A neoplasm (Greek, neo, new + plasma, thing formed) is the autonomous growth of tissues that have escaped normal restraints on cell proliferation and exhibit varying degrees of fidelity to their precursors. The structural resemblance of the neoplastic cell to its cell of origin usually enables conclusions about its source and potential behavior. In view of their space-occupying properties, solid neoplasms are termed tumors (Greek, swelling).

Tumors that remain localized are considered benign, whereas those that spread to distant sites are termed malignant, or cancer. The neoplastic process entails not only cellular proliferation but also altered differentiation of the tumor cell and, in some cases, an aberration of programmed cell death (apoptosis).

The incidence of cancer increases with age, and greater longevity in modern times necessarily enlarges
the population at risk. If all deaths from cancers caused by tobacco smoke are removed from the statistics, there has been no increase in the overall age-adjusted cancer death rate in men in the past half-century, and there has been a continually decreasing rate in women. However, the age-adjusted incidence of specific cancers has fluctuated over this time period.

In general, neoplasms are irreversible, and their growth is, for the most part, autonomous. Several observations are important:

• Neoplasms are derived from cells that normally maintain a proliferative capacity. Thus, mature neurons and cardiac myocytes do not give rise to tumors.
• A tumor may express varying degrees of differentiation, from relatively mature structures that mimic normal tissues to a collection of cells so primitive in appearance that the cell of origin cannot be identified.
• The exact stimulus responsible for the uncontrolled proliferation may not be identifiable; in fact, it is not known for most human neoplasms.
• Neoplasia arises from mutations in genes that regulate cell growth, apoptosis, or DNA repair.

Benign Versus Malignant Tumors

By definition, benign tumors do not penetrate (invade) adjacent tissue borders, nor do they spread (metastasize) to distant sites. They remain as localized overgrowths in the area in which they arise. As a rule, benign tumors are more differentiated than malignant ones—that is, they more closely resemble their tissue of origin. By contrast, malignant tumors, or cancers, have the added property of invading contiguous tissues and metastasizing to distant sites, where subpopulations of malignant cells take up residence, grow anew, and again invade.

In common usage, the terms benign and malignant refer to the overall biological behavior of a tumor rather than to its morphologic characteristics. In most circumstances, malignant tumors kill, whereas benign ones spare the host. However, so-called benign tumors in critical locations can be deadly. For example, a benign intracranial tumor of the meninges (meningioma) can kill by exerting pressure on the brain. A benign mesenchymal tumor of the left atrium (myxoma) may kill suddenly by blocking the mitral valve orifice. In certain locations, the erosion of a benign tumor of smooth muscle can lead to serious hemorrhage—witness the peptic ulceration of a stromal tumor in the gastric wall. On rare occasions, a functioning, benign endocrine adenoma can be life-threatening, as in the case of sudden hypoglycemia associated with an insulinoma of the pancreas or a hypertensive crisis produced by a pheochromocytoma of the adrenal medulla. Conversely, certain types of malignant tumors are so indolent that they are curable by surgical resection. In this category are many cancers of breast and some malignant tumors of connective tissue (e.g., fibrosarcoma).

A number of tumors are difficult to classify because they do not fit all the criteria for either benign or malignant neoplasms. The best-known example is basal cell carcinoma of the skin, which is histologically malignant (i.e., it invades aggressively) but only rarely has been reported to metastasize to distant sites. Similarly, the local growth of a pleomorphic adenoma of a salivary gland, which is classified as benign, may be so aggressive that it defies surgical cure.

Classification Of Neoplasms

The classification of tumors reflects historical concepts, technical jargon, location, origin, descriptive modifiers, and predictors of biological behavior. Although the language of tumor classification is neither rigidly logical nor consistent, it still serves as a reasonable mode of communication.

Benign Tumors Carry the Suffix “Oma”

The primary descriptor of any tumor, benign or malignant, is its cell or tissue of origin. The classification of benign tumors is the basis for the names of their malignant variants. The suffix “oma” for benign tumors is preceded by reference to the cell or tissue of origin. For example, a benign tumor that resembles chondrocytes is called a chondroma (Fig. 5-1). If the tumor resembles the precursor of the chondrocyte, it is labeled chondroblastoma.

Tumors of epithelial origin are given a variety of names based on what is believed to be their outstanding characteristic. Thus, a benign tumor of the squamous epithelium may be called simply epithelioma or, when branched and exophytic, may be termed papilloma. Benign tumors arising from glandular epithelium, such as in the colon or the endocrine glands, are named adenoma. Accordingly, we refer to a thyroid adenoma or a pancreatic islet cell adenoma. In some instances, the predominating feature is the gross appearance, in which case we speak, for example, of an adenomatous polyp of the colon.

Benign tumors that arise from germ cells and contain derivatives of different germ layers are labeled teratoma. These tumors occur principally in the gonads and occasionally in the mediastinum and may contain a variety of structures, such as skin, neurons and glial cells, thyroid, intestinal epithelium, and cartilage. Localized, disordered differentiation during embryonic development results in a hamartoma, a disorganized caricature of normal tissue components. Such tumors, which are not strictly neoplasms, contain varying combinations of cartilage, ducts or bronchi, connective tissue,
blood vessels, and lymphoid tissue. Ectopic islands of normal tissue, called choristoma, may also be mistaken for true neoplasms. These small lesions are represented by pancreatic tissue in the wall of the stomach or intestine, adrenal rests under the renal capsule, and nodules of splenic tissue in the peritoneal cavity. Certain benign growths, recognized clinically as tumors, are not truly neoplastic but rather represent overgrowth of normal tissue elements. Examples are vocal cord polyps, skin tags, and hyperplastic polyps of the colon.

Malignant Tumors are Mostly Carcinomas or Sarcomas

In general, the malignant counterparts of benign tumors usually carry the same name, except that the suffix “carcinoma” is applied to epithelial cancers and “sarcoma” to those of mesenchymal origin. For instance, a malignant tumor of the stomach is a gastric adenocarcinoma or adenocarcinoma of the stomach (Fig. 5-2). Squamous cell carcinoma is an invasive tumor of the skin or other organs lined by a squamous epithelium (e.g., the esophagus). Squamous cell carcinomas also arise in the metaplastic squamous epithelium of the bronchus or endocervix. Transitional cell carcinoma is a malignant neoplasm of the bladder or ureters. By contrast, we speak of chondrosarcoma (Fig. 5-3) or fibrosarcoma. Sometimes the name of the tumor suggests the tissue type of origin, as in osteogenic sarcoma or bronchogenic carcinoma. Some tumors display neoplastic elements of different cell types but are not germ cell tumors. For example, fibroadenoma of the breast, composed of epithelial and stromal elements, is benign, whereas, as the name implies, adenosquamous carcinoma of the uterus or the lung is malignant. A rare malignant tumor that contains intermingled carcinomatous and sarcomatous elements is known as carcinosarcoma.

The persistence of certain historical terms adds a note of confusion. Hepatoma of the liver, melanoma of the skin, seminoma of the testis, and the lymphoproliferative tumor, lymphoma, are all highly malignant. Tumors of the hematopoietic system are a special case in which the relationship to the blood is indicated by the suffix “emia.” Thus, leukemia refers to a malignant proliferation of leukocytes.

Secondary descriptors (again, with some inconsistencies) refer to a tumor’s morphologic and functional characteristics. For example, the term papillary describes a frond-like structure (Fig. 5-4). Medullary signifies a soft, cellular tumor with little connective tissue stroma, whereas scirrhous or desmoplastic implies a dense fibrous stroma (Fig. 5-5). Colloid carcinomas secrete abundant mucus, in which float islands of tumor cells. Comedocarcinoma is an intraductal neoplasm in which necrotic material can be expressed from the ducts. Certain visible secretions of the tumor cells lend their characteristics to the classification—for example, production of mucin or serous fluid. A further designation describes the gross appearance of a cystic mass. From all these considerations, we derive such common terms as papillary serous cystadenocarcinoma of the ovary, comedocarcinoma of the breast, adenoid cystic carcinoma of the salivary glands, polypoid adenocarcinoma of the stomach, and medullary carcinoma of the thyroid. Finally, tumors in which the histogenesis is poorly understood are often given an eponym—for example, Hodgkin disease, Ewing sarcoma of bone, or Brenner tumor of the ovary.

Histologic Diagnosis Of Malignancy

There are no reliable molecular indicators of malignancy, and the “gold standard” for diagnosis of cancer remains routine microscopy. The distinction between benign and malignant tumors is, from a practical point of view, the most important diagnostic challenge faced by the pathologist. In most cases, the differentiation poses few problems; in a few, careful study is required before an accurate diagnosis is secure. However, there remain tumors that defy the
diagnostic skills and experience of any pathologist. In these cases, the correct diagnosis must await the clinical outcome. In effect, the criteria used to assess the true biological nature of any tumor are based not on scientific principles but rather on a historical correlation of histologic and cytologic patterns with clinical outcomes. Although general criteria for malignancy are recognized, they must be used with caution in specific cases. For example, a reactive proliferation of connective cells termed nodular fasciitis has a more alarming histologic appearance than many fibrosarcomas, and misdiagnosis can lead to unnecessary surgery. Conversely, many well-differentiated endocrine adenocarcinomas are histologically indistinguishable from benign adenomas.

Benign Tumors Resemble their Parent Tissue

Benign tumors tend to be histologically and cytologically similar to their tissues of origin. For example, lipomas, despite their often-lobulated gross appearance, seem to be composed of normal adipocytes (Fig. 5-6). Fibromas are composed of mature fibroblasts and a collagenous stroma. Chondromas exhibit chondrocytes dispersed in a cartilaginous matrix. Thyroid adenomas form acini and produce thyroglobulin. Remember that the definition of a benign tumor resides above all in its inability to invade adjacent tissue and to metastasize.

Malignant Tumors Depart from the Parent Tissue Morphologically and Functionally

Despite the histologic divergence of malignant tumors from their tissue of origin, an accurate identification of their source depends not only on the location but also on
a morphologic resemblance to a normal tissue. Some of the histologic features that favor malignancy include the following:

- **Anaplasia or cellular atypia:** These terms refer to the lack of differentiated features in a cancer cell. In general, the degree of anaplasia correlates with the aggressiveness of the tumor. Cytologic evidence of anaplasia includes (1) variation in the size and shape of cells and cell nuclei (pleomorphism), (2) enlarged and hyperchromatic nuclei with coarsely clumped chromatin and prominent nucleoli, (3) atypical mitoses, and (4) bizarre cells, including tumor giant cells (Fig. 5-7). Many of these features are preceded by a preneoplastic dysplastic epithelium, which may lead to carcinoma in situ (see Chapter 1).

- **Mitotic activity:** Abundant mitoses are characteristic of many malignant tumors but are not a necessary criterion. However, in some cases (e.g., leiomyosarcomas), the diagnosis of malignancy is based on the finding of even a few mitoses.

- **Growth pattern:** In common with many benign tumors, malignant neoplasms often exhibit a disorganized and random growth pattern, which may be expressed as uniform sheets of cells, arrangements around blood vessels, papillary structures, whorls, rosettes, and so forth. Malignant tumors often outgrow their blood supply and display ischemic necrosis.

