the breast in women. The ability of cancer to be cured varies considerably and depends on the type of cancer and the extent of the disease at diagnosis. Cancers such as acute lymphocytic leukemia, Hodgkin's disease, testicular cancer, and osteosarcoma, which only a few decades ago had poor prognoses, are today cured in many cases. However, lung cancer, which is the leading cause of death in men and women in the United States, is resistant to therapy, and although some progress has been made in its treatment, mortality rates remain high.

Tissue renewal and repair involves cell proliferation and differentiation. *Proliferation*, or the process of cell division, is an

inherent adaptive mechanism for replacing body cells when old cells die or additional cells are needed. *Differentiation* is the process of specialization whereby new cells acquire the structure and function of the cells they replace. In adult tissues, the size of a population of cells is determined by the rates of cell proliferation, differentiation, and death by apoptosis.[3] Apoptosis, which is discussed in Chapter 2, is a form of programmed cell death designed to eliminate senescent cells or unwanted cells. A balance of cellular signals that regulate cell proliferation, differentiation, and apoptosis regulates the size of cell populations.

The Cell Cycle

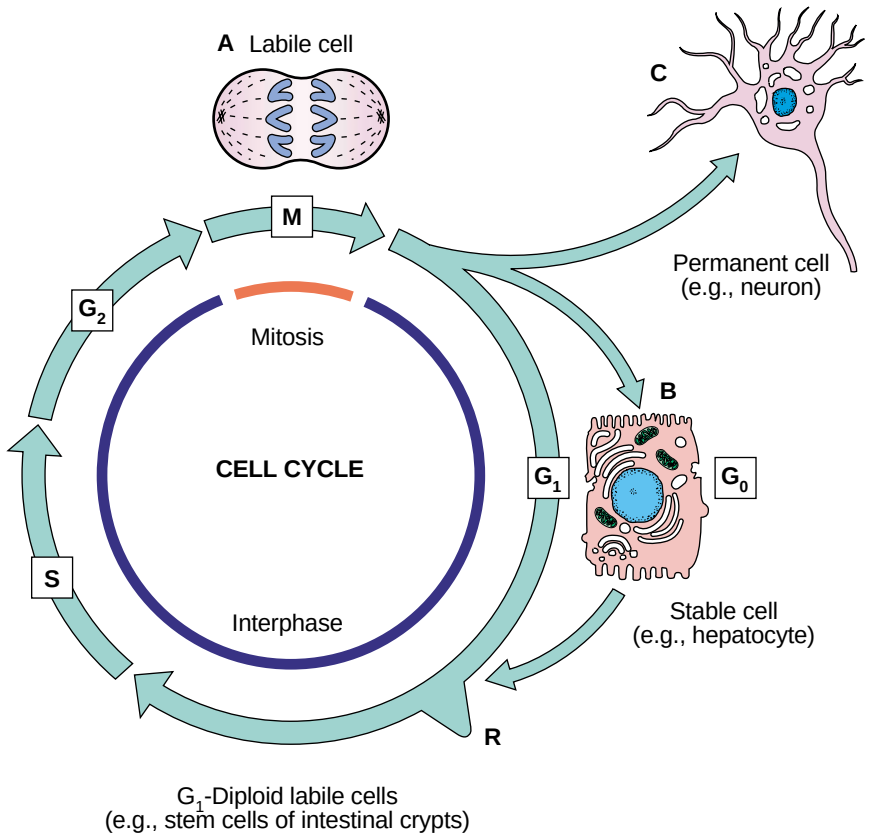
The cell cycle is the interval between each cell division. It regulates the duplication of genetic information and appropriately aligns the duplicated chromosomes to be received by the daughter cells. In addition, pauses or checkpoints in the cell cycle determine the accuracy with which deoxyribonucleic acid (DNA) is duplicated. These checkpoints allow for any defects to be edited and repaired, thereby assuring that the daughter cells receive the full complement of genetic information, identical to that of the parent cell.[3]

The cell cycle is divided into four distinct phases referred to as G_1, S, G_2, and M (Fig. 5-1). G_1 (*gap 1*), is the postmitotic phase during which DNA synthesis ceases while ribonucleic acid (RNA) and protein synthesis and cell growth take place. This is the phase during which cells pursue their own specialized type of function. Some cells such as neurons become terminally differentiated after mitosis and remain in G_1. Continually dividing cells, such as the crypt cells in the intestinal mucosa, pass through restriction point (R) in G_1 that commits them to progression to the synthesis (S) phase and a new round of cell division. During the S phase, DNA synthesis occurs, giving rise to two separate sets of chromosomes, one for each daughter cell. G_2 (*gap 2*) is the premitotic gap and is similar to G_1 in that DNA synthesis ceases while RNA and protein synthesis continues. The *M phase* is the phase of cellular division or mitosis. Stable cells, such as hepatocytes, enter a quiescent period in the cell cycle, the G_0 gap. These quiescent cells reenter the cell cycle in response to extracellular nutrients, growth factors, hormones, and other signals, such as blood loss or tissue injury, that signal for cell renewal.[4,5]

The duration of the phases of the cell cycle vary depending on the cell type, the frequency with which the cells divide, and host characteristics, such as the presence of appropriate growth factors. Very rapidly dividing cells can complete the cell cycle in less than 8 hours, whereas others can take longer than 1 year. Most of this variability occurs in the G_0 and G_1 phases. The duration of the S phase (10 to 20 hours), the G_2 phase (2 to 10 hours), and the M phase (0.5 to 1 hour) appears to be relatively constant.[5]

Cell Proliferation

Cell proliferation is the process by which cells divide and reproduce. Cell division provides the body with the means for replacing cells that have a limited life span such as skin and blood cells, increasing tissue mass during periods of growth, and providing for tissue repair and wound healing. In normal



■ **FIGURE 5-1** ■ The cell cycle. (**A**) Labile cells (*e.g.*, intestinal crypt cells) undergo continuous replication and the interval between two consecutive mitoses is designated the cell cycle. After division, the cells enter a gap (G_1) during which DNA synthesis ceases and RNA and protein synthesis takes place as the cell develops its own specialized type of function. Cells that continue in the cell cycle pass the restriction point (R), which commits them to a new round of cell division and continuation to the synthesis (S) phase during which all the chromosomes are replicated. The S phase is followed by the short gap (G_2) during which DNA synthesis ceases and protein synthesis continues. The M phase is the period of mitosis. After each cycle, one daughter cell will become committed to differentiation and the other will continue cycling. (**B**) Some cell types, such as hepatocytes, are stable. After cell mitosis, the cells take up their specialized functions (G_0) and not reenter the cell cycle unless stimulated by the loss of other cells. (**C**) Permanent cells (neurons) become terminally differentiated after mitosis and cannot reenter the cell cycle. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 85]. Philadelphia: Lippincott Williams & Wilkins)

tissue, cell proliferation is regulated so that the number of cells actively dividing is equivalent to the number dying or being shed.

In terms of cell proliferation, the 200 or more cell types of the body can be divided into 3 large groups: the well-differentiated neurons and cells of skeletal and cardiac muscle that are unable to divide and reproduce; the parent, or progenitor cells, that continue to divide and reproduce, such as blood cells, skin cells, and liver cells; and the undifferentiated stem cells that can be triggered to enter the cell cycle and produce large numbers of progenitor cells when the need arises. The rates of reproduction of these cells vary greatly. White blood cells and cells that line the gastrointestinal tract live several days and must be replaced constantly. In most tissues, the rate of cell reproduction is greatly increased when tissue is injured or lost. For example, bleeding stimulates the rapid reproduction of the blood-forming cells of the bone marrow. In some types of tissue, the genetic program for cell replication normally is repressed but can be resumed under certain conditions. For example, the liver has extensive regenerative capabilities under certain conditions.

Cell Differentiation

Cell differentiation is the process whereby proliferating cells are transformed into different and more specialized cell types. This process leads to a fully differentiated, adult cell that has achieved its specific set of structural, functional, and life expectancy characteristics. For example, a red blood cell is programmed to develop into a concave disk that functions as a vehicle for oxygen transport and lives approximately 120 days.

All of the different cell types of the body originate from a single cell—the fertilized ovum. As the embryonic cells increase in number, they engage in an orderly process of differentiation that is necessary for the development of all the various organs of the body. The process of differentiation is regulated by a combination of internal programming that involves the expression of specific genes and external stimuli provided by neighboring cells, exposure to substances in the maternal circulation, and a variety of growth factors, nutrients, oxygen, and ions.[6] What makes the cells of one organ different from those of another organ is the type of gene that is expressed. Although all cells have the same complement of genes, only a small number of these genes are expressed in postnatal life. When cells, such as those of the developing embryo, differentiate and give rise to committed cells of a particular tissue type, the appropriate genes are maintained in an active state while the remainder are inactive. Normally, the rate of cell reproduction and the process of cell differentiation are precisely controlled in prenatal and postnatal life so that both of these mechanisms cease once the appropriate numbers and types of cells are formed.

The process of differentiation occurs in orderly steps; with each progressive step, increased specialization is exchanged for a loss of ability to develop different cell characteristics and different cell lines. The more highly specialized a cell becomes, the more likely it is to lose its ability to undergo mitosis. Neurons, which are the most highly specialized cells in the body, lose their ability to divide and reproduce once development of the nervous system is complete. More important, there are no reserve or parent cells to direct their replacement. However, appropriate numbers of these cell types are generated in the embryo such that loss of a certain percentage of cells does not affect the total cell population. Although these cells never divide and are not replaced if lost, they exist in sufficient numbers to carry out their specific functions. In other, less specialized tissues, such as the skin and mucosal lining, cell renewal continues throughout life.

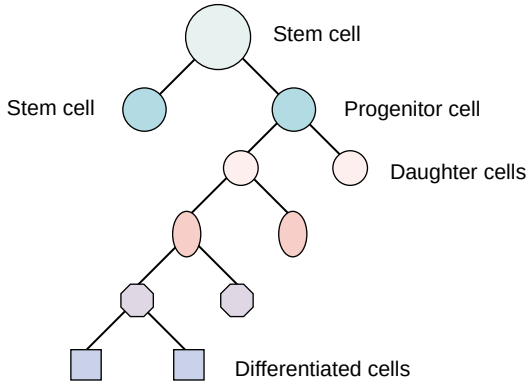
Even in the continuously renewing cell populations, highly specialized cells are similarly unable to divide. An alternative mechanism provides for their replacement. There are progenitor cells of the same lineage that have not yet differentiated to the extent that they have lost their ability to divide. These cells are sufficiently differentiated that their daughter cells are limited to the same cell line, but they are insufficiently differentiated to preclude the potential for active proliferation. As a result, these parent or progenitor cells are able to provide large numbers of replacement cells. However, the progenitor cells have limited capacity for self-renewal and they become restricted to producing a single type of cell.

Another type of cell, called a *stem cell*, remains incompletely differentiated throughout life. Stem cells are reserve cells that remain quiescent until there is a need for cell replenishment, in which case they divide, thereby producing other stem cells and cells that can carry out the functions of the differentiated cell (Fig. 5-2). There are several types of stem cells, some of which include the muscle satellite cell, the epidermal stem cell, the spermatogonium, and the basal cell of the olfactory epithelium. These stem cells are unipotent in that they give rise to only one type of differentiated cell. Oligopotent stem cells can produce a small number of cells, and pluripotent stem cells, such as those involved in hematopoiesis, give rise to numerous cell types.[4] Stem cells are the primary cellular component of bone marrow transplantation, in which the stem cells in the transplanted marrow re-establish the recipient's blood production and immune system. Peripheral blood stem cell transplantation is a transplantation procedure that by-

KEY CONCEPTS

CELL PROLIFERATION AND GROWTH

- Tissue growth and repair involve cell proliferation and differentiation.
- Cell proliferation is the process whereby tissues acquire new or replacement cells through cell division.
- Cell differentiation is the orderly process in which proliferating cells are transformed into different and more specialized types. It determines the microscopic characteristics of the cell, how the cell functions, and how long it will live.
- Cells that are fully differentiated are no longer capable of cell division.



