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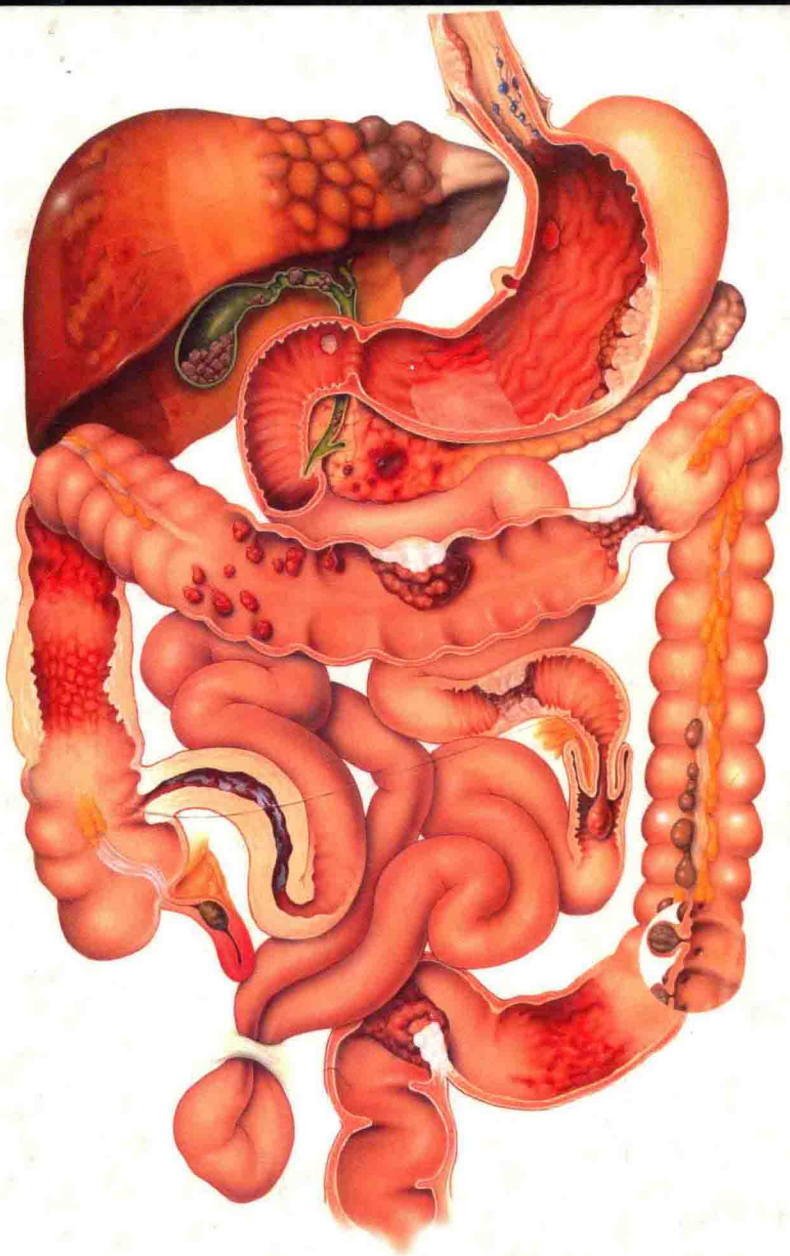
ATLAS of PATHOPHYSIOLOGY



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Foreword

As health care professionals, we've all studied anatomy — with lots of pictures to guide us. We've studied physiology and disease, and we carry a raft of facts in our heads. But facts don't always bring the deep understanding that pictures do. For crucial day-to-day disease management in a busy clinical practice, we need not only the facts, but also pictures of what's going wrong in our patients' bodies. When it comes to *pathophysiology*, the pictures aren't always there — in our minds or in our reference books — when we need them.