- **Invasion:** Malignancy is proved by the demonstration of invasion, particularly of blood vessels and lymphatics. In some circumstances (e.g., squamous carcinoma of the cervix or carcinoma arising in an adenomatous polyp), the diagnosis of malignant transformation is made on the basis of local invasion.

- **Metastases:** The presence of metastases identifies a tumor as malignant. In metastatic disease that was not preceded by a clinically diagnosed primary tumor, the site of origin is often not readily apparent from the morphologic characteristics of the tumor. In such cases, electron microscopic examination and the demonstration of specific tumor markers may establish the correct origin.

### Immunohistochemical Tumor Markers are Antigens that Point to the Origin of Neoplasms

Tumor markers are products of malignant neoplasms that can be detected in the cells themselves or in body fluids. The ultimate tumor marker would be one that allows the unequivocal distinction between benign and malignant cells, but unfortunately no such marker exists. Nevertheless, some markers are often useful in identifying the cell of origin of a metastatic or poorly differentiated primary tumor. Metastatic tumors may be so undifferentiated microscopically as to preclude even the distinction between an epithelial and a mesenchymal origin. Tumor markers rely on the preservation of characteristics of the progenitor cell or the synthesis of specialized proteins by the neoplastic cell to make this distinction. The determination of cell lineage of undifferentiated tumors is more than an academic exercise, because therapeutic decisions may be based on their appropriate identification. For example, the treatment of carcinomas usually involves surgery, whereas malignant lymphomas are treated with radiation therapy and chemotherapy. Among these diagnostically useful markers are such diverse products as immunoglobulins, fetal proteins, enzymes, hormones, and cytoskeletal, and junctional proteins.

- **Carcinomas** uniformly express cytokeratins, which are intermediate filaments belonging to a multigene family of proteins. Lineage-associated markers are often useful in establishing the origin of a poorly differentiated carcinoma. For example, prostatic carcinomas consistently express the glycoprotein prostate-specific antigen and prostate-specific acid phosphatase. By contrast, colon cancers are negative for these markers, but most of them express carcinoembryonic antigen (CEA).

- **Neuroendocrine tumors** share the positivity for cytokeratins with other carcinomas. However, they can be identified by their content of chromogranins, a family of proteins found in neurosecretory granule or synaptophysins.

- **Malignant melanomas** may be unpigmented and appear similar to other poorly differentiated carcinomas. They
can often be distinguished by immunohistochemical studies. Melanomas express HMB-45 and S-100 protein, but unlike most carcinomas, they are not positive for cytokeratins.

- **Soft tissue sarcomas** express the intermediate filament vimentin. Because this marker is also present in numerous nonmesenchymal tumors, its expression is meaningful only in concert with other markers and morphologic criteria.

- **Malignant lymphomas** are generally positive for leukocyte common antigen (CD45). Markers for lymphomas and leukemias are grouped by so-called cluster designations (CDs), at present numbering over 200. Markers for CD antigens help to discriminate between T and B lymphocytes, monocytes, and granulocytes as well as the mature and immature variants of these cells.

- **Vascular tumors** derived from endothelial cells, including hemangiomas and hemangiosarcomas, are identified by antibodies against factor VIII-related antigen or by the binding of certain lectins.

- **Proliferating cells** display Ki-67 and proliferating cell nuclear antigen. Although the presence of proliferating cells alone does not establish a diagnosis of malignancy, the presence of cycling cells at sites in which cell growth is normally absent frequently suggests a cancer.

    *Serum tumor markers are not disease-specific, but they allow monitoring of tumor recurrence after surgery.* For example, high serum levels of CEA are associated with carcinomas of the gastrointestinal tract and some carcinomas of the breast. Increased levels of serum α-fetoprotein suggest liver cancer or a yolk sac tumor. Human chorionic gonadotropin is used for monitoring the recurrence of malignant trophoblastic tumors. Increased serum levels of prostate-specific antigen accompany prostatic cancers.

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**Invasion And Metastasis**

*The two properties that are unique to cancer cells are the ability to invade locally and the capacity to metastasize to distant sites. These characteristics are responsible for the vast majority of deaths from cancer; the primary tumor itself is generally amenable to surgical extirpation.*

**Direct Extension Damages the Involved Organ and Adjacent Tissues**

*Most carcinomas begin as localized growths confined to the epithelium in which they arise. As long as these early cancers do not penetrate the basement membrane on which the epithelium rests, such tumors are termed carcinoma in situ (Fig. 5-8). In this stage, it is unfortunate that in situ tumors are asymptomatic, because they are invariably curable. When the in situ tumor acquires invasive potential and extends directly through the underlying basement membrane, it can compromise neighboring tissues and metastasize. In situations in which cancer arises from cells that are not confined by a basement membrane—such as connective tissue cells, lymphoid elements, and hepatocytes—an in situ stage is not defined.*

Malignant tumors characteristically grow within the tissue of origin, where they enlarge and infiltrate normal structures. They may also extend directly beyond the confines of that organ to involve adjacent tissues. The growth of the cancer is occasionally so extensive that replacement of the normal tissue results in functional insufficiency of the organ. Such a situation is not uncommon in primary liver cancer. Brain tumors, such as astrocytomas, infiltrate the brain until they compromise vital regions. The direct extension of malignant tumors within an organ may also be life-threatening because of their location. A common ex-
ample is the intestinal obstruction produced by cancer of the colon.

The invasive growth pattern of cancers often leads to their direct extension outside the tissue of origin, in which case the tumor may secondarily impair the function of an adjacent organ. Squamous carcinoma of the cervix frequently grows beyond the genital tract to produce vesicovaginal fistulas and to obstruct the ureters. Neglected cases of breast cancer are often complicated by extensive skin ulceration. Even small tumors can produce severe consequences when they invade vital structures. A small lung cancer can cause exsanguinating hemorrhage when it erodes a blood vessel. The agonizing pain of pancreatic carcinoma results from direct extension of the tumor to the celiac nerve plexus. Tumor cells that reach serous cavities (e.g., those of the peritoneum or pleura) spread easily by direct extension or can be carried by the fluid to new locations on the serous membranes. The most common example is the seeding of the peritoneal cavity by certain types of ovarian cancer.

Metastatic Spread is the Most Common Cause of Cancer Death

Metastasis refers to the transfer of malignant cells from one site to another not directly connected with it. The invasive properties of malignant tumors bring them into contact with blood and lymphatic vessels. In the same way that they can invade parenchymal tissue, neoplastic cells can also penetrate vascular and lymphatic channels, through which they are disseminated to distant sites. In general, metastases resemble the primary tumor histologically, although they are occasionally so anaplastic that their cell of origin is obscure.

Hematogenous Metastases
Cancer cells commonly invade capillaries and venules, whereas thicker-walled arterioles and arteries are relatively resistant. Before they can form viable metastases, circulating tumor cells must lodge in the vascular bed of the metastatic site (Fig. 5-9). Here, they presumably attach to the walls of blood vessels, either to endothelial cells or to naked basement membranes. For many tumors, this sequence of events explains why the liver and the lung are so frequently the sites of metastases. Because abdominal tumors seed the portal system, they lead to hepatic metastases; other tumors penetrate systemic veins that eventually drain into the vena cava and hence to the lungs. Some tumor cells released into the venous system survive passage through the microcirculation and are thus transported to more distant organs. For instance, tumor cells may survive passage through the pulmonary microcirculation to reach the brain, bones, and other organs through arterial dissemination. Neoplastic cells arrested in the microcirculation penetrate the vessel walls at the site of metastasis by use of the same mechanisms by which the primary tumor invades.

Lymphatic Metastases
Tumors arising in tissues that have a rich lymphatic network (e.g., the breast) often metastasize by this route, although the particular properties of specific neoplasms may
play a role in the route of spread. Basement membranes envelop only large lymphatic channels; they are lacking in lymphatic capillaries. Thus, invasive tumor cells may penetrate lymphatic channels more readily than do blood vessels. Once in lymphatic vessels, the cells are carried to the regional draining lymph nodes, where they initially lodge in the marginal sinus and then extend throughout the node. Lymph nodes bearing metastatic deposits may be enlarged to many times their normal size, often exceeding the diameter of the primary lesion. The cut surface of the lymph node usually resembles that of the primary tumor in color and consistency and may also exhibit the necrosis and hemorrhage commonly seen in primary cancers (Fig. 5-10).

The regional lymphatic pattern of metastatic spread is most prominently exemplified by breast cancer. The initial metastases are almost always lymphatic, and these regional lymphatic metastases have considerable prognostic significance. Cancers that arise in the lateral aspect of the breast characteristically spread to axillary lymph nodes; those arising in the medial portion drain to the internal mammary thoracic lymph nodes. Identification of the specific sentinel nodes that drain the site of a breast cancer is an important aid in attempting to assess whether a tumor has metastasized via the lymphatic system.

**Seeding of Body Cavities**
Malignant tumors that arise in organs adjacent to body cavities (e.g., ovaries, gastrointestinal tract, and lung) may shed malignant cells into these spaces. Such body cavities principally include the peritoneal and pleural cavities, although occasional seeding of the pericardial cavity, joint space, and subarachnoid space are observed. Similar to tissue culture, tumors in these sites grow in masses and may provoke the formation of fluid (e.g., ascites, pleural fluid), sometimes in very large quantities. Mucinous adenocarcinoma may also secrete copious amounts of mucin in these locations.

**Invasion and Metastasis are Multistep Events**
Several steps are required for malignant cells to establish a metastasis (Fig. 5-11):

![Mechanisms of tumor invasion and metastasis](image)

**FIGURE 5-11.** Mechanisms of tumor invasion and metastasis. The mechanism by which a malignant tumor initially penetrates a confining basement membrane and then invades the surrounding extracellular environment involves several steps. The tumor first acquires the ability to bind components of the extracellular matrix. These interactions are mediated by the expression of a number of adhesion molecules. Proteolytic enzymes are then released from the tumor cells, and the extracellular matrix is degraded. After moving through the extracellular environment, the invading cancer penetrates blood vessels and lymphatics by the same mechanisms.
1. Invasion of the basement membrane underlying the tumor
2. Movement through extracellular matrix
3. Penetration of vascular or lymphatic channels
4. Survival and arrest within circulating blood or lymph nodes
5. Exit from the circulation into a new tissue site
6. Survival and growth as a metastasis, a process that involves angiogenesis

Most cancers originate from the malignant transformation of a single cell (monoclonal origin of tumors). Nevertheless, the inherent genetic instability of the malignant phenotype leads to the appearance of subpopulations with diverse biological characteristics and profound variations in their metastatic potential (tumor heterogeneity). The demonstration of tumor heterogeneity has led to the concept that at each step of the metastatic cascade, only the fittest cells survive. Thus, the metastatic process can be viewed as a competition in which a subpopulation of cells within the primary cancer ultimately prevails as a metastasis.