■ **FIGURE 5-2** ■ Mechanism of stem cell–mediated cell replacement. Division of a stem cell with an unlimited potential for proliferation results in one daughter cell, which retains the characteristics of a stem cell, and a second daughter cell, which differentiates into a progenitor or parent cell, with a limited potential for differentiation and proliferation. As the daughter cells of the progenitor cell proliferate, they become more differentiated, until reaching the stage where they are fully differentiated and no longer able to divide.

passes the need for bone marrow infusion by infusing stem cells that have been separated and removed from the donor blood.

In summary, the term *neoplasm* refers to an abnormal mass of tissue in which the growth exceeds and is uncoordinated with that of the normal tissues. Unlike normal cellular adaptive processes such as hypertrophy and hyperplasia, neoplasms do not obey the laws of normal cell growth. They serve no useful purpose, they do not occur in response to an appropriate stimulus, and they continue to grow at the expense of the host.

Cell proliferation is the process whereby cells divide and bear offspring; it normally is regulated so that the number of cells that are actively dividing is equal to the number dying or being shed. The process of cell growth and division is called the *cell cycle.* It is divided into four phases: G_1, the postmitotic phase, during which DNA synthesis ceases while RNA and protein synthesis and cell growth take place; S, the phase during which DNA synthesis occurs, giving rise to two separate sets of chromosomes; G_2, the premitotic phase, during which RNA and protein synthesis continues; and M, the phase of cell mitosis or cell division. The G_0 phase is a resting or quiescent phase in which nondividing cells reside.

Cell differentiation is the process whereby cells are transformed into different and more specialized cell types as they proliferate. It determines the structure, function, and life span of a cell. There are three types of cells: well-differentiated cells that are no longer able to divide, progenitor or parent cells that continue to divide and bear offspring, and undifferentiated stem cells that can be recruited to become progenitor cells when the need arises. As a cell line becomes more differentiated, it becomes more highly specialized in its function and less able to divide.

CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS

Neoplasms are composed of two types of tissue: parenchymal tissue and the stroma or supporting tissue. The *parenchymal cells* represent the functional components of an organ. The *supporting tissue* consists of the connective tissue, blood vessels, and lymph structure. The parenchymal cells of a tumor determine its behavior and are the component for which a tumor is named. The supporting tissue carries the blood vessels and provides support for tumor survival and growth.

Terminology

By definition, a *tumor* is a swelling that can be caused by a number of conditions, including inflammation and trauma. Although they are not synonymous, the terms *tumor* and *neoplasm* often are used interchangeably. Neoplasms usually are classified as benign or malignant. Neoplasms that contain well-differentiated cells that are clustered together in a single mass are considered to be *benign.* These tumors usually do not cause death unless their location or size interferes with vital functions. In contrast, malignant neoplasms are less well differentiated and have the ability to break loose, enter the circulatory or lymphatic systems, and form secondary malignant tumors at other sites. *Malignant neoplasms* usually cause suffering and death if untreated or uncontrolled.

Tumors usually are named by adding the suffix *-oma* to the parenchymal tissue type from which the growth originated. Thus, a benign tumor of glandular epithelial tissue is called an *adenoma,* and a benign tumor of bone tissue is called an *osteoma.* The term *carcinoma* is used to designate a malignant tumor of epithelial tissue origin. In the case of a malignant adenoma, the term *adenocarcinoma* is used. Malignant tumors of mesenchymal origin are called *sarcomas* (*e.g.*, osteosarcoma). *Papillomas* are benign microscopic or macroscopic fingerlike projections that grow on any surface. A *polyp* is a growth that projects from a mucosal surface, such as the intestine. Although the term usually implies a benign neoplasm, some malignant tumors also appear as polyps.[3] *Oncology* is the study of tumors and their treatment. Table 5-1 lists the names of selected benign and malignant tumors according to tissue types.

Benign and malignant neoplasms usually are differentiated by their (1) cell characteristics, (2) manner of growth, (3) rate of growth, (4) potential for metastasizing or spreading to other parts of the body, (5) ability to produce generalized effects, (6) tendency to cause tissue destruction, and (7) capacity to cause death. The characteristics of benign and malignant neoplasms are summarized in Table 5-2.

Benign Neoplasms

Benign tumors are characterized by a slow, progressive rate of growth that may come to a standstill or regress, an expansive manner of growth, the presence of a well-defined fibrous capsule, and failure to metastasize to distant sites. Benign tumors are composed of well-differentiated cells that resemble the cells of the tissue of origin. For example, the cells of a uterine

TABLE 5-1 Names of Selected Benign and Malignant Tumors According to Tissue Types

Tissue Type	Benign Tumors	Malignant Tumors
Epithelial		
Surface	Papilloma	Squamous cell carcinoma
Glandular	Adenoma	Adenocarcinoma
Connective		
Fibrous	Fibroma	Fibrosarcoma
Adipose	Lipoma	Liposarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Blood vessels	Hemangioma	Hemangiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Lymph tissue		Lymphosarcoma
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Neural Tissue		
Nerve cell	Neuroma	Neuroblastoma
Glial tissue	Glioma (benign)	Glioblastoma, astrocytoma, medulloblastoma, oligodendroglioma
Nerve sheaths	Neurilemmoma	Neurilemmal sarcoma
Meninges	Meningioma	Meningeal sarcoma
Hematologic		
Granulocytic		Myelocytic leukemia
Erythrocytic		Erythrocytic leukemia
Plasma cells		Multiple myeloma
Lymphocytic		Lymphocytic leukemia or lymphoma
Monocytic		Monocytic leukemia
Endothelial Tissue		
Blood vessels	Hemangioma	Hemangiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma

TABLE 5-2 Characteristics of Benign and Malignant Neoplasms

Characteristics	Benign	Malignant
Cell characteristics	Well-differentiated cells that resemble normal cells of the tissue from which the tumor originated	Cells are undifferentiated and often bear little resemblance to the normal cells of the tissue from which they arose
Mode of growth	Tumor grows by expansion and does not infiltrate the surrounding tissues; usually encapsulated	Grows at the periphery and sends out processes that infiltrate and destroy the surrounding tissues
Rate of growth	Rate of growth usually is slow	Rate of growth is variable and depends on level of differentiation; the more anaplastic the tumor, the more rapid the rate of growth
Metastasis	Does not spread by metastasis	Gains access to the blood and lymph channels and metastasizes to other areas of the body
General effects	Usually is a localized phenomenon that does not cause generalized effects unless its location interferes with vital functions	Often causes generalized effects such as anemia, weakness, and weight loss
Tissue destruction	Usually does not cause tissue damage unless its location interferes with blood flow	Often causes extensive tissue damage as the tumor outgrows its blood supply or encroaches on blood flow to the area; also may produce substances that cause cell damage
Ability to cause death	Usually does not cause death unless its location interferes with vital functions	Usually causes death unless growth can be controlled

leiomyoma resemble uterine smooth muscle cells. For unknown reasons, benign tumors seem to have lost the ability to suppress the genetic program for cell replication but retain the program for normal cell differentiation. Benign tumors grow by expansion and are enclosed in a fibrous capsule. This is in sharp contrast to malignant neoplasms, which grow by infiltrating the surrounding tissue (Fig. 5-3). The capsule is responsible for a sharp line of demarcation between the benign tumor and the adjacent tissues, a factor that facilitates surgical removal. The formation of the capsule is thought to represent the reaction of the surrounding tissues to the tumor.[6]

Benign tumors do not undergo degenerative changes as readily as malignant tumors, and they usually do not cause death unless they interfere with vital functions because of their location. For instance, a benign tumor growing in the cranial cavity can eventually cause death by compressing brain structures. Benign tumors also can cause disturbances in the function of adjacent or distant structures by producing pressure on tissues, blood vessels, or nerves. Some benign tumors are also known for their ability to cause alterations in body function through abnormal elaboration of hormones.

KEY CONCEPTS

BENIGN AND MALIGNANT NEOPLASMS

- A tumor is a new growth or neoplasm.
- Benign neoplasms are well-differentiated tumors that resemble the tissues of origin but have lost the ability to control cell proliferation. They grow by expansion, are enclosed in a fibrous capsule, and do not cause death unless their location is such that it interrupts vital body functions.
- Malignant neoplasms are less well-differentiated tumors that have lost the ability to control both cell proliferation and differentiation. They grow in a crablike manner to invade surrounding tissues, have cells that break loose and travel to distant sites to form metastases, and inevitably cause suffering and death unless their growth can be controlled through treatment.

■ **FIGURE 5-3** ■ Photographs of a benign encapsulated fibroadenoma of the breast (**top**) and a bronchogenic carcinoma of the lung (**bottom**). The fibroadenoma has sharply defined edges, but the bronchogenic carcinoma is diffuse and infiltrates the surrounding tissues.

Malignant Neoplasms

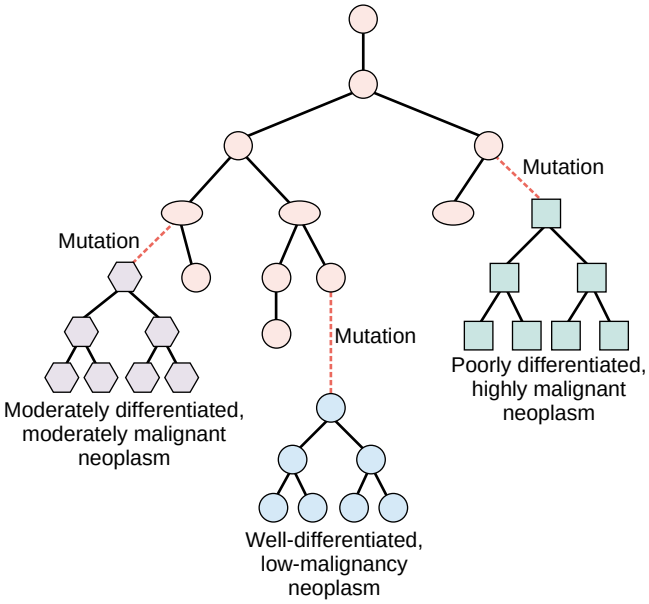
Malignant neoplasms tend to grow rapidly, spread widely, and kill regardless of their original location. Because of their rapid rate of growth, malignant tumors tend to compress blood vessels and outgrow their blood supply, causing ischemia and tissue necrosis; rob normal tissues of essential nutrients; and liberate enzymes and toxins that destroy tumor tissue and normal tissue. The destructive nature of malignant tumors is related to their lack of cell differentiation, cell characteristics, rate of growth, and ability to spread and metastasize.

There are two categories of cancer—solid tumors and hematologic cancers. Solid tumors initially are confined to a specific tissue or organ. As the growth of a solid tumor progresses, cells are shed from the original tumor mass and travel through the blood and lymph system to produce metastasis in distant sites. Hematologic cancers involve the blood-forming cells that naturally migrate to the blood and lymph systems, thereby making them disseminated diseases from the beginning.