How does high plasma glucose affect the diabetic patient's blood vessels and nerves? What process is driving disseminated intravascular coagulation? Why does Cushing's disease have such far-reaching clinical implications? Knowing the answers can speed patient assessment, guide diagnostic testing, and make appropriate treatment apparent.

Atlas of Pathophysiology is a stunningly visual reference that provides the answers to guide your clinical steps. For more than 150 diseases, this outstanding reference provides beautifully detailed illustrations of pathophysiology along with comprehensive explanations and clinical guidance side by side — a uniquely helpful arrangement.

The atlas begins with introductory chapters that discuss cell physiology and injury, homeostasis, and the ways disease disrupts the body's equilibrium. Discussions follow of cancer, infection, immune and genetic disorders, and fluid and electrolyte imbalances. Succeeding chapters cover disorders in every body system, and alphabetical arrangement within each chapter makes finding a specific disease easy. Each discussion begins with a brief overview of the disease followed by a framework that describes pathophysiology and lists causes, signs and symptoms, diagnostic tests, and treatments. Bulleted facts provide quick, concise, up-to-date information under each heading.

It's all there — hypervolemia, cardiac arrhythmias, anemias, Crohn's disease, osteoarthritis, leukemia, pneumonia, renal failure, and more. Whether you wish to quickly review an entire disease or to merely update your understanding of the disease process, the facts and illustrations are there, together, for targeted physical assessment and diagnostic testing, appropriate care, and patient counseling.

The layout of the book is extremely well suited for busy professionals. Each disease explanation features clearly labeled, full-color illustrations from the Anatomical Chart Company that provide excellent visual understanding of the anatomical structures and pathologic processes involved. Throughout the book, color logos call your attention to key information about age-related disease incidence and effects plus helpful tips to use in clinical practice. A glossary of common pathophysiology terms provides further information.

In addition to serving as an excellent student reference, *Atlas of Pathophysiology* can greatly simplify patient counseling, as the full-color illustrations make disease readily understandable. Often patients best understand information that is visually presented. This helps to clarify misunderstanding of the disease process — a common clinical problem. The beautiful color and overall visual attractiveness ensure this atlas's use as the perfect teaching aid — regardless of a patient's native language.

In the classroom, as well as in clinical practice, the need exists for clear illustrations of the disease process to use as teaching and learning tools. Anyone who teaches pathophysiology knows that students want a reference that provides them with a quick, easy-to-understand overview and illustrations that make learning easier. Such a book is difficult, if not impossible, to find. Thus, most students accumulate multiple references to supplement their learning.

A book that meets all needs is a rare find. *Atlas of Pathophysiology* is just such a find. I envision that this reference book will soon be found in professional offices, at nursing stations throughout the hospital, in students' book bags, in instructors' offices, on library shelves, and anywhere else that an excellent pathophysiology resource is needed. *Atlas of Pathophysiology*, with its concise, clear illustrations and functional layout, provides a unique way to give professionals quick access to a wealth of information about disease mechanisms.

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Contents

PART I

CENTRAL CONCEPTS

CELLS, HOMEOSTASIS, AND DISEASE

The cell is the smallest living component of a living organism. Organisms can be made up of a single cell, such as bacteria, or billions of cells, such as human beings. In large organisms, highly specialized cells that perform a common function are organized into tissue. Tissues, in turn, form organs, which are integrated into body systems.

CELL COMPONENTS

Cells are complex organizations of specialized components, each component having its own specific function. The largest components of a normal cell are the cytoplasm, the nucleus, and the cell membrane. (See *Cell components.*)

Cytoplasm

The cytoplasm consists primarily of a fluid in which the tiny structures that perform the necessary functions to maintain the life of the cell are suspended. These tiny structures, called organelles, are the cell's metabolic machinery. Each performs a specific function to maintain the life of the cell. Organelles include:

- *mitochondria* — spherical or rod-shaped structures that produce most of the body's adenosine triphosphate (ATP). ATP contains high-energy phosphate chemical bonds that fuel many cellular activities. Mitochondria are the sites of cellular respiration — the metabolic use of oxygen to produce energy, carbon dioxide, and water.
- *ribosomes* — the sites of protein synthesis
- *endoplasmic reticulum* — an extensive network of two varieties of membrane-enclosed tubules:
  - *rough endoplasmic reticulum*, which is covered with ribosomes
  - *smooth endoplasmic reticulum*, which contains enzymes that synthesize lipids
- *Golgi apparatus* — synthesizes carbohydrate molecules that combine with protein produced by the rough endoplasmic reticulum and lipids produced by the smooth endoplasmic reticulum to form such products as lipoproteins, glycoproteins, and enzymes
- *lysosomes* — digest nutrients as well as foreign or damaged material in cells. A membrane surrounding each lysosome separates its digestive enzymes from the rest of the cytoplasm. The enzymes digest nutrient matter brought into the cell by means of endocytosis, in which a portion of the cell membrane surrounds and engulfs matter to form a membrane-bound intracellular vesicle. The membrane of the lysosome fuses with the membrane of the vesicle surrounding the endocytosed material. The lysosomal enzymes then digest the engulfed material. Lysosomes digest the foreign matter ingested by white blood cells by a similar process, which is called *phagocytosis.*
- *peroxisomes* — contain oxidases, enzymes that chemically reduce oxygen to hydrogen peroxide and hydrogen peroxide to water
- *cytoskeletal elements* — a network of protein structures that maintain the cell's shape
- *centrosomes* — contain centrioles, short cylinders adjacent to the nucleus that take part in cell division
- *microfilaments* and *microtubules* — enable movement of intracellular vesicles (allowing axons to transport neurotransmitters) and formation of the mitotic spindle, the framework for cell division.

Nucleus

The cell's control center is the nucleus, which plays a role in cell growth, metabolism, and reproduction. Within the nucleus, one or more nucleoli (dark-staining intranuclear structures) synthesize ribonucleic acid (RNA), a complex polynucleotide that controls protein synthesis. The nucleus also stores deoxyribonucleic acid (DNA), the double helix that carries genetic material and is responsible for cellular reproduction or division.

Cell membrane

The semipermeable cell membrane forms the cell's external boundary, separating it from other cells and from the external environment. The cell membrane consists of a double layer of phospholipids with protein molecules embedded in it. These protein molecules act as receptors, ion channels, or carriers for specific substances.

CELL DIVISION

Each cell must replicate itself for life to continue. Cells replicate by division in one of two ways: mitosis (produces two daughter cells with the same DNA and chromosome content as the mother cell) or meiosis (produces four gametocytes, each containing half the number of chromosomes of the original cell). Most cells divide by mitosis; meiosis occurs only in reproductive cells. Some cells, such as nerve and muscle cells, typically lose their ability to reproduce after birth.

CELL FUNCTIONS

In the human body, most cells are specialized to perform one function. Respiration and reproduction occur in all cells. The specialized functions are:

- *movement* — the result of coordinated action of nerve and muscle cells to change the position of a specific body part, contents within an organ, or the entire organism
- *conduction* — the transmission of a stimulus, such as a nerve impulse, heat, or sound wave, from one body part to another
- *absorption* — movement of substances through a cell membrane (For example, nutrients are absorbed and transported ultimately to be used as energy sources or as building blocks to form or repair structural and functional cellular components.)
- *secretion* — release of substances that act in another part of the body
- *excretion* — release of waste products generated by normal metabolic processes.

Cell types

Each of the following four types of tissue consists of several specialized cell types, which perform specific functions.

- *Epithelial cells* line most of the internal and external surfaces of the body. Their functions include support, protection, absorption, excretion, and secretion.
- *Connective tissue cells* are present in skin, bones and joints, artery walls, fascia, and body fat. Their major functions are protection, metabolism, support, temperature maintenance, and elasticity.
- *Nerve cells* comprise the nervous system and are classified as neurons or neuroglial cells. Neurons perform the following functions:
  - generating electrical impulses
  - conducting electrical impulses
  - influencing other neurons, muscle cells, and cells of glands by transmitting impulses.