**Invasion**

Inherent in the definition of a malignant cell is the capacity to invade surrounding tissue. In epithelial tumors, invasion requires disruption of, and penetration through, the underlying basement membrane and passage through the extracellular matrix. Similarly, circulating cells destined to establish metastases must reproduce these same events to exit from the vascular or lymphatic compartment and establish residence at a distant site.

**Adhesion Molecules**

The entire metastatic sequence, from the initial binding of the tumor cell to the underlying extracellular matrix, to its growth in a distant location, depends on the expression of numerous adhesion molecules by the malignant cells. The display of such surface molecules varies with (1) the type of tumor, (2) the individual clone (tumor heterogeneity), (3) the stage of the malignant progression, and (4) the specific step in the metastatic process. Among some of the most important cell adhesion molecules active in the process of invasion are the following:

- **Integrins** directly mediate cell-cell and cell-matrix interactions and indirectly act to promote cell division and migration. They bind to and target matrix metalloproteins (MMPS) such as collagenase, so as to pave the way for metastatic cells (see below).
- **Immunoglobulin supergene family** such as ICAM-1, correlates positively with the aggressiveness of a number of tumor types.
- **Cadherins** are a family of calcium (Ca$^{2+}$)-dependent, transmembrane, cell-cell adhesion molecules. E-cadherin, is expressed on the surface of all epithelia and mediates cell-cell adhesion by mutual zipper interactions. It appears to suppress metastasis, as its expression is lost in most carcinomas thereby permitting malignant cells to leave the tumor mass.
- **Catenins** are proteins that interact with the intracellular domain of E-cadherin and create a mechanical linkage between that molecule and the cytoskeleton, which is essential for effective epithelial cell interactions. Like E-cadherin (above) catenin expression is reduced or lost in most carcinomas. Interestingly, β-catenin also binds to the adenomatous polyposis coli (APC) gene product. Mutations in either the APC or β-catenin gene are implicated in the development of colon cancer (see later and Chapter 13).

**Growth Factors and Cytokines**

Growth factors and cytokines orchestrate cellular responses during development, differentiation, and repair. Aberrant production of growth factors by tumors contributes to neoangiogenesis and the attraction of inflammatory cells. They also enhance proliferation, migration, and invasive properties of the tumor cells.

**Proteolytic Enzymes**

A breach of the basement membrane that separates an epithelium from the underlying mesenchymal compartment is the first event in tumor cell invasion. The basement membrane is composed of a number of extracellular matrix components, including type IV collagen, laminin, and proteoglycans (see Chapter 3). Malignant cells and stromal cells associated with cancers elaborate a variety of proteases that degrade one or more of the basement membrane components. Such enzymes include the urokinase-type plasminogen activator (u-PA) and MMPs, including collagenases.

u-PA converts serum plasminogen to plasmin, a serine protease that degrades laminin and activates type IV procollagenase. u-PA activity is balanced by plasminogen activator inhibitor (PAI); changes in the expression of u-PA, the u-PA receptor, and PAI have been reported in different cancers.

The MMPs comprise a family of zinc-dependent endopeptidases that are susceptible to tissue inhibitors of MMPs. MMPs include interstitial collagenases, stromelysins, gelatinases, and membrane-type MMPs. These enzymes are synthesized and secreted by normal cells under conditions associated with physiologic tissue remodeling, such as wound healing and placental implantation. Under these circumstances, a balance between MMPs and tissue inhibitors of MMPs is strictly regulated. By contrast, the invasive and metastatic phenotypes of cancer cells are characterized by dysregulation of this balance. A direct correlation between increased expression of MMPs and augmented invasive capacity or metastatic potential of tumor
cells has been observed in many cancers. Deregulated MMP activity permits entry of cancer cells into and through the extracellular matrix.

Metastasis
Following the invasion of surrounding tissue, malignant cells may spread to distant sites by a process that includes a number of steps:

1. **Invasion of the circulation:** After invading interstitial tissue, malignant cells penetrate lymphatic or vascular channels. In lymph nodes, communications between lymphatics and venous tributaries allow the cells access to the systemic circulation. Most tumor cells do not survive their journey in the bloodstream, and less than 0.1% remain to establish a new colony.

2. **Escape from the circulation:** Circulating tumor cells may arrest mechanically in capillaries and venules, where they attach to endothelial cells. This adherence causes retraction of the endothelium, thereby exposing the underlying basement membrane to which tumor cells now bind. Clumps of circulating tumor cells may also arrest in arterioles, where they grow within vascular lumens. In both situations, tumor cells eventually extravasate by mechanisms similar to those responsible for local invasion.

3. **Local growth:** In a hospitable site, the extravasated cancer cells grow in response to autocrine and possibly local growth factors produced by the host tissue. However, a new vascular supply is necessary for the tumor to grow to a diameter greater than 0.5 mm. Thus, many tumors secrete polypeptides (e.g., fibroblast growth factor, vascular endothelial growth factor), transforming growth factor-β, and platelet-derived growth factor [PDGF]), which together trigger and regulate the process of **angiogenesis** (see below). The metastasis can metastasize again, either within the same organ or to distant sites.

The establishment of a metastatic colony does not mean that it inevitably enlarges. It is well known clinically that tumors may recur locally or at metastatic sites many years after the primary cancer has been surgically removed. For example, patients treated for breast cancer or malignant melanoma may be apparently cured for 20 or more years, only to have the tumor suddenly recur. The molecular basis for this phenomenon, termed **tumor dormancy**, is not well understood.

**Target Organs in Metastatic Disease**
It was recognized more than a century ago that the distribution of metastases in breast cancer is not random. In 1889, Paget proposed that the spread of tumor cells to specific secondary sites depends on compatibility between the tumor cells (the seed) and favorable microenvironment factors in the secondary site (the soil). By contrast, others have argued that metastatic spread depends solely on anatomical factors and the blood flow to an organ. Today, there is evidence that both mechanisms operate, depending on the tumor. For example, cancers of the breast, prostate, and thyroid metastasize to bone, a tropism that suggests a favored “soil.” Conversely, despite their size and abundant blood flow, neither the spleen nor skeletal muscle is a common site of metastases. Yet for many cancers, the vascular anatomy unquestionably influences the pattern of metastatic spread. Malignant tumors of the gastrointestinal tract commonly metastasize to the first capillary bed they encounter, namely the liver. Similarly, lung cancers often spread to the brain. An additional factor that regulates homing of malignant cells may be the expression of complementary adhesion molecules, either by the cancer cells or those of the organ to which they home.

**The Grading And Staging Of Cancers**
In an attempt to predict the clinical behavior of a malignant tumor and to establish criteria for therapy, many cancers are classified according to cytologic and histologic grading schemes or by staging protocols that describe the extent of spread.

**Cancer Grading Reflects Cellular Characteristics**
Low-grade tumors are **well differentiated**; high-grade ones tend to be **anaplastic** (that is, they lack those differentiated features that indicate the tissue of origin). Cytologic and histologic grading, which are necessarily subjective and at best semiquantitative, are based on the degree of anaplasia and on the number of proliferating cells. The degree of anaplasia is determined from the shape and regularity of the cells and from the presence of distinct differentiated features, such as functioning gland-like structures in adenocarcinomas or epithelial pearls in squamous carcinomas. The presence of such characteristics identify a tumor as well differentiated. By contrast, the cells of “poorly differentiated” malignancies bear little resemblance to their normal counterparts. Evidence of rapid or abnormal growth is provided by (1) large numbers of mitoses, (2) atypical mitoses, (3) nuclear pleomorphism, and (4) tumor giant cells. Most grading schemes classify tumors into three or four grades of increasing malignancy. The general correlation between the cytologic grade and the biological behavior of a neoplasm is not invariable: There are many examples of tumors of low cytologic grades that exhibit substantial malignant properties.
Cancer Staging Refers to the Extent of Spread

The choice of a surgical approach or the selection of treatment modalities is influenced more by the stage of a cancer than by its cytologic grade. Moreover, most statistical data related to cancer survival are based on the stage rather than the cytologic grade of the tumor. Clinical staging is independent of cytologic grading. The significant criteria used for staging vary with different organs. Commonly used criteria include:

- Tumor size
- Extent of local growth, whether within or without the organ
- Presence of lymph node metastases
- Presence of distant metastases

These criteria have been codified in the international TNM cancer staging system, in which “T” refers to the size of the primary tumor, “N” to regional node metastases, and “M” to the presence and extent of distant metastases. The definitions of numerical scores for T, N, and M (e.g., T1–T4, N1–N3) vary according to specific tumor types.

Tumor size and degree of local spread influence prognosis and therapy. For instance, a primary breast cancer smaller than 2 cm in diameter can be treated with local excision and radiation therapy; larger masses often necessitate mastectomy. Duke classification of colorectal cancer penetration of the tumor into the muscularis and serosa of the bowel is associated with a poorer prognosis than that of a more superficial tumor. Clearly, the presence of lymph node metastases mandates more aggressive treatment than does their absence, whereas the presence of distant metastases is generally a contraindication to surgical intervention other than for palliation.

The Clonal Origin Of Cancer

Studies of human and experimental tumors have provided strong evidence that most cancers arise from a single transformed cell. This theory has been most thoroughly examined in connection with proliferative disorders of the hematopoietic system. Cell surface markers have been used to establish a monoclonal origin for many hematopoietic malignant disorders. For example, B-cell lymphomas are composed of cells that exclusively display either κ or λ light chains on their surface, whereas polyclonal lymphoid proliferations exhibit both types of cells. Monoclonality has also been demonstrated in the individual metastases of a number of solid tumors. An early observation in regard to the monoclonal origin of cancer was derived from the study of glucose-6-phosphate dehydrogenase in women who were heterozygous for its two isozymes, A and B (Fig. 5-12). These

![FIGURE 5-12. Monoclonal origin of human tumors.](image-url)
isozymes are encoded by genes located on the X chromosome. Because one X chromosome is randomly inactivated, only one of these genes is expressed in any given cell. Thus, although the genotypes of all cells are the same, their phenotypes vary with regard to the expression of isozyme A or B. An examination of benign uterine smooth muscle tumors (leiomyomas, or “fibroids”) revealed that all the cells in an individual tumor expressed either A or B but not both, indicating that each tumor was derived from a single progenitor cell.

**The Growth Of Cancers**

Historically, cancer was considered to result from a totally unregulated growth of cells, and a logical corollary was that neoplastic cells divide at a faster rate than normal ones. It is now clear that tumor cells do not necessarily proliferate more rapidly than their normal counterparts. Tumor growth depends on other factors, such as the growth fraction (proportion of cycling cells) and the rate of cell death. In normal proliferating tissues (e.g., intestine and bone marrow), an exquisite balance between cell renewal and cell death is strictly maintained. By contrast, the major determinant of tumor growth is clearly the fact that more cells are produced than die in a given time. Such an effect can reflect either an excess of cell proliferation over programmed cell death or normal rates of cell renewal in the face of reduced apoptosis.