Cancer Cell Characteristics

Cancer cells, unlike normal cells, fail to undergo normal cell proliferation and differentiation. It is thought that cancer cells develop from mutations that occur during the differentiation process (Fig. 5-4). When the mutation occurs early in the process, the resulting tumor is poorly differentiated and highly malignant; when it occurs later in the process, better differentiated and less malignant tumors result.

The term *anaplasia* is used to describe the lack of cell differentiation in cancerous tissue. Undifferentiated cancer cells are altered in appearance and nuclear size and shape from the cells in the tissue from which the cancer originated. In descending the scale of differentiation, enzymes and specialized pathways of metabolism are lost and cells undergo functional simplification.[3] Highly anaplastic cancer cells, whatever their tissue of origin, begin to resemble each other more than they do their tissue of origin. For example, when examined under the



■ **FIGURE 5-4** ■ Mutation of a cell line. Generally, mutations that occur early in the differentiation process result in poorly differentiated neoplasms and those that appear late in the differentiation process result in relatively well-differentiated neoplasms.

microscope, cancerous tissue that originates in the liver does not have the appearance of normal liver tissue. Some cancers display only slight anaplasia, and others display marked anaplasia.

Because cancer cells lack differentiation, they do not function properly, nor do they die in the time frame of normal cells. For example, in some types of leukemia the lymphocytes do not follow the normal developmental process. They do not differentiate fully, acquire the ability to destroy bacteria, or die on schedule. Instead, these long-lived, defective cells continue to grow, crowding the normal developing blood cells, thereby affecting the development of other cell lineages, such as the erythrocytes, platelets, and other white blood cells. This results in reduced numbers of mature, effectively functioning cells, producing white blood cells that cannot effectively fight infection, erythrocytes that cannot effectively transport oxygen to tissues, or platelets that cannot participate in the clotting system.

Alterations in cell differentiation also are accompanied by changes in cell characteristics and cell function that distinguish cancer cells from their fully differentiated normal counterparts. These changes include (1) alterations in contact inhibition, (2) loss of cohesiveness and adhesion, (3) impaired cell-to-cell communication, (4) expression of altered tissue antigens, and (5) elaboration of degradative enzymes that participate in invasion and metastatic spread.

Contact inhibition is the cessation of growth after a cell comes in contact with another cell. Contact inhibition usually switches off cell growth by blocking the synthesis of DNA, RNA, and protein. In wound healing, contact inhibition causes fibrous tissue growth to cease at the point where the edges of the wound come together. However, cancer cells tend to grow rampantly without regard for other tissue. The reduced tendency of cancer cells to stick together (*i.e., cohesiveness* and *adhesiveness*) permits shedding of the tumor's surface cells; these cells appear in the surrounding body fluids or secretions and can often be detected using the *Papanicolaou* (Pap) test.

Chemical messengers carry out cell-to-cell communication. These messengers bind to specific cell surface receptors and serve to control cell growth and modulate cell behavior. Impaired cell-to-cell communication may interfere with the formation of intercellular connections and responsiveness to membrane-derived signals.

Cancer cells express a number of cell surface molecules or antigens that are immunologically identified as foreign. These *tissue antigens* are coded by the genes of a cell. Many transformed cancer cells revert to earlier stages of gene expression and produce antigens that are immunologically distinct from the antigens that are expressed by cells of the well-differentiated tissue from which the cancer originated. Some cancers express fetal antigens that are not produced by comparable cells in the adult. Tumor antigens may be used clinically as markers to indicate the presence or progressive growth of a cancer.

Most cancers synthesize and secrete enzymes (*i.e.*, proteases and glycosidases) that break down proteins involved in ensuring intracellular organization and cell-to-cell cohesion. The degradation of the extracellular matrix by these enzymes facilitates invasiveness of the tumor. The production of degradative enzymes, such as fibrinolysins, contributes to the breakdown of the intercellular matrix, which leads to changes in the organization of the cell's cytoskeleton and affects cell-to-cell adhesion, cellular migration, and cellular communication. Cancers of nonendocrine tissues may assume hormone synthesis to produce so-called *ectopic hormones* (discussed with paraneoplastic syndromes in the section on general effects).

Invasion and Metastasis

Unlike benign tumors, which grow by expansion and usually are surrounded by a capsule, malignant tumors grow by extensive infiltration and invasion of the surrounding tissues. The word *cancer* is derived from the Latin word meaning *crablike* because cancerous growth spreads by sending crablike projections into the surrounding tissues. The lack of a sharp line of demarcation separating them from the surrounding tissue makes the complete surgical removal of malignant tumors more difficult than removal of benign tumors. *Seeding* of cancer cells into body cavities occurs when a tumor erodes into these spaces. Most often, the peritoneal cavity is involved, but other spaces such as the pleural cavity, pericardial cavity, and joint spaces may be involved. Seeding into the peritoneal cavity is particularly common with ovarian cancers.

The term *metastasis* is used to describe the development of a secondary tumor in a location distant from the primary tumor. Metastatic tumors retain many of the characteristics of the primary tumor from which they were derived. Because of this, it usually is possible to determine the site of the primary tumor from the cellular characteristics of the metastatic tumor. Some tumors tend to metastasize early in their developmental course, but others do not metastasize until later. Occasionally, the metastatic tumor is far advanced before the primary tumor becomes clinically detectable. For example, malignant tumors of the kidney may go undetected and be asymptomatic, even when a metastatic lesion is found in the lung.

Metastasis occurs by way of the lymph channels (*i.e.*, lymphatic spread) and the blood vessels (*i.e.*, hematogenic spread).[3,7] In many types of cancer, the first evidence of disseminated disease is the presence of tumor cells in the lymph nodes that drain the tumor area. When metastasis occurs by way of the lymphatic channels, the tumor cells lodge first in the regional lymph nodes that received drainage from the tumor site. Once in the lymph node, the cells may die because of the lack of a proper environment, grow into a discernible mass, or remain dormant for unknown reasons. Because the lymphatic channels empty into the venous system, cancer cells that survive may eventually break loose and gain access to the venous system.

With hematologic spread, the blood-borne cancer cells typically follow the venous flow that drains the site of the neoplasm. Before entering the general circulation, venous blood from the gastrointestinal tract, pancreas, and spleen is routed through the portal vein to the liver. Thus, the liver is a common site for metastatic spread for cancers that originate in these organs. Although the site of hematologic spread is generally related to vascular drainage of the primary tumor, some tumors metastasize to distant and unrelated sites. One explanation is that cells of different tumors tend to metastasize to specific target organs that provide substances such as hormones or growth factors that are needed for their survival. For example, prostatic cancer preferentially spreads to bone, bronchiogenic cancer spreads to the adrenal glands and brain, and neuroblastoma spreads to the liver and bones.

The selective nature of hematologic spread indicates that metastasis is a finely orchestrated, multistep process, and only a small, select clone of cancer cells has the right combination of gene products to perform all of the steps needed for establishment of a secondary tumor. It has been estimated that fewer than 1 in 10,000 tumor cells that leave a primary tumor survives to start a secondary tumor.[8] To metastasize, a cancer cell must be able to break loose from the primary tumor, invade the surrounding extracellular matrix, gain access to a blood vessel, survive its passage in the bloodstream, emerge from the bloodstream at a favorable location, invade the surrounding tissue, and begin to grow (Fig. 5-5).

Considerable evidence suggests that cancer cells capable of metastasis secrete enzymes that break down the surrounding extracellular matrix, allowing them to move through the degraded matrix and gain access to a blood vessel. Once in the circulation, the tumor cells are vulnerable to destruction by host immune cells. Some tumor cells gain protection from the antitumor host cells by aggregating and adhering to circulating blood components, particularly platelets, to form tumor emboli. Tumor cells that survive their travel in the circulation must be able to halt their passage by adhering to the vessel wall. After that, they must be able to exit the vessel, move through the extracellular matrix of the target tissue, and subsequently establish growth of a secondary tumor.

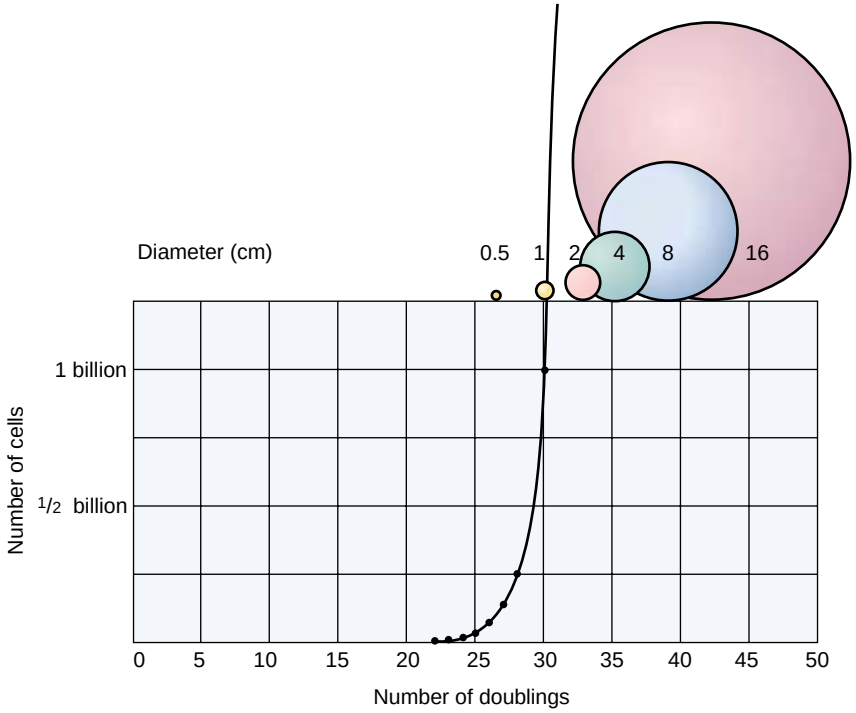
Once in the target tissue, the process of tumor development depends on the establishment of blood vessels and specific growth factors that promote proliferation of the tumor cells. Tumor cells secrete tumor angiogenesis factor, which enables the development of new blood vessels in the tumor.[7] The presence of stimulatory or inhibitor growth factors correlates with the site-specific pattern of metastasis. For example, a potent growth-stimulating factor has been isolated from lung tissue, and stromal cells in bone have been shown to produce a factor that stimulates growth of prostatic cancer cells.[7]

Tumor Growth

The rate of tissue growth in normal and cancerous tissue depends on three factors: (1) the number of cells that are actively dividing or moving through the cell cycle, (2) the duration of the cell cycle, and (3) the number of cells that are being lost compared with the number of new cells being produced. One of the reasons cancerous tumors often seem to grow so rapidly relates to the size of the cell pool that is actively engaged in cycling. It has been shown that the cell cycle time of cancerous tissue cells is not necessarily shorter than that of normal cells; rather, cancer cells do not die on schedule. Also, the growth factors that allow cells to enter the resting or G_0 phase when they are not needed for cell replacement are lacking. Thus, a greater percentage of cells are actively engaged in moving through the cell cycle than occurs in normal tissue.

The ratio of dividing cells to resting cells in a tissue mass is called the *growth fraction.* The doubling time is the length of time it takes for the total mass of cells in a tumor to double. As the growth fraction increases, the doubling time decreases. When normal tissues reach their adult size, an equilibrium between cell birth and cell death is reached. However, cancer cells continue to divide until limitations in blood supply and nutrients inhibit their growth. As this happens, the doubling time for cancer cells decreases. If tumor growth is plotted against time on a semilogarithmic scale, the initial growth rate is exponential and then tends to decrease or flatten with time. This characterization of tumor growth is called the *Gompertzian model.*[5]

A tumor usually is undetectable until it has doubled 30 times and contains more than 1 billion (10^9) cells. At this



■ **FIGURE 5-6** ■ Growth curve of a hypothetical tumor on arithmetic coordinates. Notice the number of doubling times before the tumor reaches an appreciable size. (Adapted from Collins V.P., et al. [1956]. Observations of growth rates of human tumors. *Am J Roent Rad Ther Nuclear Med* 76, 988.)

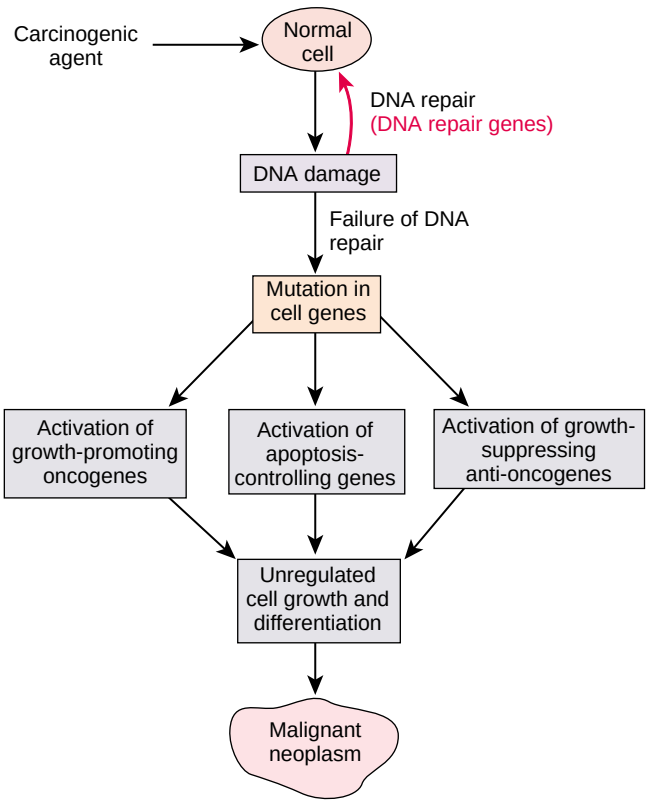
point, it is approximately 1 cm in size (Fig. 5-6). After 35 doublings, the mass contains more than 1 trillion (10^{12}) cells, which is a sufficient number to kill the host.

CARCINOGENESIS AND CAUSES OF CANCER

Carcinogenesis, or the development of cancer, is a multistep process that involves both the molecular aspects of cell transformation and the overall growth and spread of the tumor mass. Because cancer is not a single disease, it is reasonable to assume that it does not have a single cause. More likely, cancer occurs because of interactions between multiple risk factors or repeated exposure to a single carcinogenic (cancer-producing) agent. Among the risk factors that have been linked to cancer are heredity, chemical and environmental carcinogens, cancer-causing viruses, and immunologic defects.

Oncogenesis: The Molecular Basis of Cancer

The term *oncogenesis* refers to a genetic mechanism whereby normal cells are transformed into cancer cells. There are three kinds of genes that control cell growth and replication: *proto-oncogenes*, *anti-oncogenes*, and genes that control programmed cell death or *apoptosis*.[3] In addition to these three classes of genes, a fourth category of genes, those that regulate repair of damaged DNA, is implicated in the process of oncogenesis (Fig. 5-7). The DNA repair genes affect cell proliferation and survival indirectly through their ability to repair nonlethal damage in other genes, including proto-oncogenes, anti-oncogenes, and the genes that control apoptosis.[3] These

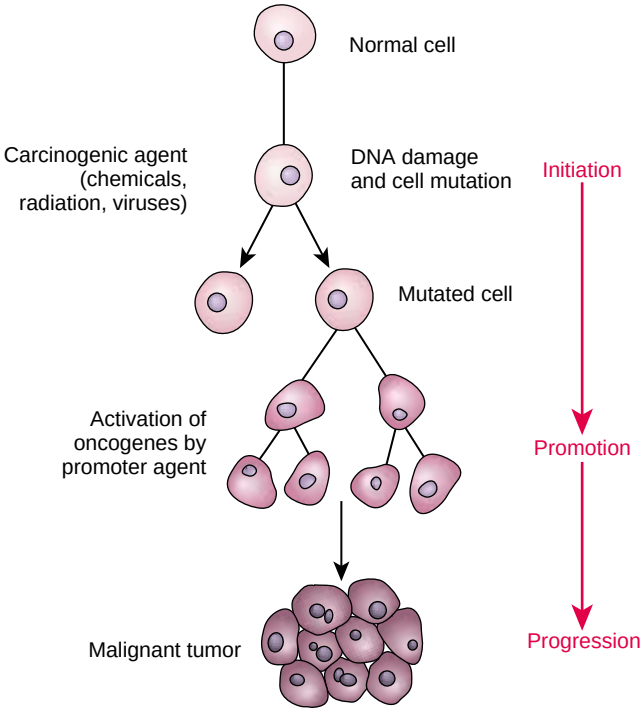


■ **FIGURE 5-7** ■ Flowchart depicting the stages in the development of a malignant neoplasm resulting from exposure to an oncogenic agent that produces DNA damage. When DNA repair genes are present (red arrow), the DNA is repaired and gene mutation does not occur.

genes have been implicated as the principal targets of genetic damage occurring during the development of cancer cells.[9,10] Such genetic damage may be acquired by the action of chemicals, radiation, or viruses, or it may be inherited in the germ line. Significantly, it appears that the acquisition of a single gene mutation is not sufficient to transform normal cells into cancer cells. Instead, cancerous transformation appears to require the activation of many independently mutated genes.

Proto-oncogenes have essential roles in regulating the growth and proliferation of normal cells. Proto-oncogene products may act as growth factors, as receptors for growth factors, or as second messengers that transmit growth factor signals. The involvement of these genes in the cancer process is attributable to a somatic mutation that takes place in a specific target tissue, converting its proto-oncogenes into oncogenes.

Cancer suppressor genes, or anti-oncogenes, inhibit the proliferation of cells in a tumor. When this type of gene is inactivated, a genetic signal that normally inhibits proliferation is removed, thereby causing the cell to begin unregulated growth. Several human tumor suppressor genes have been identified.[3] Of particular interest in this group is the p53 gene, located on the short arm of chromosome 17, that codes for a protein that is pivotal in growth regulation and functions as a suppressor of tumor growth. Mutation of the p53 gene has been implicated in the development of lung, breast, and colon cancer—the three leading causes of cancer death.[3] The p53 gene also appears to initiate apoptosis of radiation- and chemotherapy-damaged tumor cells. Thus, tumors that retain normal p53 function are more likely to respond to such therapy than are tumors that carry a defective p53 gene.[3]



■ **FIGURE 5-8** ■ The process of initiation, promotion, and progression in the clonal evolution of malignant tumors. Initiation involves the exposure of cells to appropriate doses of a carcinogenic agent; promotion, the unregulated and accelerated growth of the mutated cells; and progression, the acquisition of malignant characteristics by the tumor cells.

Tumor Cell Transformation

The transformation of normal cells to cancer cells by carcinogenic agents is a multistep process that can be divided into three stages: (1) initiation, (2) promotion, and (3) progression[3] (Fig. 5-8). *Initiation* involves the exposure of cells to appropriate doses of a carcinogenic agent that makes them susceptible to malignant transformation. The carcinogenic agents can be chemical, physical, or biologic, and produce irreversible changes in the genome of a previously normal cell. Because the effects of initiating agents are irreversible, multiple divided doses may achieve the same effects as single exposures of the same comparable dose or small amounts of highly carcinogenic substances. The most susceptible cells for mutagenic alterations in the genome are the cells that are actively synthesizing DNA.[11]

Promotion involves the induction of unregulated accelerated growth in already initiated cells by various chemicals and growth factors. Promotion is reversible if the promoter substance is removed. Cells that have been irreversibly initiated may be promoted even after long latency periods. The latency period varies with the type of agent, the dosage, and the characteristics of the target cells. Many chemical carcinogens are called *complete carcinogens* because they can initiate and promote neoplastic transformation. *Progression* is the process whereby tumor cells acquire malignant phenotypic changes that promote invasiveness, metastatic competence, a tendency for autonomous growth, and increased karyotypic instability.[11]

KEY CONCEPTS

ONCOGENESIS

- Normal cell growth is controlled by growth-promoting proto-oncogenes and growth-suppressing anti-oncogenes. Normally, cell growth is genetically controlled so that potentially malignant cells are targeted for elimination by tumor-suppressing genes.
- Oncogenesis is a genetic process whereby normal cells are transformed into cancer cells. It involves mutations in the normal growth-regulating genes.
- The transformation of normal cells into cancer cells is multifactorial, involving the inheritance of cancer susceptibility genes and environmental factors such as chemicals, radiation, and viruses.

Heredity

A hereditary predisposition has been observed in approximately 50 types of cancer. For example, breast cancer occurs more frequently in women whose grandmothers, mothers, aunts, and sisters also have experienced a breast malignancy.

The genetic predisposition for development of cancer has been documented for a number of cancerous and precancerous lesions that follow mendelian inheritance patterns. Cancer is found in approximately 10% of persons having one affected first-degree relative, in approximately 15% of persons having two affected family members, and in 30% of persons having three affected family members. The risk increases to approximately 50% in women 65 years of age who have multiple family members with breast cancer. Two oncogenes, called BRAC1 (breast carcinoma 1) and BRAC2 (breast carcinoma 2), have been implicated in a genetic susceptibility to breast cancer.[6]

Several cancers exhibit an autosomal dominant inheritance pattern. In approximately 40% of cases, retinoblastoma (a malignant eye tumor that occurs in children) is inherited as an autosomal dominant trait; the remaining cases are nonhereditary. The penetrance of the genetic trait is high; in carriers of the dominant retinoblastoma gene, the penetrance for this gene is 95% for at least one tumor, and the affected person may be unilaterally or bilaterally affected.[12] Familial adenomatous polyposis of the colon also follows an autosomal dominant inheritance pattern. In people who inherit this gene, hundreds of adenomatous polyps may develop, some of which inevitably become malignant.[3]

Carcinogenic Agents

A carcinogen is an agent capable of causing cancer. The role of environmental agents in causation of cancer was first noted in 1775 by Sir Percivall Pott, who related the high incidence of scrotal cancer in chimney sweeps to their exposure to coal soot.[13] In 1915, a group of Japanese investigators conducted the first experiments in which a chemical agent was used to produce cancer.[13] These investigators found that a cancerous growth developed when they painted a rabbit's ear with coal tar. Coal tar has since been found to contain potent polycyclic aromatic hydrocarbons. Since then, many carcinogenic agents have been identified (Chart 5-1).

Chemical Carcinogens

More than six million chemicals have been identified. It is estimated that less than 1000 of these have been extensively examined for their carcinogenic potential.[14] Some have been found to cause cancers in animals, and others are known to cause cancers in humans. These agents include both natural (*e.g.*, aflatoxin B_1) and artificial products (*e.g.*, vinyl chloride).