**Tumor Growth Rates may be Expressed as Doubling Times**

*Tumor doubling time is the time taken for the number of cells in the mass to double.* Internal cancers are not usually detected before they attain a size of about 1 cm³ (1 g), which corresponds to $10^8$ to $10^9$ cells. The origin of most tumors from a single cell implies that the mass has doubled at least 30 times to reach this size. If the cancer is neglected and enlarges to the impressive size of 1 kg, it now contains $10^{12}$ cells. Yet, the growth from 1 g to 1 kg (assuming no cell death) can be achieved by only 10 additional population doublings. Thus, when cancers are initially detected clinically, they are already far advanced in their natural history. Because of the variable death rate of tumor cells and differences in cell cycle kinetics, the actual doubling time of human tumors is highly unpredictable. Furthermore, the doubling time is not necessarily correlated with the growth fraction (i.e., the proportion of cells that are within the cell cycle) or the number of proliferated tumor cells that survive to further reproduce. It has been estimated that in human skin tumors, as many as 97% of proliferated cells die spontaneously. The causes of tumor cell death are not precisely defined but probably include such factors as (1) programmed cell death (apoptosis), (2) inadequate blood supply, with consequent ischemia, (3) a paucity of nutrients, and (4) vulnerability to specific and nonspecific host defenses. From a practical point of view, the prior history of a malignant tumor cannot be reasonably estimated from its size when it is first discovered.

**Tumor Angiogenesis Refers to the Sprouting of New Capillaries**

In the absence of new vessels to supply nutrients and remove waste products, malignant tumors do not grow larger than 1 to 2 mm in diameter. In this context, the density of capillaries within the primary tumor (e.g., cancers of the breast, prostate, and colon) correlates directly with metastases and decreased host survival. Importantly, tumor angiogenesis occurs in non-neoplastic host tissue and is comparable to that in wound healing and other physiologic circumstances (see Chapter 3). A number of factors can stimulate angiogenesis, of which vascular endothelial growth factor and fibroblast growth factor-2 are thought to be the most important. The role of such angiogenic factors is underscored by the growth suppression of many solid tumors by both endogenous and synthetic inhibitors of angiogenesis factors, some of which are in clinical use.

**The Molecular Genetics Of Cancer**

It is now recognized that the unregulated growth of cancer cells results from the sequential acquisition of somatic mutations in genes that control cell growth, differentiation, and apoptosis, or that maintain genomic integrity. Similar mutations may also be present in the germ line of persons with hereditary cancer predispositions. Mutations can be produced by environmental mutagens such as chemical carcinogens or radiation (see below). They can also arise during normal cellular metabolism, particularly from the formation of activated oxygen species (see Chapter 1).

It is likely that the most common mechanism of mutation relates to spontaneous errors in DNA replication and repair. Assuming a mutation rate of about $2.5 \times 10^{-8}$ per nucleotide, it has been estimated that humans acquire about 175 mutations per generation. Thus, it is inevitable that everyone is a somatic mosaic at many genetic loci. If the mutation involves genes that control growth or stabilize the genome, it may give rise to a clone of cells that possess a growth advantage over their normal neighbors. Successive mutations in similar genes result in increasingly aberrant clones until a malignant phenotype eventually emerges. *In a sense, the emergence of malignancy may be viewed as an evolutionary process wherein we see only the surviving clones.*
CHAPTER 5: NEOPLASIA

Transformed Cells Share Common Attributes

Cancer cells are remarkably heterogeneous in appearance, growth rate, invasiveness, and metastatic potential, presumably due to the interplay between diverse acquired mutations and the inherent gene expression of specific cell lineages. Nevertheless, transformed cells share certain biological features. The disruption of a limited number of regulatory pathways (involving about 4 to 7 mutated genes) leads to deregulation of cell proliferation and suppression of apoptosis and confers a neoplastic phenotype to diverse cell types. This is a multistep process, which takes place over a period of years. The process involves:

- Autonomous generation of mitogenic signals
- Insensitivity to exogenous antigrowth signals
- Resistance to apoptosis
- Limitless replicative potential (immortalization)
- Blocked differentiation
- Ability to sustain angiogenesis
- Capacity to invade surrounding tissues
- Potential to metastasize

The normal genes that are mutated in various cancers, include cell cycle regulators, signal transduction factors, transcriptional factors, DNA-binding proteins, growth factor receptors, adhesion molecules, effectors of apoptosis, and telomerase. Such “transforming genes” genes can be grouped into three categories:

- **Oncogenes** are altered versions of normal genes, termed protooncogenes, which regulate normal cell growth, differentiation, and survival. Gain-of-function (dominant) mutations activate protooncogenes to become oncogenes. Such mutated genes are positive effectors of the neoplastic phenotype.

- **Tumor suppressor genes** are normal genes with products that inhibit cellular proliferation. Loss-of-function (recessive) mutations inactivate the normal inhibitory activities of tumor suppressor genes. By permitting unregulated cell growth, tumor suppressor genes serve as negative effectors of the neoplastic phenotype.

- **Mutator genes (DNA mismatch repair genes)** normally maintain the integrity of the genome and the fidelity of DNA replication. Inactivating mutations of these genes allow the successive accumulation of further mutations.

Oncogenes are Counterparts of Normal Genes

The transfer of specific genes (oncogenes) from human tumor cells into rodent cells by virus vectors in vitro can transform the recipient cells. The transforming genes were discovered to be mutant versions of normal genes involved in growth regulation and were termed protooncogenes. Transforming viral oncogenes were termed v-onc genes, and their cellular counterparts (c-) were individual normal genes (e.g., c-myc, c-jun, c-src).

Mechanisms of Activation of Cellular Oncogenes

There are three general mechanisms by which protooncogene activation is accomplished:

- An activating mutation of a protooncogene leads to the constitutive (dysregulated) production of an abnormal protein. The mutations may involve (1) point mutations, (2) deletions, or (3) chromosomal translocations.
- An increase in the expression of the protooncogene may cause overproduction of a normal gene product.
- The activation of protooncogenes is regulated by numerous autoinhibitory mechanisms, which operate as a safeguard against inappropriate activity. Thus, many mutations in protooncogenes lead to resistance to normal autoinhibitory and regulatory constraints.

Activation by Mutation

Activating, or gain-of-function, mutations in protooncogenes are usually somatic rather than germline alterations. Germline mutations in protooncogenes, which are known to be important regulators of growth during development, are ordinarily lethal in utero. There are several exceptions to this rule. For example, c-ret is inactivated in the pathogenesis of certain heritable endocrine cancers, and c-met, which encodes the receptor for hepatocyte growth factor, is associated with a hereditary form of renal cancer.

Activation by Chromosomal Translocation

Chromosomal translocations (i.e., the transfer of a portion of one chromosome to another) have been implicated in the pathogenesis of several human leukemias and lymphomas (See Chapter 20). The first and still the best-known example of an acquired chromosomal translocation in a human cancer is the Philadelphia chromosome, which is found in 95% of patients with chronic myelogenous leukemia (Fig. 5-13). The translocation activates the c-abl protooncogene (a nonreceptor protein kinase) by the formation of an aberrant fusion protein. The resultant BCR/ABL oncogene has very high tyrosine kinase activity, which generates mitogenic and antiapoptotic signals. In Burkitt lymphoma the c-myc protooncogene involved in cell cycle progression is translocated next to genes that control transcription of immunoglobulin light or heavy chains thereby leading to the overproduction of a normal product. The excessive amount of the normal c-myc product, probably in association with other genetic alterations, leads to the emergence of a dominant clone of B cells, driven relentlessly to proliferate as a monoclonal neoplasm.
Although the above malignant conditions are initiated by chromosomal translocations, during the progression of many cancers, myriad chromosomal abnormalities take place (translocations, breaks, aneuploidy, etc.).

**Activation by Gene Amplification**
Chromosomal alterations that result in an increased number of gene copies (i.e., gene amplification) have been found primarily in human solid tumors. The erbB protooncogene is amplified in up to one third of breast and ovarian cancers. The erbB2 gene (also designated HER2/neu) encodes a receptor-type tyrosine kinase that shows close structural similarity to the EGF receptor. Amplification of erbB2 in breast and ovarian cancer may be associated with poor overall survival and decreased time to relapse. In this context, an antibody targeted against HER2/neu (trastuzumab) is now used as adjunctive therapy for breast cancers that overexpress this protein.

**Mechanisms of Oncogene Action**
Oncogenes can be classified according to the roles of their normal counterparts (protooncogenes) in the biochemical pathways that regulate growth and differentiation. These include the following (Fig. 5-14):

- Growth factors
- Cell surface receptors
- Intracellular signal transduction pathways
- DNA-binding nuclear proteins (transcription factors)
- Cell cycle proteins (cyclins and cyclin-dependent protein kinases)
- Inhibitors of apoptosis (bcl-2)

**Oncogenes and Growth Factors**
The binding of soluble extracellular growth factors to their specific surface receptors initiates signaling cascades that eventuate in entry of the cell into the mitotic cycle. A few protooncogenes encode growth factors that stimulate tumor cell growth. In some instances, a growth factor acts upon the same cell that produces it (autocrine stimulation). Other growth factors act upon the receptors of neighboring cells (paracrine stimulation).

PDGF is the protein product of the c-sis protooncogene and is a potent mitogen for fibroblasts, smooth muscle
Ras Oncogenes

Activation of ras genes (Ha-ras, Ki-ras, or N-ras) is the most frequent dominant mutation in human cancers. Ras is an effector molecule in the signal transduction cascade that couples the activation of growth factor receptors to changes in nuclear gene transcription. The ras protooncogene codes for a product, p21, that belongs to a family of small cytoplasmic proteins (G proteins) that bind guanosine triphosphate (GTP) and guanosine diphosphate (GDP) (Fig. 5-15). The protein p21 is active when it binds GTP. Bound GTP is converted to GDP by the intrinsic GTPase of p21, an activity that is stimulated by a GTPase-activating protein (GAP). The intrinsic GTPase activity is the “off” switch for the molecule. Point mutations of ras, which either directly reduce p21 GTPase activity or render it resistant to GAP, result in uncontrolled stimulation of ras-related functions, because p21 is locked in the “on” position.

Oncogenes and Nuclear Regulatory Proteins

A number of nuclear proteins encoded by protooncogenes are intimately involved in the sequential expression of genes that regulate cellular proliferation and differentiation. Many of these proteins can bind to DNA, where they regulate the expression of other genes. The transitory expression of several protooncogenes is necessary for the cells to pass through specific points in the cell cycle. Protooncogenes that are expressed early in the cell cycle (such as c-myc, c-fos and c-jun) render the cells competent to receive the final signals for mitosis and are, therefore, termed competence genes. In general, competence genes play a role in (1) progression from the G1 to the S phase in the cell cycle, (2) stability of the genome, (3) apoptosis, and (4) positive or negative effects on cellular maturation. However, the cells are not yet fully programmed to divide after the expression of these genes and will enter the S phase and mitosis only after further stimulation by other factors, such as EGF or IGF-I (progression factors).

Bcl-2 and Apoptosis

Normal tissue requires an exquisite balance between cell proliferation and cell death mediated by apoptosis (see Chapter 1). The most prominent example of suppression of apoptosis in a tumor cell is the upregulation of the antiapoptotic protein bcl-2 in B-cell neoplasia. Bcl-2 and its family regulate the permeability of mitochondrial membranes. Bcl-2 itself exerts an antiapoptotic effect by preventing the release of cytochrome c, thereby protecting the cell from the mitochondrial apoptotic pathway. Follicular B-cell lymphomas (see Chapter 20) display a characteristic chromosomal translocation, t(14;18), in which the bcl-2 gene on chromosome 18 is brought under the transcriptional control of the immunoglobulin light-chain gene promoter.

cells, and glial cells. Cells derived from human sarcomas and glioblastomas (malignant glial cell tumors) produce PDGF-like polypeptides; their normal counterparts do not. Thus, a normal human gene (c-sis) that encodes a growth factor (PDGF) acquires transforming capacity when it is constitutively expressed in a cell that responds to this signal.

Oncogenes and Growth Factor Receptors

The regulation of the functional responses to growth factors—including cell proliferation, differentiation, and survival—depends principally on the expression of, and relative balance between, various growth factor receptors. Binding of a ligand to the extracellular domain of its receptor stimulates an intrinsic kinase activity in the cytoplasmic domain of the receptor that phosphorylates tyrosine residues on intracellular signaling molecules. Thus, because growth factor receptors can generate potent mitogenic signals, they harbor a latent oncogenic potential, which when activated, overrides the normal controls of signaling pathways.

Under normal circumstances, transient binding of a growth factor to its receptor leads to activation of the cytoplasmic tyrosine kinase domain, after which the receptor reverts to its resting state. Certain mutations of growth factor receptors, including truncation of the extracellular or intracellular domains, point mutations, and deletions, result in unrestrained (constitutive) activation of the receptor, independent of ligand binding and promotion of dysregulated growth. For example, germline point mutations in c-ret lead to constitutive activation of the receptor and are associated with multiple endocrine neoplasia syndromes and familial medullary thyroid carcinoma (see Chapter 21).
thereby causing overexpression of bcl-2. As a result of the antiapoptotic properties of bcl-2, the neoplastic clone accumulates in the affected lymph nodes.

Tumor Suppressor Genes Negatively Regulate Cell Growth

A second general mechanism by which a genetic alteration contributes to carcinogenesis is a mutation that creates a deficiency of a normal gene product (tumor suppressors or “gate keepers”) that exerts a negative regulatory control of cell growth and thereby suppresses tumor formation (“loss of function mutations”). Such genes encode negative transcriptional regulators of the cell cycle, signal-transducing molecules, and cell surface receptors.

Because both alleles of tumor suppressor genes must be inactivated to produce the deficit that allows the development of a tumor, the normal suppressor gene is functionally dominant. In this circumstance, the heterozygous state is sufficient to protect against cancer. Loss of heterozygosity in a tumor suppressor gene by deletion or somatic mutation of the remaining normal allele predisposes to tumor development.

The Role of Tumor Suppressor Genes in Carcinogenesis

Tumor suppressor genes are increasingly being incriminated in the pathogenesis of both hereditary and spontaneous cancers in humans. Two such genes have been particularly well studied. The Rb and p53 gene products serve to restrain cell division in many tissues, and their absence or inactivation is linked to the development of malignant tumors. In this context, oncogenic DNA viruses encode products that interact with these suppressor proteins, thereby inactivating their functions. Thus, the mechanisms underlying the development of some tumors associated with germline and somatic mutations and infections with DNA viruses involve the same cellular gene products.

Retinoblastoma Gene

Retinoblastoma, a rare childhood cancer, is the prototype of a human tumor in which the origin is attributed to the inactivation of a specific tumor suppressor gene (the Rb gene) located on the long arm of chromosome 13. About 40% of cases are associated with a germline mutation; the remainder are sporadic. In sporadic cases of retinoblastoma, the child begins life with two normal Rb alleles in all somatic cells, but both are inactivated by somatic mutations in the retina. Because somatic mutations in the Rb gene are uncommon, the incidence of sporadic retinoblastoma is very low (1/30,000).

In patients with hereditary retinoblastoma, all somatic cells carry one missing or mutated allele of the Rb gene. This heterozygous state is not associated with any observable changes in the retina, presumably because 50% of the Rb gene product is sufficient to prevent the development of disease. If the remaining normal Rb allele is inactivated by deletion or mutation (loss of heterozygosity), loss of the Rb gene product allows the appearance of a retinoblastoma, in which both alleles of the Rb gene are inactive in all tumor cells. Thus, the Rb gene exerts a tumor suppressor function, and the development of hereditary retinoblastoma is associated with two genetic events (Knudson’s “two-hit” hy-
The p53 Gene Family

The p53 tumor suppressor gene is a principal mediator of growth arrest, senescence, and apoptosis. Therefore, loss of p53 function is, not unexpectedly, associated with cancer. In response to DNA damage, oncogenic activation of other proteins, and other stresses (e.g., hypoxia), p53 levels rise. Increased p53 levels enhance the synthesis of cyclin-dependent kinase inhibitors and the inactivation of cyclin–cyclin-dependant kinase (CDK) complexes, thereby leading to cell arrest at the G1–S phase transition. Hence, cells are prevented from entering the S phase of the cell cycle. Such arrested cells may repair DNA damage or undergo apoptosis. In this manner, p53 acts as a “guardian of the genome” by restricting uncontrolled cellular proliferation under circumstances in which cells with abnormal DNA might propagate.

The p53 gene is located on the small arm of chromosome 17, and its protein product is present in virtually all normal tissues. This gene is deleted or mutated in 75% of cases of colorectal cancer and frequently in breast cancer, small cell carcinoma of the lung, hepatocellular carcinoma, astrocytoma, and numerous other tumors. In fact, mutations of p53 seem to be the most common genetic change in human cancer. Many human cancers exhibit deletion of both p53 alleles, in which case the cell contains no p53 gene product. By contrast, in some cancers, the malignant cells express one normal p53 allele and one mutant version. In these cases, the mutant p53 protein forms complexes with the normal p53 protein and inactivates the function of the normal suppressor gene. When a mutant allele inactivates the normal one, the mutant allele is said to be a dominant negative gene. Theoretically, a cell containing one mutant p53 allele (i.e., a heterozygote) might have a growth advantage over normal cells, a situation that would increase the number of cells at risk for a second mutation (loss of heterozygosity) and the development of cancer.

Li-Fraumeni syndrome refers to an inherited predisposition to develop cancers in many organs due to germline mutations of p53. Persons with this condition carry germline mutations in one p53 allele, but their tumors display mutations at both alleles. This situation is similar to that determining inherited retinoblastoma and is another example of the two-hit hypothesis (see Fig. 5-16) and loss of heterozygosity.

Other Tumor Suppressor Genes

A number of unrelated syndromes have now been shown to result from germline mutations in various tumor suppressor genes. For example, the APC gene is implicated in the pathogenesis of familial adenomatous polyposis coli and most sporadic colorectal cancers (see Chapter 13). The APC gene product binds to and inhibits the function of β-catenin (see above), Mutations in both APC and β-catenin genes have also been described in other malignant tumors, including malignant melanoma and ovarian cancer. Hereditary Wilms’ tumor, neurofibromatosis type 1, von Hippel-Lindau syndrome (associated with renal cell carcinoma), hemangioblastoma of the brain, and pheochromocytoma are all associated with germline mutations of genes with tumor suppressor functions.

Tumor Suppressor Genes and Oncogenic DNA Viruses

Unlike RNA tumor viruses that have oncogenes with have normal cellular counterparts, the transforming genes of DNA viruses are not homologous with any cellular genes. The gene products of oncogenic DNA viruses lead to the inactivation of tumor suppressor proteins. This phenomenon is analogous to the ability of mutant tumor suppressor proteins to inhibit their normal counterparts. For example, the binding of an HPV protein to p53 accelerates the degradation of this suppressor protein. The transforming proteins of polyoma viruses (including SV40), adenoviruses, HPVs, and human herpes virus (HHV)-8 also bind and inactivate Rb. These observations indicate that oncogenic DNA viruses use common mechanisms for altering growth regulation and, thereby, transforming cells.

DNA Repair Genes Protect the Integrity of the Genome

The third class of genes in which mutations contribute to the pathogenesis of cancer are those involved in DNA mismatch repair, so-called mutator genes or caretaker genes. The loss of these gene functions renders the DNA susceptible to the progressive accumulation of mutations; when these affect protooncogenes or tumor suppressor genes, cancer may result. A number of syndromes demonstrating
a familial predisposition to cancer have been associated with mutations in genes involved in DNA repair. For example, hereditary nonpolyposis colon cancer (or Lynch syndrome) reflects a familial predisposition to the development of colorectal cancer (not associated with APC), which accounts for about 5% of the disease (see Chapter 13). Patients are heterozygous for one of five genes involved in DNA mismatch repair. Tumors have lost the function of both alleles and demonstrate microsatellite instability associated with uncorrected nucleotide mispairing. Several other syndromes with cancer susceptibility, including ataxia telangiectasia, xeroderma pigmentosum, and Bloom syndrome, all demonstrate an increased risk of cancer related to mutations in genes involved in DNA repair.

Telomerase is Activated in Most Cancers

As cells in tissue culture continue to divide, the tips of the chromosomes, termed telomeres, progressively shorten (see Chapter 1). Somatic cells do not normally express telomerase, an enzyme that recognizes the end of a chromosome and adds repetitive telomeric sequences to maintain telomere length. Most human cancers show activation of the gene for the catalytic subunit of telomerase, namely human telomerase reverse transcriptase. Telomerase is not classified as an oncogene because it does not lead to growth deregulation. Many immortalized cell lines that express telomerase show no evidence of neoplastic capacity. Thus, despite extensive research in the field, the role of telomerase in oncogenesis remains controversial.

Viruses And Human Cancer

Despite the existence of viral oncogenes, the number of human cancers definitely associated with viral infections is limited. Nevertheless, it is estimated that viral infections are responsible for some 15% of all human cancers. The strongest associations between the presence of viruses and the development of cancer in humans are:

- Human T-cell leukemia virus type I (HTLV-I) (RNA retrovirus) and T-cell leukemia/lymphoma
- HPV (DNA virus) and carcinoma of the cervix
- Hepatitis B virus (HBV) (DNA virus) and hepatitis C virus (RNA) and primary hepatocellular carcinoma
- Epstein-Barr virus (EBV) (DNA virus) and certain forms of lymphoma and nasopharyngeal carcinoma
- HHV 8 (DNA virus) and Kaposi sarcoma.

Worldwide, infections with hepatitis B and C viruses and HPVs alone account for 80% of all virus-associated cancers.
**Human T-Cell Leukemia Virus-I (HTLV-I) is a Lymphotropic Agent**

The one human cancer that has been firmly linked to infection with an RNA retrovirus is the rare adult T-cell leukemia, which is endemic in southern Japan as well as the Caribbean basin and occurs sporadically in other parts of the world. The etiological agent, HTLV-I, is tropic for CD4+ T lymphocytes and has also been incriminated in the pathogenesis of a number of neurologic disorders. It is estimated that leukemia develops in less than 5% of persons infected with HTLV-I and exhibits a latency period on the order of 40 years for its development. Oncogenic stimulation by HTLV-I is mediated principally by the viral transcriptional activation protein tax. Tax protein not only increases the transcription from its own viral genome, but it also promotes the activity of other genes involved in host cell proliferation.