Chemical carcinogens can be divided into two groups: direct-reacting agents, which do not require activation in the body to become carcinogenic, and indirect-reacting agents, called *procarcinogens* or *initiators*, which become active only after metabolic conversion. Direct- and indirect-acting initiators form highly reactive species (*i.e.*, electrophiles and free radicals) that bind with the nucleophilic residues on DNA, RNA, or cellular proteins. The action of these reactive species tends to cause cell mutation or alteration in synthesis of cell enzymes and structural proteins in a manner that alters cell replication and interferes with cell regulatory controls. The carcinogenicity of some chemicals, called *promoters*, is augmented by agents that by themselves have little or no cancer-causing ability. It is believed that promoters exert their effect by changing the expression of genetic material in a cell, increasing DNA synthesis, enhancing gene amplification (*i.e.*, number of gene copies that are made), and altering intercellular communication.

CHART 5-1 Chemical and Environmental Agents Known to be Carcinogenic in Humans

Polycyclic Hydrocarbons

Soots, tars, and oils
Cigarette smoke

Industrial Agents

Aniline and azo dyes
Arsenic compounds
Asbestos
β-Naphthylamine
Benzene
Benzo[*a*]pyrene
Carbon tetrachloride
Insecticides, fungicides
Nickel and chromium compounds
Polychlorinated biphenyls
Vinyl chloride

Food and Drugs

Smoked foods
Nitrosamines
Aflatoxin B_1
Diethylstilbestrol
Anticancer drugs (*e.g.*, alkylating agents, cyclophosphamide, chlorambucil, nitrosourea)

The exposure to many chemical carcinogens is associated with lifestyle risk factors, such as smoking, dietary factors, and alcohol consumption. Cigarette smoke contains both procarcinogens and promoters. It is directly associated with lung and laryngeal cancer[15] and has been linked with cancers of the esophagus, pancreas, kidney, uterine cervix, and bladder. Chewing tobacco or tobacco products increases the risk of cancers of the oral cavity and esophagus. It has been estimated that 30% of current cancer deaths in the United States are related to tobacco. Not only is the smoker at risk, but others passively exposed to cigarette smoke are at risk. Environmental tobacco smoke has been classified as a "group A" carcinogen based on the U.S. Environmental Protection Agency's system of carcinogen classification. It also is estimated that between 20% and 60% of the deaths that occur each year from nonsmoking-related lung cancers may be caused by environmental tobacco smoke.[16]

There is strong evidence that certain elements in the diet contain chemicals that contribute to cancer risk. For example, benzo[a]pyrene and other polycyclic hydrocarbons are converted to carcinogens when foods are fried in fat that has been reused multiple times. Nitrosamines, which are powerful carcinogens, may be formed from nitrites that are derived from nitrates added to vegetables and foods as a preservative. Among the most potent of the procarcinogens are the polycyclic hydrocarbons. The polycyclic hydrocarbons are of particular interest because they are produced in the combustion of tobacco and

are present in cigarette smoke. They also are produced from animal fat in the process of broiling meats and are present in smoked meats and fish. Formation of these nitrosamines may be inhibited by the presence of antioxidants such as vitamin C in the stomach. Cancer of the colon has been associated with high dietary intake of fat, protein, and beef and low intake of dietary fiber. The carcinogenic factors associated with a high-fat diet have yet to be confirmed. However, some studies have shown a relationship between high levels of fecally excreted bile acids and colon cancer. A high-fat diet increases the flow of primary bile acids. These acids are converted to secondary bile acids in the presence of anaerobic bacteria in the colon. These acids are thought to be tumor promoters, rather than initiators.[7]

Alcohol modifies the metabolism of carcinogens in the liver and esophagus.[17] It is believed to influence the transport of carcinogens, increasing the contact between an externally induced carcinogen and the stem cells that line the upper oral cavity and esophagus. The carcinogenic effect of cigarette smoke can be enhanced by concomitant consumption of alcohol; persons who smoke and drink considerable amounts of alcohol are at increased risk for the development of cancer of the oral cavity and esophagus.

The effects of carcinogenic agents usually are dose dependent—the larger the dose or the longer the duration of exposure, the greater the risk that cancer will develop. Some chemical carcinogens may act in concert with other carcinogenic influences, such as viruses or radiation, to induce neoplasia. There usually is a time delay ranging from 5 to 30 years from the time of chemical carcinogen exposure to the development of overt cancer. This is unfortunate because many people may have been exposed to the agent and its carcinogenic effects before the association was recognized. This occurred with the use of diethylstilbestrol, which was widely used in the United States from the mid-1940s to 1970 to prevent miscarriages. But it was not until the late 1960s that many cases of vaginal adenosis and adenocarcinoma in young women were found to be the result of their exposure in utero to diethylstilbestrol.[18]

Radiation Oncogenesis

The effects of *ionizing radiation* in carcinogenesis have been well documented in atomic bomb survivors, in patients diagnostically exposed, and in industrial workers, scientists, and physicians who were exposed during employment. Malignant epitheliomas of the skin and leukemia were significantly elevated in these populations.[6] Between 1950 and 1970, the death rate from leukemia alone in the most heavily exposed population groups of the atomic bomb survivors in Hiroshima and Nagasaki was 147 per 100,000 persons, 30 times the expected rate.[19]

The type of cancer that developed depended on the dose of radiation, the gender of the person, and the age at which exposure occurred. For instance, approximately 25 to 30 years after total body or trunk irradiation, there were increased incidences of leukemia and cancers of the breast, lung, stomach, thyroid, salivary gland, gastrointestinal system, and lymphoid tissues. The length of time between exposure and the onset of cancer is related to the age of the individual. For example, children exposed to ionizing radiation in utero have an increased risk for developing leukemias and childhood tumors, particularly 2 to 3 years after birth. This latency period for leukemia extends to 5 to 10 years if the child was exposed after birth and to 20 years for certain solid tumors.[6] As another example, the latency period for the development of thyroid cancer in infants and small children who received radiation to the head and neck to decrease the size of the tonsils or thymus was as long as 35 years after exposure.

The association between sunlight and the development of skin cancer has been reported for more than 100 years. *Ultraviolet radiation* emits relatively low-energy rays that do not deeply penetrate the skin (see Chapter 44). As with other carcinogens, the effects of ultraviolet radiation usually are additive, and there usually is a long delay between the time of exposure and the time that cancer can be detected.

Oncogenic Viruses

An oncogenic virus is one that can induce cancer. Viruses, which are small particles containing genetic (DNA or RNA) material, enter a host cell and become incorporated into its chromosomal DNA or take control of the cell's machinery for the purpose of producing viral proteins. A large number of DNA and RNA viruses (*i.e.*, retroviruses) have been shown to be oncogenic in animals. However, only a few viruses have been linked to cancer in humans.[3] Among the recognized oncogenic viruses in humans are the human papilloma virus (HPV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), and human T-cell leukemia virus-1 (HTLV-1).[6] Herpes simplex type 2 also has been associated with cervical cancer, but the evidence supporting its role as a carcinogenic influence is less clear.

Three DNA viruses have been implicated in human cancers: HPV, EBV, and HBV. The transforming DNA viruses form stable associations with the human genome using genes that allow them to complete their replication cycle and be expressed in transformed cells. There is strong evidence to suggest that the DNA viruses act in concert with other factors to cause cancer.

There are more than 60 genetically different types of HPV. Some types (*i.e.*, types 1, 2, 4, 7) have been shown to cause benign squamous papillomas (*i.e.*, warts). HPVs also have been implicated in squamous cell carcinoma of the cervix and anogenital region. HPV types 16 and 18 and, less commonly, types 31, 33, 35, and 51, have been found in approximately 85% of squamous cell carcinomas of the cervix and presumed precursors (*i.e.*, severe cervical dysplasia and carcinoma in situ).[3]

EBV is a member of the herpesvirus family. It has been implicated in the pathogenesis of four human cancers: Burkitt's lymphoma, nasopharyngeal cancer, B-cell lymphomas in immunosuppressed individuals such as those with acquired immunodeficiency syndrome (AIDS), and in some cases of Hodgkin's lymphoma. Burkitt's lymphoma, a tumor of B lymphocytes, is endemic in parts of East Africa and occurs sporadically in other areas worldwide. In persons with normal immune function, the EBV-driven, B-cell proliferation is readily controlled, and the person becomes asymptomatic or experiences a self-limited episode of infectious mononucleosis (see Chapter 11). In regions of the world where Burkitt's lymphoma is endemic, concurrent malaria or other infections cause impaired immune function, allowing sustained B-lymphocyte proliferation. The incidence of nasopharyngeal cancer is high in some areas of China, particularly southern China, and in the Cantonese population in Singapore.

HBV is the etiologic agent in the development of hepatitis B, cirrhosis, and hepatocellular carcinoma. There is a significant correlation between elevated rates of hepatocellular carcinoma worldwide and the prevalence of HBV carriers. Other etiologic factors also may contribute to the development of liver cancer. Ingestion of aflatoxin and infection with HCV, the hepatitis C virus, have been implicated. The precise mechanism by which HBV induces hepatocellular cancer has not been determined, although it has been suggested that it may be the result of prolonged HBV-induced liver damage and regeneration.

HTLV-1, a retrovirus, is associated with a form of T-cell leukemia that is endemic in certain parts of Japan and some areas of the Caribbean and Africa and is found sporadically elsewhere, including the United States and Europe.[3] Similar to the AIDS virus, HTLV-1 is attracted to the $CD4^+$ T cells, and this subset of T cells is therefore the major target for cancerous transformation. The virus requires transmission of infected T cells by way of sexual intercourse, infected blood, or breast milk. A second type of HTLV virus, HTLV-2, has been isolated from individuals with an unusual form of hairy cell leukemia. Hairy cell leukemia is usually the result of an alteration in the B-lymphocyte lineage. However, the HTLV-2 variant involves the T-lymphocyte lineage.[20]

Immunologic Defects

There is growing evidence for the immune system's participation in resistance against the progression and spread of cancer. The central concept, known as the *immune surveillance hypothesis,* which was first proposed by Paul Ehrlich in 1909, postulates that the immune system plays a central role in resistance against the development of tumors.[21] In addition to cancer–host interactions as a mechanism of cancer development, immunologic mechanisms provide a means for the detection, classification, and prognostic evaluation of cancers and as a potential method of treatment. *Immunotherapy* (discussed later in this chapter) is a cancer treatment modality designed to heighten the patient's general immune responses to increase tumor destruction.

It has been suggested that the development of cancer might be associated with impairment or decline in the surveillance capacity of the immune system. For example, increases in cancer incidence have been observed in people with immunodeficiency diseases and in those with organ transplants who are receiving immunosuppressant drugs. The incidence of cancer also is increased in the elderly, in whom there is a known decrease in immune activity. The association of Kaposi's sarcoma with AIDS further emphasizes the role of the immune system in preventing malignant cell proliferation.[13]

It has been shown that most tumor cells have molecular configurations that can be specifically recognized by immune T cells or by antibodies and thus are termed tumor antigens. The most relevant tumor antigens fall into two categories: unique tumor-specific antigens found only on tumor cells, and tumor-associated antigens found on tumor cells and on normal cells. Quantitative and qualitative differences permit the use of these tumor-associated antigens to distinguish cancer cells from normal cells.[22]

Virtually all of the components of the immune system have the potential for eradicating cancer cells, including T lymphocytes, B lymphocytes, antibodies, macrophages, and natural killer (NK) cells (see Chapter 9). The T-cell response is undoubtedly one of the most important host responses for controlling the growth of antigenic tumor cells; it is responsible for the direct killing of tumor cells and for activation of other components of the immune system. The T-cell response to cancer cells reflects the function of two subsets of T cells: the $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells. The finding of tumor-reactive antibodies in the serum of people with cancer supports the role of the B cell as a member of the immune surveillance team. Antibodies can destroy cancer cells through complement-mediated mechanisms or through antibody-dependent cellular cytotoxicity, in which the antibody binds the cancer cell to another effector cell, such as the NK cell, that does the actual killing of the cancer cell. NK cells do not require antigen recognition and can lyse a wide variety of target cells. The cytotoxic activity of NK cells can be augmented by the lymphokines, IL-2, and interferon, and NK activity can be amplified by immune T-cell responses.[23] Macrophages are important in tumor immunity as antigen-presenting cells to initiate the immune response and as potential effector cells to participate in tumor cell lysis.

In summary, neoplasms may be benign or malignant. Benign and malignant tumors differ in terms of cell characteristics, manner of growth, rate of growth, potential for metastasis, ability to produce generalized effects, tendency to cause tissue destruction, and capacity to cause death. The growth of a benign tumor is restricted to the site of origin, and the tumor usually does not cause death unless it interferes with vital functions. However, cancers or malignant neoplasms grow wildly and without organization, spread to distant parts of the body, and cause death unless their growth is inhibited or stopped by treatment.

There are two types of cancer: solid tumors and hematologic tumors. Solid tumors initially are confined to a specific organ or tissue, but hematologic cancers are disseminated from the onset. Cancer is a disorder of cell proliferation and differentiation. Cancer cells often are poorly differentiated compared with normal cells, and they display abnormal membrane characteristics, have abnormal antigens, produce abnormal biochemical products, and have abnormal karyotypes. All cancers result from nonlethal genetic changes that transform a normal cell into a cancer cell. The spread of cancer occurs through three pathways: direct invasion and extension, seeding of cancer cells in body cavities, and metastatic spread through vascular or lymphatic pathways. Only a proportionately small clone of cancer cells is capable of metastasis. To metastasize, a cancer cell must be able to break loose from the primary tumor, invade the surrounding extracellular matrix, gain access to a blood vessel, survive its passage in the bloodstream, emerge from the bloodstream at a favorable location, invade the surrounding tissue, and begin to grow.

Because cancer is not a single disease, it is reasonable to assume that it does not have a single cause. Multiple factors probably interact at the genetic level to transform normal cells into cancer cells. This transformation process is called *oncogenesis.* Four kinds of genes control normal cell growth and replication: growth-promoting regulatory genes (*i.e.,* proto-oncogenes) and growth-inhibiting regulatory

genes (*i.e.*, anti-oncogenes), genes that control apoptosis, and gene-repair genes. These genes are implicated as principal targets of the genetic damage that occurs during the development of a cancer cell. Such genetic damage may be acquired by the action of chemicals (*i.e.*, chemical carcinogens), radiation, or viruses, or it may be inherited in the cell line.

CLINICAL FEATURES

There probably is no single body function left unaffected by the presence of cancer (Table 5-3). Because tumor cells replace normally functioning parenchymal tissue, the initial manifestations of cancer usually reflect the primary site of involvement. For example, cancer of the lung initially produces impairment of respiratory function; as the tumor grows and metastasizes, other body structures become affected.

Cancer disrupts tissue integrity. As cancers grow, they compress and erode blood vessels, causing ulceration and necrosis along with frank bleeding and sometimes hemorrhage. One of the early warning signals of colorectal cancer is blood in the stool. Cancer cells also may produce enzymes and metabolic toxins that are destructive to the surrounding tissues. Usually, tissue damaged by cancerous growth does not heal normally. Instead, the damaged area persists and often continues to grow; a sore that does not heal is another warning signal of cancer. Cancer has no regard for normal anatomic boundaries; as it grows, it invades and compresses adjacent structures. For example, abdominal cancer often compresses the viscera and causes bowel obstruction. Cancer may obstruct lymph flow and penetrate serous cavities, causing pleural effusion and ascites. In its late stages, cancer often causes pain (see Chapter 39). Pain is probably one of the most dreaded aspects of cancer, and pain management is one of the major treatment concerns for persons with incurable cancers.

Abnormalities in energy, carbohydrate, lipid, and protein regulation are common manifestations during progressive tumor growth. Many cancers are associated with weight loss and wasting of body fat and lean protein, a condition called *cancer cachexia*. Although anorexia, reduced food intake, and abnormalities of taste are common in people with cancer and often are accentuated by treatment methods, the extent of weight loss and protein wasting cannot be explained in terms of diminished food intake alone. There also is a disparity between the size of the tumor and the severity of cachexia, which supports the existence of other mediators in the development of cachexia. Cachexia is thought to be the result of tumor-derived or host-derived factors that cause anorexia directly by acting on satiety centers in the hypothalamus or indirectly by injuring tissues that subsequently release anorexigenic substances.

Cachectin was the first identified cytokine associated with wasting. Cachectin was later found to be identical to tumor necrosis factor (TNF), a cytokine secreted primarily from macrophages in response to tumor cell growth or gram-negative bacterial infections.[24] TNF causes anorexia by suppressing satiety centers and by suppressing the synthesis of lipoprotein lipase, an enzyme that facilitates the release of fatty acids from lipoproteins so they can be used by tissues. TNF is an endogenous pyrogen that induces fever by its actions on cells in the hypothalamic regulatory regions of the brain. TNF also induces a number of inflammatory responses, activates the coagulation system, suppresses bone marrow stem cell division, acts on hepatocytes to increase the synthesis of specific serum proteins in response to inflammatory stimuli, and mediates endotoxic shock secondary to trauma, burns, and sepsis.[25] The role of TNF and its full impact on cancer cachexia are uncertain. It has been suggested by some that the cytokine may be an endogenous antineoplastic agent. Interleukin (IL)-1, another cytokine secreted from macrophages, shares with TNF the ability to initiate cachexia.

TABLE 5-3 General Effects on Body Function Associated With Cancer Growth

Overall Effect	Related Tumor Action
Altered function of the involved tissue	Destruction and replacement of parenchymal tissue by neoplastic growth
Bleeding and hemorrhage	Compression of blood vessels, with ischemia and necrosis of tissue; or tumor may outgrow its blood supply
Ulceration, necrosis, and infection of tumor area	Ischemia associated with rapid growth, with subsequent bacterial invasion
Obstruction of hollow viscera or communication pathways	Expansive growth of tumor with compression and invasion of tissues
Effusion in serous cavities	Impaired lymph flow from the serous cavity or erosion of tumor into the cavity
Increased risk of vascular thrombosis	Abnormal production of coagulation factors by the tumor, obstruction of venous channels, and immobility
Anemia	Bleeding and depression of red blood cell production
Bone destruction	Metastatic invasion of bony structures
Hypercalcemia	Destruction of bone due to metastasis or production by the tumor of parathyroid-like hormone
Pain	Liberation of pain mediators by the tumor, compression, or ischemia of structures
Cachexia, weakness, wasting of tissues	Catabolic effect of the tumor on body metabolism along with selective trapping of nutrients by rapidly growing tumor cells
Inappropriate hormone production (*e.g.*, ADH or ACTH secretion by cancers such as bronchogenic carcinoma)	Production by the tumor of hormones or hormone-like substances that are not regulated by normal feedback mechanisms

In addition to signs and symptoms at the sites of primary and metastatic disease, cancer can produce manifestations in sites that are not directly affected by the disease. Such manifestations are collectively referred to as *paraneoplastic syndromes.* Some of these manifestations are caused by the elaboration of hormones by cancer cells, and others result from the production of circulating factors that produce nonmetastatic hematopoietic, neurologic, and dermatologic syndromes. For example, cancers may produce procoagulation factors that contribute to an increased risk of venous thrombosis. It is estimated that approximately 10% of persons with cancer are affected by these syndromes.[3] The three most common endocrine syndromes associated with cancer are the syndrome of inappropriate antidiuretic hormone secretion (see Chapter 6), Cushing's syndrome caused by ectopic adrenocorticotropic hormone (now called *corticotropin*) production (see Chapter 31), and hypercalcemia (see Chapter 6). Hypercalcemia of malignancy does not appear to be related to parathyroid hormone (PTH) but to PTH-related protein, which shares several biologic actions with PTH. It also can be caused by osteolytic processes induced by cancer such as multiple myeloma or bony metastases from other cancers. The paraneoplastic syndromes may be the earliest indication that a person has cancer; they also may signal early recurrence of the disease in previously treated patients.

Diagnosis and Staging

The methods used in the diagnosis and staging of cancer are determined largely by the location and type of cancer suspected. A number of procedures are used in the diagnosis of cancer, including x-ray studies, endoscopic examinations, urine and stool tests, blood tests for tumor markers, bone marrow aspirations, ultrasound imaging, magnetic resonance imaging (MRI), and computed tomography (CT) scan.

The Pap Smear

The Pap smear is an example of the type of test called *exfoliative cytology*. It consists of a microscopic examination of a properly prepared slide by a cytotechnologist or pathologist for the purpose of detecting the presence of abnormal cells. The usefulness of exfoliative cytology relies on the fact that the cancer cells lack the cohesive properties and intercellular junctions that are characteristic of normal tissue; without these characteristics, cancer cells tend to exfoliate and become mixed with secretions surrounding the tumor growth. The American Cancer Society recommends that the test be done annually to detect cervical cancer in women who are or have been sexually active and who have reached 18 years of age. After three consecutive normal findings, the test may be performed less frequently at the discretion of the physician.[26] Exfoliative cytology also can be performed on other body secretions, including nipple drainage, pleural or peritoneal fluid, and gastric washings.

Biopsy

Tissue biopsy is the removal of a tissue specimen for microscopic study. Biopsies are obtained in a number of ways, including needle aspiration (*i.e.*, fine, percutaneous, or core needle); by endoscopic methods, such as bronchoscopy or cystoscopy, which involve the passage of an endoscope through an orifice and into the involved structure; or by laparoscopic methods. In some instances, a surgical incision is made from which biopsy specimens are obtained. Excisional biopsies are those in which all of the tumor is removed. The tumors usually are small, solid, palpable masses. If the tumor is too large to be completely removed, a wedge of tissue from the mass can be excised for examination. Tissue diagnosis is of critical importance in designing the treatment plan should cancer cells be found.[27]

Tumor Markers

Tumor markers are antigens that are expressed on the surface of tumor cells or substances released from normal cells in response to the presence of tumor. Some substances, such as hormones and enzymes, are produced normally by the tissue involved but become overexpressed as a result of cancer. Other tumor markers, such as oncofetal proteins, are produced during fetal development and are induced to re-appear later in life as a result of benign and malignant neoplasms. Tumor markers are used for screening, diagnosis, establishing prognosis, monitoring treatment, and detecting recurrent disease.

As diagnostic tools, tumor markers have limitations. The value of a marker depends on its sensitivity, specificity, proportionality, and feasibility.[28] *Sensitivity* implies that the marker is apparent early in the development of the tumor and has few false-negative results. *Specificity* indicates that the marker is specific for the specific cancer and is not elevated in other disease conditions (*i.e.*, has few false-positive results). *Proportionality* means that the level of marker accurately reflects the growth of the tumor, such that higher levels reflect a larger growth. *Feasibility* implies that the methods are readily available, easy to use, and that the cost is not prohibitive. Nearly all markers can be elevated in benign conditions, and most are not elevated in the early stages of malignancy. Thus, tumor markers have limited value as screening tests. Extremely elevated levels of a tumor marker can indicate a poor prognosis or the need for more aggressive treatment. Perhaps the greatest value of tumor markers is in monitoring therapy in people with widespread cancer. Nearly all markers show an association with the clinical course of the disease. The levels of most markers decline with successful treatment and increase with recurrence of the tumor.