**DNA Viruses Encode Proteins that Bind Regulatory Proteins**

Four DNA viruses (HPV, EBV, HBV, and HHV 8) are implicated in the development of human cancers. The transforming genes of oncogenic DNA viruses exhibit virtually no homology with cellular genes, whereas those of RNA retroviruses (oncogenes) are derived from, and are homologous with, their cellular counterparts (protooncogenes). As discussed above, oncogenic DNA viruses have genes that encode protein products that bind to, and inactivate, specific host proteins (the products of tumor suppressor genes, e.g., Rb, p53) involved in the regulation of cell proliferation and apoptosis.

**HPVs**

HPVs induce lesions in humans that progress to squamous cell carcinoma. Papillomaviruses manifest a pronounced tropism for epithelial tissues, and their full productive life cycle occurs only in squamous cells. At least 20 HPV types are associated with cancer of the uterine cervix, especially HPV 16 and 18 (see Chapter 18). The major oncoproteins encoded by HPV are E6 and E7. E6 binds to p53 and targets it for degradation. E7 binds to Rb, thereby releasing its inhibitory effect on cell cycle progression.

**EBV**

EBV is a human herpesvirus that is so widely disseminated that 95% of adults in the world have antibodies against it. EBV infects B lymphocytes, transforming them into lymphoblasts with an indefinite lifespan. In a small proportion of primary infections with EBV, this lymphoblastoid transformation is manifested as infectious mononucleosis (see Chapter 9), a short-lived lymphoproliferative disease. However, EBV is also intimately associated with the development of certain human cancers.

When B lymphocytes are infected with EBV, they acquire the ability to proliferate indefinitely in vitro. A number of EBV genes are implicated in this lymphocyte immortalization, including Epstein-Barr nuclear antigens (EBNAs) and latent-infection—associated membrane proteins (LMPs). The EBNAs maintain the EBV genome in its episomal state and activate the transcription of viral and cellular genes. LMP1 interacts with cellular proteins that normally transduce signals from the TNF receptor, a critical pathway in lymphocyte activation and proliferation. Both EBNAs and LMPs can be demonstrated in most EBV-associated cancers. These include the following:

**BURKITT LYMPHOMA:** African Burkitt lymphoma is a B-cell tumor, in which the neoplastic lymphocytes invariably contain EBV in their DNA and manifest EBV-related antigens (see Chapter 20). The tumor has also been recognized in non-African populations, but in those cases, only about 20% contain the EBV genome. The localization of Burkitt lymphoma to equatorial Africa is not understood, but it has been suggested that prolonged stimulation of the immune system by endemic malaria may be important. As discussed above, lymphoma production in African Burkitt lymphoma is associated with a chromosomal translocation, in which the c-myc protooncogene is deregulated by being brought into proximity with an immunoglobulin promoter region. Ultimately, this leads to uncontrolled proliferation of a malignant clone of B lymphocytes.

**POLYCLONAL LYMPHOPROLIFERATION IN IMMUNODEFICIENT STATES:** Congenital or acquired immunodeficiency states can be complicated by the development of EBV-induced, B-cell proliferative disorders. These lesions may be clinically and pathologically indistinguishable from true malignant lymphomas, but they differ in that most of them are polyclonal. The incidence of lymphoid neoplasia in immunosuppressed renal transplant recipients is 30 to 50 times that of the general population. In virtually all cases of lymphoproliferations associated with organ transplantation, EBNA or EBV genomic material is present in the neoplastic tissue. Similar B-cell lymphoproliferative disorders are seen in a number of other acquired immunodeficiencies, notably, AIDS.

**NASOPHARYNGEAL CARCINOMA:** Nasopharyngeal carcinoma is a variant of squamous cell carcinoma that has a worldwide distribution and is particularly common in certain parts of Africa and Asia. EBV, DNA, and EBNA are present in virtually all of these cancers. The pathogenesis of nasopharyngeal carcinoma may be related to infection with EBV in early childhood, with reactivation at 40 to 50 years of age and the appearance of tumors 1 to 2 years thereafter.
Chemical Carcinogens are Mostly Mutagens

A mutagen is an agent that can permanently alter the genetic constitution of a cell. About 90% of known carcinogens are mutagenic in a variety of in vitro systems, which detect mutations in bacteria and in cultured animal and human cells. Moreover, most, but not all, mutagens are carcinogenic. This close correlation between carcinogenicity and mutagenicity presumably occurs because both reflect damage to DNA. Although not infallible, in vitro mutagenicity assays have proved to be valuable tools in screening for the carcinogenic potential of chemicals.

Chemical Carcinogenesis is a Multistep Process

Chemical carcinogenesis is best understood as a multistep process that involves numerous mutations. Four stages of chemical carcinogenesis summarize this process:

1. **Initiation** likely represents a mutation in a single cell.
2. **Promotion** reflects the clonal expansion of the initiated cell, in which the mutation has conferred a growth advantage. During promotion, the altered cells remain dependent on the continued presence of the promoting stimulus. This stimulus may be an exogenous chemical or physical agent or may reflect an endogenous mechanism (e.g., hormonal stimulation in the breast and prostate).
3. **Progression** is the stage in which growth becomes autonomous (i.e., independent of the carcinogen or the promoter). By this time, sufficient mutations have accumulated to immortalize cells.
4. **Cancer**, the end result of the entire sequence, is established when the cells acquire the capacity to invade and metastasize.

The morphologic changes that reflect multistep carcinogenesis in humans are best exemplified in epithelia, such as those of the skin, cervix, and colon. Although initiation has no visible counterpart, promotion and progression are represented by the sequence of hyperplasia, dysplasia, and carcinoma in situ.

Chemical Carcinogens Usually Undergo Metabolic Activation

About 75 chemicals are recognized as human carcinogens. Chemicals cause cancer either directly or, more often, after metabolic activation. The direct-acting carcinogens are inherently reactive enough to bind covalently to cellular...
macromolecules. Most organic carcinogens, however, require conversion to an ultimate, more reactive compound. This conversion is enzymatic and, for the most part, is effected by the cellular systems involved in drug metabolism and detoxification. Many cells in the body, particularly liver cells, possess enzyme systems that can convert procarcinogens to their active forms. Yet each carcinogen has its own spectrum of target tissues, often limited to a single organ. The basis for organ specificity in chemical carcinogenesis is not well understood.

POLYCYCLIC AROMATIC HYDROCARBONS: The polycyclic aromatic hydrocarbons are among the most extensively studied carcinogens. Found in cigarette smoke, they may well be involved in the production of lung cancer. These compounds have a broad range of target organs and, in experimental models, generally produce cancers at the site of application including the skin, soft tissues, and breast.

Polycyclic hydrocarbons are metabolized by cytochrome P450-dependent mixed-function oxidases to electrophilic epoxides, which in turn react with proteins and nucleic acids. For example, vinyl chloride, the simple two-carbon molecule from which the widely used plastic polyvinyl chloride is synthesized, is metabolized to an epoxide, which is responsible for its carcinogenic properties. Workers exposed to the vinyl chloride monomer in the ambient atmosphere later developed hepatic angiosarcomas.

ALKYLATING AGENTS: Many chemotherapeutic drugs (e.g., cyclophosphamide, cisplatin, busulfan) are alkylating agents that transfer alkyl groups (methyl, ethyl, etc.) to macromolecules, including guanines within DNA. Although such drugs destroy cancer cells by damaging DNA, they also injure normal cells. Thus, alkylating chemotherapy carries a significant risk of solid and hematological malignancies at a later time.

AFLATOXIN: Aflatoxin B<sub>1</sub>, a natural product of the fungus Aspergillus flavus, is among the most potent liver carcinogens recognized. Like the polycyclic aromatic hydrocarbons, aflatoxin B<sub>1</sub> is metabolized to an epoxide, which can bind covalently to DNA. Because Aspergillus species are ubiquitous, contamination of peanuts and grains exposed to warm moist conditions may result in the formation of significant amounts of aflatoxin B<sub>1</sub>. It has been suggested that in addition to hepatitis B and C, aflatoxin-rich foods may contribute to the high incidence of cancer of the liver in parts of Africa and Asia. Interestingly, human liver cancers in areas of high dietary concentrations of aflatoxin carry a specific inactivating mutation in the p53 gene (G:C T:A transversion at codon 249) as do aflatoxin-dosed rodents.

AROMATIC AMINES AND AZO DYES: Aromatic amines and azo (aniline) dyes, in contrast to the polycyclic aromatic hydrocarbons, are not ordinarily carcinogenic at the point of application. However, occupational exposure to aniline dyes has resulted in bladder cancer. Both aromatic amines and azo dyes are primarily metabolized in the liver to form the hydroxylamine derivatives, which are then detoxified by conjugation with glucuronic acid. In the bladder, hydrolysis of the glucuronide releases the reactive hydroxylamine.

NITROSAMINES: Carcinogenic nitrosamines are a subject of considerable study because it is suspected that they may play a role in human gastrointestinal neoplasms and possibly other cancers. Nitrosamines are potent carcinogens in primates, although unambiguous evidence of cancer induction in humans is lacking. However, the extremely high incidence of esophageal carcinoma in the Hunan province of China (100 times higher than in other areas) has been correlated with the high nitrosamine content of the diet. Nitrosamines may also be implicated in other gastrointestinal cancers because nitrites, commonly added to preserve processed meats and other foods, may react with other dietary components to form nitrosamines. Nitrosamines are activated by hydroxylation, followed by formation of a reactive alkyl carbonium ion.

METALS: A number of metals or metal compounds can induce cancer, but the carcinogenic mechanisms are unknown. Divalent metal cations, such as nickel (Ni<sup>2+</sup>), lead (Pb<sup>2+</sup>), cadmium (Cd<sup>2+</sup>), cobalt (Co<sup>2+</sup>), and beryllium (Be<sup>2+</sup>) are electrophilic and can, therefore, react with macromolecules. Most metal-induced cancers occur in an occupational setting (see Chapter 9).

Endogenous and Environmental Factors Influence Chemical Carcinogenesis

Chemical carcinogenesis in experimental animals involves consideration of genetic aspects, species and strain, age and gender of the animal, hormonal status, diet, and the presence or absence of inducers of drug-metabolizing systems and tumor promoters. A similar role for such factors in humans has been postulated on the basis of epidemiologic studies, but details remain unclear.

Physical Carcinogenesis

The physical agents of carcinogenesis discussed here are ultraviolet (UV) light, asbestos, and foreign bodies. Radiation carcinogenesis is discussed in Chapter 9.