The markers that have been most useful in practice have been human chorionic gonadotropin (hCG), CA 125, prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), α-fetoprotein (AFP), and carcinoembryonic antigen (CEA). HCG is a hormone normally produced by the placenta. It is used as a marker for diagnosing, prescribing treatment, and following the disease course in persons with high-risk gestational trophoblastic tumors. PSA and PAP are used as markers in prostate cancer, and CA 125 is used as a marker in ovarian cancer.

Some cancers express oncofetal antigens, which are differentiation antigens normally present only during embryonal development.[3] The two that have proven the most useful as tumor markers are AFP and CEA. AFP is synthesized by the fetal liver, yolk sac, and gastrointestinal tract and is the major serum protein in the fetus. Elevated levels are encountered in people with primary liver cancers and have also been observed in some testicular, ovarian, pancreatic, and stomach cancers. CEA

normally is produced by embryonic tissue in the gut, pancreas, and liver and is elaborated by a number of different cancers. Depending on the serum level adopted for significant elevation, CEA is elevated in approximately 60% to 90% of colorectal carcinomas, 50% to 80% of pancreatic cancers, and 25% to 50% of gastric and breast tumors.[3] As with most other tumor markers, elevated levels of CEA and AFP are found in other, noncancerous conditions, and elevated levels of both depend on tumor size so that neither is useful as an early test for cancer.

Staging and Grading of Tumors

The two basic methods for classifying cancers are grading according to the histologic or cellular characteristics of the tumor and staging according to the clinical spread of the disease. Both methods are used to determine the course of the disease and aid in selecting an appropriate treatment or management plan. Grading of tumors involves the microscopic examination of cancer cells to determine their level of differentiation and the number of mitoses. Cancers are classified as grades I, II, III, and IV with increasing anaplasia or lack of differentiation. Staging of cancers uses methods to determine the progress and spread of the disease. Surgery may be used to determine tumor size and lymph node involvement.

The clinical staging of cancer is intended to provide a means by which information related to the progress of the disease, the methods and success of treatment modalities, and the prognosis can be communicated to others. The TNM system, which has evolved from the work of the International Union Against Cancer (IUAC) and the American Joint Committee on Cancer Staging and End Stage Reporting (AJCCS), is used by many cancer facilities. This system, which is briefly described in Chart 5-2, classifies the disease into stages using three tumor components: *T* stands for the extent of the primary tumor, *N* refers to the involvement of the regional lymph nodes, and *M* describes the extent of the metastatic involvement. The time of staging is indicated as cTNM, clinical-diagnostic staging; pTNM, postsurgical resection-pathologic staging; sTNM, surgical-evaluative staging; rTNM, retreatment staging; and aTNM, autopsy staging.[29]

CHART 5-2 TNM Classification System

T (tumor)	
Tx	Tumor cannot be adequately assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1–4	Progressive increase in tumor size or involvement
N (nodes)	
Nx	Regional lymph nodes cannot be assessed
N0	No evidence of regional node metastasis
N 1–3	Increasing involvement of regional lymph nodes
M (metastasis)	
Mx	Not assessed
M0	No distant metastasis
M1	Distant metastasis present, specify sites

Cancer Treatment

The goals of cancer treatment methods fall into three categories: curative, controlling, and palliative. The most common modalities are surgery, radiation, chemotherapy, hormonal therapy, and biotherapy. The treatment of cancer involves the use of a carefully planned program that combines the benefits of multiple treatment modalities and the expertise of an interdisciplinary team of specialists including medical, surgical, and radiation oncologists; clinical nurse specialists; nurse practitioners; pharmacists; and a variety of ancillary personnel.

Surgery

Surgery is used for diagnosis, the staging of cancer, tumor removal, and palliation (*i.e.*, relief of symptoms) when a cure cannot be achieved. The type of surgery to be used is determined by the extent of the disease, the location and structures involved, the tumor growth rate and invasiveness, the surgical risk to the patient, and the quality of life the patient will experience after the surgery. If the tumor is small and has well-defined margins, the entire tumor often can be removed. However, if the tumor is large or involves vital tissues, surgical removal may be difficult if not impossible.

Surgical techniques have expanded to include electrosurgery, cryosurgery, chemosurgery, cytoreductive surgery, and laser surgery. Electrosurgery uses the cutting and coagulating effects of high-frequency current applied by needle, blade, or electrodes. Once considered a palliative procedure, it now is being used as an alternative treatment for certain cancers of the skin, oral cavity, and rectum. Cryosurgery involves the instillation of liquid nitrogen into the tumor through a probe. It is used in treating cancers of the oral cavity, brain, and prostate. Chemosurgery is used in skin cancers. It involves the use of a corrosive paste in combination with multiple frozen sections to ensure complete removal of the tumor. Laser surgery uses a laser beam to resect a tumor. It has been used effectively in retinal and vocal cord surgery.

Radiation Therapy

Radiation can be used singly as the primary method of treatment, as preoperative or postoperative treatment, with chemotherapy, or with chemotherapy and surgery. It can also be used as a palliative treatment to reduce symptoms in persons with advanced cancers. It is effective in reducing the pain associated with bone metastasis and, in some cases, improves mobility. Radiation also is used to treat several oncologic emergencies such as superior vena cava syndrome, spinal cord compression, bronchial obstruction, and hemorrhage.[30]

Radiation therapy exerts its effects by direct or indirect ionization. Indirect ionization produced by x-rays or gamma rays causes cellular damage when these rays are absorbed into tissue and give up their energy by producing fast-moving electrons. These electrons interact with free or loosely bonded electrons of the absorber cells and subsequently produce free radicals that interact with critical cell components (see Chapter 3). It can immediately kill cells, delay or halt cell cycle progression, or at dose levels commonly used in radiation therapy, cause damage to the cell nucleus that results in cell death after replication. Cell damage can be sublethal, in which case a single break in the strand can repair itself before the next radiation insult. Double-stranded breaks in DNA are generally

believed to be the primary damage that leads to radiation death of cells. The result of unrepaired DNA is that cells may continue to function until they undergo cell mitosis, at which time the genetic damage from the irradiation may result in death of the cell. The clinical significance is that the rapidly proliferating and poorly differentiated cells of a cancerous tumor are more likely to be injured by radiation therapy than are the slower proliferating cells of normal tissue. However, to some extent radiation is injurious to all rapidly proliferating cells, including those of the bone marrow and the mucosal lining of the gastrointestinal tract. This results in many of the common adverse effects of radiation therapy, including infection, bleeding, and anemia due to loss of blood cells and nausea and vomiting due to loss of gastrointestinal cells. In addition to its lethal effects, radiation also produces sublethal injury. Recovery from sublethal doses of radiation occurs in the interval between the first dose of radiation and subsequent doses. This is why large total doses of radiation can be tolerated when they are divided into multiple smaller fractionated doses. Normal tissue is usually able to recover from radiation damage more readily than is cancerous tissue.

Systemic Cancer Therapy

The use of chemotherapy drugs, hormones, antihormones, and biotherapy has become a highly specialized and increasingly effective means of treating cancers. The therapies rely on systemic agents that are distributed throughout the body. Gene therapy, although investigational, may provide a foundation for the development of more effective treatments in the future.

Bone marrow transplantation and peripheral blood stem cell transplantation are two treatment approaches for leukemias, certain solid tumors, and other cancers previously thought to be incurable.

Chemotherapy. Since the early 1960s, cancer chemotherapy has evolved as a major treatment modality. More than 30 different chemotherapeutic drugs are used alone or in various combinations. Administering higher doses of multiple drugs may be used as a strategy to achieve cure or optimal palliation; however, the adverse drug interactions and side effects can be unpredictable and intense. Chemotherapeutic drugs may be the primary form of treatment, or they may be used as adjuncts to other treatments. Chemotherapy is the primary treatment for most hematologic and some solid tumors, including choriocarcinoma, testicular cancer, acute and chronic leukemia, Burkitt's lymphoma, Hodgkin's disease, and multiple myeloma.

Cancer chemotherapeutic drugs exert their effects through several mechanisms. At the cellular level, they exert their lethal action by creating adverse conditions that prevent cell growth and replication. These mechanisms include disrupting production of essential enzymes; inhibiting DNA, RNA, and protein synthesis; and preventing cell mitosis.[6,31]

For most chemotherapy drugs, the relationship between tumor cell survival and drug dose is exponential, with the number of cells surviving being proportional to drug dose, and the number of cells at risk for exposure being proportional to the destructive action of the drug. Chemotherapeutic drugs are most effective in treating tumors that have a high growth fraction because of their ability to kill rapidly dividing cells. Exponential killing implies that a proportion or percentage of tumor cells are killed, rather than an absolute number. This proportion is a constant percentage of the total number of cells. For this reason, multiple courses of treatment are needed if the tumor is to be eradicated.[5]

The anticancer drugs may be classified as either cell cycle specific or cell cycle nonspecific. Drugs are cell cycle specific if they exert their action during a specific phase of the cell cycle. For example, methotrexate, an antimetabolite, acts by interfering with DNA synthesis and thereby interrupts the S phase of the cell cycle. Drugs that are cell cycle nonspecific affect cancer cells through all the phases of the cell cycle. The alkylating agents, which are cell cycle nonspecific, act by disrupting DNA when the cells are in the resting state and when they are dividing. The site of action of various cancer drugs varies. Chemotherapeutic drugs that have similar structures and effects on cell function usually are grouped together, and these drugs usually have similar toxic and side effects. Because they differ in their mechanisms of action, combinations of cell cycle-specific and cell cycle-nonspecific agents often are used to treat cancer.

Combination chemotherapy has been found to be more effective than treatment with a single drug. With this method, several drugs with different mechanisms of action, metabolic pathways, times of onset of action and recovery, side effects, and onset of side effects are used. Drugs used in combinations are individually effective against the tumor and synergistic with each other. The regimens for combination therapy often are referred to by acronyms. Two well-known combinations are CHOP (cyclophosphamide, doxorubicin, Oncovin [vincristine], and prednisone), used in the treatment of Hodgkin's disease, and CMF (cyclophosphamide, methotrexate, and 5-fluorouracil), used in the treatment of breast cancer. The maximum possible drug doses usually are used to ensure the maximum cell killing. Routes of administration and dosage schedules are carefully designed to ensure optimal delivery of the active forms of the drugs to a tumor during the sensitive phase of the cell cycle.

Hormone and Antihormone Therapy. Hormone therapy consists of administration of hormones or hormone-blocking drugs. It is used for cancers that are responsive to or dependent on hormones for growth. The actions of hormones depend on the presence of specific receptors in the tumor. Among the tumors known to be responsive to hormonal manipulations are those of the breast, prostate, adrenal gland, and uterine endometrium. Hormones commonly used for cancer treatment include estrogens (*e.g.*, diethylstilbestrol, estradiol), androgens (*e.g.*, testosterone), and progestins (*e.g.*, hydroxyprogesterone). Hormone therapy also involves use of the adrenal corticosteroid hormones such as prednisone, dexamethasone, and methylprednisolone. These compounds inhibit mitosis and are cytotoxic to cells of lymphocytic origin. Hormones are cell cycle nonspecific and are thought to alter the synthesis of RNA and proteins by binding to receptor sites. The side effects of hormonal treatment are directly related to the normal action of the hormones. Because dosages of these drugs are usually higher than those that normally occur in the body, the normal actions of the hormone are accentuated.[31]

Hormone-blocking drugs include the antiestrogen drugs tamoxifen and leuprolide (*i.e.*, a gonadotropin-releasing hormone analog that blocks both estrogens and androgens) and the antiadrenal drug aminoglutethimide.