UV Radiation Causes Skin Cancers

The current fad for a tanned complexion has been accompanied not only by cosmetic deterioration of facial skin but also by an increased incidence of the major skin cancers.
Cancers attributed to sun exposure, namely, basal cell carcinoma, squamous carcinoma, and melanoma occur predominantly in the white population. The skin of persons of the darker races is protected by the increased concentration of melanin pigment, which absorbs UV radiation. In fair-skinned people, the areas exposed to the sun are most prone to develop skin cancer. Moreover, there is a direct correlation between total exposure to sunlight and the incidence of skin cancer.

Only certain portions of the UV spectrum are associated with tissue damage, and a carcinogenic effect occurs at wavelengths between 290 and 320 nm. The effects of UV radiation on cells include enzyme inactivation, inhibition of cell division, mutagenesis, cell death, and cancer. The most important biochemical effect of UV radiation is the formation of pyrimidine dimers in DNA, a type of DNA damage that is not seen with any other carcinogen. Dimer formation leads to a cyclobutane ring, which distorts the phosphodiester backbone of the double helix in the region of each dimer. Unless efficiently eliminated by the nucleotide excision repair pathway, genomic injury produced by UV radiation is mutagenic and carcinogenic.

Xeroderma pigmentosum, an autosomal recessive disease, exemplifies the importance of DNA repair in protecting against the harmful effects of UV radiation. In this rare disorder, sensitivity to sunlight is accompanied by a high incidence of skin cancers, including basal cell carcinoma, squamous cell carcinoma, and melanoma. Both the neoplastic and non-neoplastic disorders of the skin in xeroderma pigmentosum are attributed to an impairment in the excision of UV-damaged DNA.

**Asbestos Causes Mesothelioma**

Pulmonary asbestosis and asbestosis-associated neoplasms are discussed in Chapter 12. Asbestos, a material widely used in construction, insulation, and manufacturing, is a family of related fibrous silicates that occur in several different physical forms.

The characteristic tumor associated with asbestos exposure is malignant mesothelioma of the pleural and peritoneal cavities. This cancer, which is exceedingly rare in the general population, has been reported to occur in 2% to 3% (in some studies even more) of heavily exposed workers. The latent period (i.e., the interval between exposure and the appearance of a tumor) is usually about 20 years but may be twice that figure. It is reasonable to surmise that mesotheliomas of both pleura and peritoneum reflect the close contact of these membranes with asbestos fibers transported to them by lymphatic channels. Although the pathogenesis of asbestos-associated mesotheliomas is obscure, the significant public health risk is well recognized and has led to great care in the use of the material.

**Tumor Immunology: Immunologic Defenses Against Cancer In Animals and Humans**

It has long been recognized that malignant tumors elicit a chronic inflammatory response that is unrelated to necrosis or infection of the tumor. This observation led early investigators to postulate a host immune reaction to the neoplastic cells. The inflammatory reaction is correlated with a better prognosis in some tumors, such as medullary carcinoma of the breast and seminoma, but in general, no clear correlation exists. Although the infiltrate is composed principally of T cells and macrophages, suggesting a cell-mediated immune response, the antigens to which the cells respond have not been identified. Despite the paucity of direct evidence in human cancers, it is clear from animal experiments that immune defenses against malignant tumors exist.

To invoke a role for an immune defense against cancer, it is necessary to postulate that tumor cells express antigens that differ from those of normal cells and that are recognized as foreign by the host. Such a condition has been indirectly demonstrated in experiments with inbred mice. When cells from a chemically induced or virally induced tumor are transplanted into a syngeneic mouse, the cells form a tumor. If the transplanted tumor is removed before it metastasizes (i.e., the mouse is cured of its tumor), reinjection of the tumor cells back into the cured mouse will not produce a tumor (although the cells remain capable of forming a tumor in a second naive mouse). The transplanted tumor is rejected because of immunity acquired as a result of the initial tumor transplant. Why the original tumor is not destroyed by the immunologic reaction remains unexplained.

An important observation is that tumors induced by the same chemical in different mice are antigenically distinct, whereas those induced by the same virus express the same virally determined antigens. Accordingly, mice sensitized to one chemically induced tumor do not reject a second tumor induced by the same chemical. By contrast, mice that have received a virus-induced tumor reject another similar tumor. These experiments provide compelling evidence that immunologic mechanisms can play a role in host defenses against tumors, at least against experimental tumors in animals.

**Tumor Antigens are Potential Targets for the Immune Response**

The immune response to experimental tumors must necessarily be directed against tumor antigens on the surface of malignant cells. Such antigens can be tumor-specific, that
is, they are uniquely expressed by the cancer cells but not by their normal cellular counterparts. Alternatively, other tumor antigens represent proteins that are expressed by some normal cells, such as those in developing embryos. Such antigens are tumor-associated, rather than tumor-specific.

As noted above, tumor-specific antigens have been demonstrated in animal models. It is much more difficult to document the presence of tumor-specific antigens in human cancers because of technical and ethical limitations. Nevertheless, candidate human tumor-specific antigens have begun to emerge, for example, virally encoded antigens in tumors with a pathogenesis that is linked to viruses (e.g., HPV). In this context, an anti-HPV vaccine is now used to prevent the development of cancer of the uterine cervix. The tumor-specific antigens identified to date are peptides complexed to human leukocyte antigen (HLA) molecules on tumor cell surfaces.

There has been even more progress in identifying tumor-associated antigens, which correspond to proteins that are present in small amounts in the adult but are abundant during development. Such tumor-associated oncodevelopmental antigens are not specific for a given patient’s tumor per se but instead are shared by cancers in different people and sometimes of varying histologic type. Although there is no reason to believe that immune responses to these fetal antigens play any role in the host defense against cancer, their presence in the blood or the tumor (e.g., CEA, serum \( \alpha \)-fetoprotein) is useful in clinical diagnosis and monitoring efficacy of treatment.

Inroads into the identification of tumor antigens have created new opportunities for developing immunotherapies against human cancers, at least in theory. Passive immunotherapies can draw upon tumor-infiltrating lymphocytes with specificity for HLA-associated tumor peptide antigens and antibodies directed against various tumor surface proteins. Alternatively as noted above, active immunotherapeutic strategies can invoke tumor antigens as vaccines to elicit systemic antitumor immune responses.

### Mechanisms of Immunologic Response to Tumors

Although some circumstantial evidence exists for the participation of immunologic defenses in the resistance to cancer in humans, conclusive proof that immunologic tumor surveillance is an ongoing process is lacking. Perhaps the strongest argument for immunologic tumor rejection in humans is the observation that immunodeficiency, whether acquired or congenital, is associated with an increased incidence of cancers, almost all of which are B-cell lymphomas. The potential contribution of any specific immunologic mechanism to tumor cell destruction in vivo has not been clearly defined. A number of possible mechanisms are recognized.

- **T-cell-mediated cytotoxicity**: The capacity of cytotoxic T cells to mediate the specific rejection of transplanted tumors is evidenced by the demonstration that lymphocytes from tumor-bearing hosts can transfer tumor immunity when injected into healthy animals. Moreover, the transferred immunity is eliminated by the administration of antibodies directed against T-cell antigens. The mechanisms of T-cell-mediated immunological cell killing are discussed in Chapter 4.

- **Natural killer (NK) cell-mediated cytotoxicity**: Another set of lymphocytes, the NK cells, have tumoricidal activity that does not depend on prior sensitization. These lymphocytes are generally more effective than untransformed cells in killing tumor cells. Tumor cells that are resistant to the action of NK cells may be lysed by NK cells that have been activated by IL-2. Such activated NK cells are referred to as lymphokine-activated killer cells.

- **Macrophage-mediated cytotoxicity**: Macrophages are capable of killing tumor cells in a nonspecific manner. However, their role in the control of malignant tumors is far from clear, because under some circumstances, in vitro factors derived from macrophages can actually stimulate the proliferation of tumor cells.

- **Antibody-dependent cell-mediated cytotoxicity**: Tumor-associated antigens can elicit a humoral antibody response, but these immunoglobulins by themselves do not kill tumor cells. However, as discussed in Chapter 4, such antibodies can participate in antibody-dependent cell-mediated cytotoxicity. The antibody binds both to the tumor antigen and to the Fc receptor of the effector cell, thereby bringing the effector cell into direct contact with its target. Depending on the conditions, the effector cells may be a lymphocyte killer cell (null cell), macrophage, or neutrophil.

- **Complement-mediated cytotoxicity**: Tumor cells that have been coated with specific antibodies may be lysed by the activation of complement.

### Evasion of Immunologic Responses by Tumors

The fact that cancer is alive and well despite the presence of potential immunologic defenses implies that such mechanisms are either ineffective or that tumor cells can evade immunologic destruction. A number of factors have been proposed to account for the failure of immune responses to limit tumor growth. These explanations remain theoretical and even controversial. These include:

- Absence or paucity of tumor-specific antigens on the neoplastic cell
• Absence or paucity of necessary cell surface molecules necessary for antigenic recognition (such as HLA) on the tumor cell
• Tumor heterogeneity leading to the selection of resistant tumor clones (as described above)
• Expression of immunosuppressive molecules by tumor cells

Defining and tackling these immune evasion mechanisms will be essential for developing effective immunotherapies for cancer.

Systemic Effects Of Cancer On The Host

The symptoms of cancer are, for the most part, referable to the local effects of either the primary tumor or its metastases. However, in a minority of patients, cancer produces remote effects that are not attributable to tumor invasion or to metastasis but may be related to the synthesis of bioactive compounds by the tumor. Such effects are collectively termed paraneoplastic syndromes. Although such effects are rarely lethal, in some cases, they dominate the clinical course. Paraneoplastic syndromes are also of diagnostic and therapeutic significance.

Common systemic effects include:

• **Fever:** It is not uncommon for cancer patients to present initially with fever of unknown origin that cannot be explained by an infectious disease. Fever attributed to cancer (1) correlates with tumor growth, (2) disappears after treatment, and (3) reappears on recurrence. This is likely related to the release of pyrogens by the tumor or associated stromal inflammatory cells.

• **Anorexia and weight loss:** A paraneoplastic syndrome of anorexia, weight loss, and cachexia is very common in patients with cancer, often appearing before its malignant cause becomes apparent. The mechanisms responsible for this phenomenon are poorly understood but may be related to the production of a variety of cytokines, including TNF-α, interferons, and IL-6.

• **Endocrine syndromes:** Malignant tumors may produce a number of peptide hormones with secretion that is not under normal regulatory control. Most of these hormones are usually present in the brain, gastrointestinal tract, or endocrine organs. Their inappropriate secretion can cause a variety of effects. Cushing syndrome (see Chapter 21), inappropriate antidiuresis, hyper- and hypocalcemia, gonadotropin syndromes, and hypoglycemia may all result from inappropriate hormone secretion by tumors.

Organ-Specific Effects Of Cancer On The Host

Cancer may have specific effects on different host organ systems that may result from mechanical, metabolic, or other poorly defined causes related to the growth of the tumor.

Neurologic Syndromes Are Common in Cancer Patients

Neurologic disorders usually result from metastases or from endocrine or electrolyte disturbances. Vascular, hemorrhagic, and infectious conditions affecting the nervous system are also common. However, there remains a small group of cancer patients who suffer from a variety of neurologic complaints without any demonstrable cause. Most of these cases reflect an autoimmune etiology mediated by circulating antibodies directed against neural antigens or by reactive T cells. Cerebral complications include dementia, subacute cerebellar degeneration, limbic encephalitis, and optic neuritis.

Spinal Cord

Subacute motor neuropathy, a disorder of the spinal cord, is characterized by slowly developing lower motor neuron weakness without sensory changes. It is so strongly associated with cancer that an intensive search for an occult neoplasm, often a lymphoma, should be made in patients who present with these symptoms.

Amyotrophic lateral sclerosis is well described among cancer patients. Conversely, as many as 10% of patients with this neurologic disease are found to have cancer.

Peripheral Nerves

Sensorimotor peripheral neuropathy, characterized by distal weakness, wasting, and sensory loss, is common in cancer patients and when not associated with an overt neoplasm suggests the possibility of an occult tumor. Interestingly, the removal of the primary tumor usually does not reverse the neuropathy.

Purely sensory neuropathy, resulting from degenerative changes in the dorsal root ganglia, may also develop in persons with cancer.

Autonomic and gastrointestinal neuropathies, manifested as orthostatic hypotension, neurogenic bladder, and intestinal pseudoobstruction, are associated with small cell carcinoma of the lung.

Skeletal Muscle Syndromes can be Strongly Associated with Cancer

Patients with dermatomyositis or polymyositis have an incidence of cancer five to seven times higher than that in the general population.
The association is most conspicuous in affected men older than 50 years; in this group, more than 70% have cancer. In most cases, the muscle disorder and cancer present within a year of each other.

Hematologic Syndromes Commonly Relate to Marrow Infiltration

The most common hematologic complications of neoplastic diseases result either from direct infiltration of the marrow or from treatment. However, hematologic paraneoplastic syndromes, which antedate the modern era of chemotherapy and radiation therapy, are well described. Erythrocytosis (polycythemia), anemias, and defects of leukocytes and platelets may have a paraneoplastic (or possibly autoimmune) etiology. Treatment-related hematologic defects are, of course, also common.

A Hypercoagulable State is Often Associated with Cancer

The association between cancer and venous thrombosis was noted more than a century ago. Since then, other abnormalities resulting from a hypercoagulable state (e.g., disseminated intravascular coagulation and nonbacterial thrombotic endocarditis) have been recognized. The cause of this hypercoagulable state is still debated.

VENOUS THROMBOSIS: This condition is most distinctly associated with carcinoma of the pancreas, in which there is a 50-fold increased incidence of this complication. Venous thrombosis, normally in the deep veins of the legs, is also particularly common in association with other mucin-secreting adenocarcinomas of the gastrointestinal tract and with lung cancer.

DISSEMINATED INTRAVASCULAR COAGULATION: This complication is most commonly found with acute promyelocytic leukemia and adenocarcinomas.

NONBACTERIAL THROMBOTIC ENDOCARDITIS: The presence of noninfected verrucous deposits of fibrin and platelets on the left-sided heart valves occurs in cancer patients, particularly in those who are debilitated (see Chapter 11). Although the effects on the heart are not of clinical importance, emboli to the brain and rarely the coronary arteries present a great danger. This cardiac complication is most common with solid tumors but may occasionally be noted with leukemias and lymphomas.

Amyloidosis may be a Systemic Effect of Cancer

About 15% of cases of amyloidosis occur in association with cancers, particularly with multiple myeloma and renal cell carcinoma but also with other solid tumors and lymphomas (see Chapter 23). The presence of amyloidosis implies a poor prognosis; in patients with myeloma, amyloidosis is associated with a median survival of 14 months or less.

Epidemiology Of Cancer

Cancer accounts for one fifth of the total mortality in the United States and is the second leading cause of death after cardiovascular diseases and stroke. For most cancers, death rates in the United States have largely remained flat for more than half a century, with some notable exceptions (Fig. 5-17). The death rate from lung cancer among men has risen dramatically from 1930, when it was an uncommon tumor, to the present, when it is by far the most common cause of death from cancer in men. As discussed in Chapter 8, the entire epidemic of lung cancer deaths is attributable to smoking. Among women, smoking did not become fashionable until
World War II. Considering the time lag needed between starting to smoke and the development of lung cancer, it is not surprising that the increased death rate from lung cancer in women did not become significant until after 1965. In the United States, the death rate from lung cancer in women now exceeds that for breast cancer, and it is now, as in men, the most common fatal cancer. By contrast, for reasons difficult to fathom, cancer of the stomach, which in 1930 was by far the most common cancer in men and was more common than breast cancer in women, has shown a remarkable and sustained decline in frequency. Similarly, there has been a conspicuous decline in the death rate from cancer of the uterus corpus and cervix, possibly explained by better screening, diagnostic techniques, and therapeutic methods. Overall, after decades of steady increases, the age-adjusted mortality rate due to all cancers has now reached a plateau. The ranking of the incidence of tumors in men and women in the United States is shown in Table 5-1.

Individual cancers have their own age-related profiles, but for most, increased age is associated with an increased incidence. The most striking example of the dependency on age is carcinoma of the prostate, in which the incidence increases 30-fold in men between the ages of 50 and 85. Certain neoplastic diseases, such as acute lymphoblastic leukemia in children and testicular cancer in young adults, show different age-related peaks of incidence.

Geographic and Ethnic Differences Influence Cancer Incidence

It is difficult to find a cancer that does not show significant differences in incidence in different ethnic groups or geographical regions. It is equally difficult to find an explanation for such differences. This in part relates to the complexity in undertaking human population-based studies, the plethora of potential genetic and environmental variables between populations, and the uncertainty involved in translating animal experimental data to humans. Hypotheses attempting to explain population-based differences in frequency for some types of cancer death rates in the United States, 1930 to 2002, among men (A) and women (B).

![Cancer death rates in the United States, 1930 to 2002, among men (A) and women (B).](image)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>33</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>14</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>11</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>6</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>3</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2</td>
</tr>
<tr>
<td>All other sites</td>
<td>17</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>32</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>12</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>11</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>6</td>
</tr>
<tr>
<td>Ovary</td>
<td>4</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>2</td>
</tr>
<tr>
<td>All other sites</td>
<td>20</td>
</tr>
</tbody>
</table>

![TABLE 5-1](image)
cancer have achieved some level of acceptance. These include:

**LIVER CANCER:** There is a strong correlation between the incidence of primary hepatocellular carcinoma and the prevalence of hepatitis B and C. Endemic regions for both diseases include large parts of sub-Saharan Africa and most of Asia, Indonesia, and the Philippines. It must be remembered that levels of aflatoxin B1 are high in the staple diets of many of the high-risk areas.

**SKIN CANCER:** The rates for skin cancers vary with skin color and exposure to the sun. Thus, particularly high rates have been reported in northern Australia, where sun exposure is intense and much of the current population is derived from the British Isles (and fair skinned). Although the data are scanty, darker aboriginal Australians appear to have lower rates of skin cancer. Increased rates of skin cancer have also been noted among the white population of the American Southwest. The lowest rates are found among those with pigmented skin (e.g., Japanese, Chinese, and Indians). The rates for African blacks, despite their heavily pigmented skin, are occasionally higher than those for Asians because of the higher incidence of melanomas of the soles and palms in blacks.

**CERVICAL CARCINOMA:** Striking differences in the incidence of squamous carcinoma of the cervix exist between ethnic groups and different socioeconomic levels. For instance, the very low rate in Ashkenazi Jews of Israel contrasts with a 25 times greater rate in the Hispanic population of Texas. In general, groups of low socioeconomic status have a higher incidence of cervical cancer than the more prosperous and better educated. This cancer is also directly correlated with early sexual activity and multiparity and is rare among women who are not sexually active, such as nuns. It is also uncommon among women whose husbands are circumcised. A strong association with infection by HPVs has been demonstrated, and cervical cancer should be classed as a venereal disease. Hence, differences in frequency correlate with sexual practices and the use of condoms.

**BURKITT LYMPHOMA:** Burkitt lymphoma, a disease of children, was first described in Uganda, where it accounts for half of all childhood tumors. Since then, a high frequency has been observed in other African countries, particularly in hot, humid lowlands. It has been noted that these are areas where malaria is also endemic. High rates have been recorded in other tropical areas, such as Malaysia and New Guinea, but European and American cases are encountered only sporadically. An interaction between chronic malarial infection and EBV virus appears likely (see above).

**STUDIES OF MIGRANT POPULATIONS GIVE CLUES TO CANCER DEVELOPMENT**

Although planned experiments on the etiology of human cancer are rarely feasible, certain populations have unwittingly performed such experiments by migrating from one environment to another. Initially at least, the genetic characteristics of such persons remained the same, but the new environment differed in climate, diet, infectious agents, occupations, and so on. Consequently, epidemiologic studies of migrant populations have provided many intriguing clues to the factors that may influence the pathogenesis of cancer. The United States, which has been the destination of one of the greatest population movements of all time, is the source of most of the important data in this field.

**CANCER OF THE STOMACH:** A study of Japanese residents of Hawaii found that emigrants from Japanese regions with the highest risk of stomach cancer continued to exhibit an excess risk in Hawaii. By contrast, their offspring who were born in Hawaii had the same incidence of this cancer as American whites. Although dietary factors, such as pickled vegetables and salted fish, have been postulated to account for the higher incidence in Japan and the lower incidence in Hawaii, no firm evidence has been adduced to support this contention. More recently, it has been shown in Japan that the population in regions at high risk for stomach cancer also displays a high prevalence of chronic atrophic gastritis with intestinal metaplasia, lesions that are considered precursors of gastric cancer. Interestingly, when people from these regions move to low-risk areas, they carry the high prevalence of intestinal metaplasia with them. Thus, the environmental factors associated with stomach cancer may not be directly carcinogenic but rather may be related to atrophic gastritis and intestinal metaplasia.

**COLORECTAL, BREAST, ENDOMETRIAL, OVARIAN, AND PROSTATIC CANCERS:** Emigrant studies of the incidence of colorectal cancer show opposite trends to those of stomach cancer. Emigrants from low-risk areas in Europe and Japan exhibit an increased risk of colorectal cancer in the United States. Moreover, their offspring continue at a higher risk and reach the incidence levels of the general American population. This rule for colorectal cancer also prevails for cancers of the breast, endometrium, ovary, and prostate.

**CANCER OF THE LIVER:** As noted above, primary hepatocellular carcinoma is common in Asia and Africa, where it has been associated with hepatitis B and C. In American blacks and Asians, however, the neoplasm is no more common than in American whites, a situation that presumably reflects the relatively low prevalence of chronic viral hepatitis in the United States.
HODGKIN DISEASE: In poorly developed countries, the childhood form of Hodgkin disease is the type reported most often. In developed Western countries, by contrast, the disease is most common among young adults. Such a pattern is characteristic of certain viral infections, although there is no evidence for an infectious etiology of Hodgkin disease. An exception to this generalization is noted in Japan, a developed country where young adult disease is distinctly uncommon. Further evidence for an environmental influence is the higher incidence of Hodgkin disease in Americans of Japanese descent than that in Japan.