Biotherapy. Biotherapy involves the use of biologic response modifiers (BRMs) that change the person's own biologic response to cancer. The BRMs are products normally produced in the body that serve as regulators and messengers of normal cellular function. Although biotherapy relies heavily on immune mechanisms, it is not limited to them. Three major mechanisms by which biotherapy exerts its effects are: (1) modification of host responses, (2) direct destruction of cancer cells by suppressing tumor growth or killing the tumor cell, and (3) modification of tumor cell biology.

Immunotherapy techniques include active and passive immunotherapy. Active immunotherapy involves nonspecific techniques, such as bacille Calmette-Guérin (BCG) and levamisole, and specific techniques, such as purified or recombinant antigens. Passive immunotherapy is divided into nonspecific techniques such as lymphokine-activated killer (LAK) cells and cytokine therapy, specific techniques such as antibody therapy, and combined techniques that include LAK cells and antibodies. Active immunotherapy focuses on stimulating immune response. BCG is an attenuated strain of the bacterium that causes bovine tuberculosis. BCG acts as a nonspecific stimulant of the immune system. A second method involves the use of vaccines made from the patient's own tumor (autologous) or from pooled tumor-associated antigens (allogeneic) that have been obtained from a number of tumors. Active immunotherapy has been studied as treatment for melanoma, renal cell carcinoma, and leukemia.[32]

Adoptive immunotherapy is a technique that uses lymphokine-activated NK cells or tumor-specific T-cell immunity as a means of eradicating cancer cells. Originally, only LAK cells were used. These NK cells are grown in culture supported by IL-2. Because NK cells are nonspecific in their function, LAK cells attack both normal and tumor cells. The technique of adoptive therapy has been expanded to the production of tumor-specific T cells. These cells are derived from a person's own *tumor-infiltrating lymphocytes* (TILs) that have been expanded in the laboratory so that a large amount of cells are available for reinfusion. Because the TILs are tumor specific, they do not attack normal host cells.

Four types of biologic response modifiers are being used or investigated: interferon therapy, interleukin therapy, monoclonal antibodies, and hematopoietic growth factors. Some agents, such as the interferons, have more than one biologic action, including antiviral, immunomodulatory, and antiproliferative actions. The *interferons* are endogenous polypeptides that are synthesized by a number of cells in response to a variety of cellular or viral stimuli. The three major types of interferons are alpha (α), beta (β) and gamma (γ), each group differing in terms of their cell surface receptors. The exact physiologic roles of each of the interferons remain unclear. They appear to inhibit viral replication and also may be involved in inhibiting tumor protein synthesis and in prolonging the cell cycle and increasing the percentage of cells in the G_0 phase. Interferons stimulate NK cells and T-lymphocyte killer cells. Although 17 *interleukins* have been identified, only one, IL-2, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic renal cell carcinoma. IL-2 has been found to reduce tumor size in a minority of patients with metastatic renal cancer and melanoma.[32]

Monoclonal antibodies (MoAbs) are highly specific antibodies derived from cloned cells or hybridomas. Scientists were able to produce large quantities of these MoAbs that were specific for tumor cells. Several MoAbs have been approved: muromonab-CD3 (OKT-3), which targets the CD3 receptor of human T cells, for the treatment of acute allograft rejection in renal transplant recipients; satumomab pendetide, used in the detection of colorectal and ovarian cancers,[33] and rituximab, an anti-CD20 MoAb used in the treatment of B-cell malignant lymphomas.[34]

Hematopoietic growth factors are growth and maturation factors that include the colony-stimulating factors (CSFs). The CSFs are factors that control the production of neutrophils and monocytes/macrophages, erythropoietin, and thrombopoietin (see Chapter 11).[34]

In summary, cancer compresses and erodes blood vessels; obstructs lymph flow; penetrates serous cavities; and compresses visceral structures. It produces chemical mediators, such as TNF, that produce pain, sap energy reserves, and cause weight loss and tissue wasting. Paraneoplastic syndromes arise from the ability of cancers to elaborate hormones and other chemical messengers that produce nonmetastatic endocrine, hematopoietic, neurologic, and dermatologic syndromes.

The methods used in the diagnosis of cancer vary with the type of cancer and its location. Because many cancers are curable if diagnosed early, health care practices designed to promote early detection are important. Pap smears, tissue biopsies, and tumor markers are used to detect the presence of cancer cells and in diagnosis. There are two basic methods of classifying tumors: (1) grading according to the histologic or tissue characteristics, and (2) clinical staging according to spread of the disease. Histologic studies are done in the laboratory using cells or tissue specimens. The TNM system for clinical staging of cancer uses tumor size, lymph node involvement, and presence of metastasis.

Treatment plans that use more than one type of therapy, often in combination, are providing cures for a number of cancers that a few decades ago had a poor prognosis and are increasing the life expectancy in other types of cancer. Surgical procedures are more precise as a result of improved diagnostic equipment and new techniques, such as laser surgery. Radiation equipment and radioactive sources permit greater and more controlled destruction of cancer cells while causing less damage to normal tissues. Chemotherapy involves the use of drugs that exert their effects at the cellular level to prevent cell replication. Successes with immunotherapy techniques offer hope that the body's own defenses can be used in fighting cancer.

CHILDHOOD CANCERS

In the United States, cancer is the second leading cause of death in children 1 to 14 years of age.[1] Between 1974 and 1991, children younger than 14 years of age exhibited a 1% average yearly increase in the incidence of all malignant neoplasms, with a 1.6% average increase in the incidence of acute lymphocytic leukemia and a greater than 2% increase for astroglial tumors, rhabdomyosarcomas, germ cell tumors, and

osteosarcomas.[35] The spectrum of cancers that affect children differs markedly from those that affect adults. Although most adult cancers are of epithelial cell origin (*e.g.*, lung cancer, breast cancer, colorectal cancers), childhood cancers usually involve the hematopoietic system, nervous system, or connective tissue. Chart 5-3 lists the most common forms of solid childhood cancers.

As with adult cancers, there probably is no one cause of childhood cancer. However, many forms of childhood cancer repeat in families and may result from polygenic or single-gene inheritance, chromosomal aberrations (*e.g.*, translocations, deletions, insertions, inversions, duplications), exposure to mutagenic environmental agents, or a combination of these factors (see Chapter 4). If cancer develops in one child, the risk of cancer in siblings is approximately twice that of the general population, and if the disease develops in two children, the risk is even greater.

Heritable forms of cancer tend to have an earlier age of onset, a higher frequency of multifocal lesions in a single organ, and bilateral involvement of paired organs or multiple primary tumors. The two-hit hypothesis has been used as one explanation of heritable cancers.[3] The first "hit" or mutation occurs prezygotically (*i.e.*, in germ cells before conception) and is present in the genetic material of all somatic cells. Cancer subsequently develops in one or several somatic cell lines that undergo a second mutation.

Children with heritable disorders are at increased risk for developing certain forms of cancer. For example, Down syndrome is associated with increased risk of leukemia; primary immunodeficiency disorders (see Chapter 10) are associated with lymphoma, leukemia, and brain cancer; and xeroderma pigmentosum is associated with basal and squamous cell carcinoma and melanoma.

Diagnosis and Treatment

The early diagnosis of childhood cancers often is overlooked because the signs and symptoms often are similar to those of common childhood diseases and because cancer occurs less frequently in children than in adults.[36] Symptoms of prolonged fever, unexplained weight loss, and growing masses (especially in association with weight loss) should be viewed as warning signs of cancer in children. Diagnosis of childhood cancers involves many of the same methods that are used in adults. Accurate disease staging is especially beneficial in childhood cancers, in which the potential benefits of treatment must be carefully weighed against potential long-term effects.

CHART 5-3 Common Solid Tumors of Childhood

Brain and nervous system tumors
- Medulloblastoma
- Glioma

Neuroblastoma
Wilms' tumor
Rhabdomyosarcoma and embryonal sarcoma
Retinoblastoma
Osteosarcoma
Ewing's sarcoma

Adult Survivors of Childhood Cancer

With improvement in treatment methods, the number of children who survive childhood cancer is continuing to increase.[37] Unfortunately, therapy may produce late sequelae, such as impaired growth, neurologic dysfunction, hormonal dysfunction, cardiomyopathy, pulmonary fibrosis, and risk of second malignancies. Although cures for large numbers of children have been possible only since the 1970s, much already is known about the potential for delayed effects.

Children reaching adulthood after cancer therapy may have reduced physical stature because of the therapy they received, particularly radiation, which retards the growth of normal tissues along with cancer tissue. The younger the age and the higher the radiation dose, the greater the deviation from normal growth. There also is concern that central nervous system radiation as a prophylactic measure in childhood leukemia has an effect on cognition and learning. Children younger than 6 years of age at the time of radiation and those receiving the highest radiation doses are most likely to have subsequent cognitive difficulties.

Delayed sexual maturation in both boys and girls can result from irradiation of the gonads. Delayed sexual maturation also is related to the treatment of children with alkylating agents. Cranial irradiation may result in premature menarche in girls, with subsequent early closure of the epiphysis and a reduction in final growth achieved. Data related to fertility and health of the offspring of childhood cancer survivors are just becoming available.

Vital organs such as the heart and lungs may be affected by cancer treatment. Children who received anthracyclines (*i.e.*, doxorubicin or daunorubicin) may be at risk for cardiomyopathy and congestive heart failure developing. Pulmonary irradiation may cause lung dysfunction and restrictive lung disease. Drugs such as bleomycin, methotrexate, and busulfan also can cause lung disease.

For survivors of childhood cancers, the risk of second cancers is reported to range from 3% to 12%. There is a special risk of second cancers in children with the retinoblastoma gene. Because of this risk, children who have been treated for cancer should be followed up routinely.

In summary, although most adult cancers are of epithelial cell origin, most childhood cancers usually involve the hematopoietic system, nervous system, or connective tissue. Heritable forms of cancer tend to have an earlier age of onset, a higher frequency of multifocal lesions in a single organ, and bilateral involvement of paired organs or multiple primary tumors. The early diagnosis of childhood cancers often is overlooked because the signs and symptoms often are similar to those of other childhood diseases. With improvement in treatment methods, the number of children who survive childhood cancer is continuing to increase. As these children approach adulthood, there is continued concern that the life-saving therapy they received during childhood may produce late sequelae, such as impaired growth, neurologic dysfunction, hormonal dysfunction, cardiomyopathy, pulmonary fibrosis, and risk of second malignancies.

REVIEW QUESTIONS

- Use the cell cycle to explain the difference in regenerative capabilities of cells in self-renewing tissues such as the skin, stable cells such as liver cells, and permanent cells such as neurons.
- Define *neoplasm* and explain how neoplastic growth differs from the normal adaptive changes seen in atrophy, hypertrophy, and hyperplasia.
- Relate the properties of cell differentiation to the development of a cancer cell line and the behavior of the tumor.
- Trace the pathway for hematologic spread of a metastatic cancer cell and explain why some cancers preferentially metastasize to certain tissues in the body.
- Use the concepts of growth fraction and doubling time to explain the number of cancer cells that would be present in a breast cancer lesion at the time it can be detected by breast self exam.
- Describe the role of proto-oncogenes and anti-oncogenes in the transformation of a normal cell line to a cancer cell line.
- Compare methods used in histological grading of tumors and clinical staging of cancers.
- Cite the early warning signs of cancer in children.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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