Neuroglial cells support, nourish, and protect the neurons. The four types are:

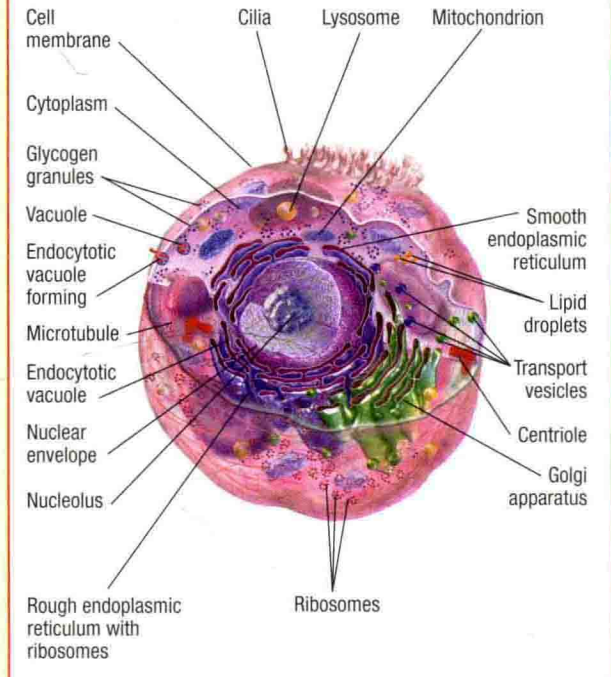
- *oligodendroglia* — produce myelin within the central nervous system (CNS)
- *astrocytes* — provide essential nutrients to neurons and assist neurons in maintaining the proper bioelectrical potentials for impulse conduction and synaptic transmission
- *ependymal cells* — involved in the production of cerebrospinal fluid
- *microglia* — ingest and digest tissue debris when nervous tissue is damaged.

- *Muscle cells* contract to produce movement or tension.
  - *Skeletal (striated) muscle cells* extend along the entire length of skeletal muscles. These cells cause voluntary movement by contracting or relaxing together in a specific muscle. Contraction shortens the muscle; relaxation permits the muscle to return to its resting length.
  - *Smooth (nonstriated) muscle cells* are present in the walls of hollow internal organs, blood vessels, and bronchioles. By involuntarily contracting and relaxing, these cells change the luminal diameter of the hollow structure and thereby move substances through the organ.
  - *Striated cardiac muscle cells* branch out across the smooth muscle of the chambers of the heart and contract involuntarily. They produce and transmit cardiac action potentials, which cause cardiac muscle cells to contract.

Age alert

In older adults, skeletal muscle cells become smaller and many are replaced by fibrous connective tissue. The result is loss of muscle strength and mass.

Cell components



Pathophysiologic concepts

The cell faces a number of challenges through its life. Stressors, changes in the body's health, disease, and other extrinsic and intrinsic factors can change the cell's normal functioning.

Adaptation

Cells generally continue functioning despite changing conditions or stressors. However, severe or prolonged stress or changes may injure or destroy cells. When cell integrity is threatened, the cell reacts by drawing on its reserves to keep functioning, by adaptive changes, or by cellular dysfunction. If cellular reserve is insufficient, the cell dies. If enough cellular reserve is available and the body doesn't detect abnormalities, the cell adapts by atrophy, hypertrophy, hyperplasia, metaplasia, or dysplasia. (See *Adaptive cell changes*, page 4.)

Atrophy

Atrophy is a reduction in the size of a cell or organ due to disuse, insufficient blood flow, malnutrition, or reduced stimulation. An example is loss of muscle mass after prolonged bed rest.

Hypertrophy

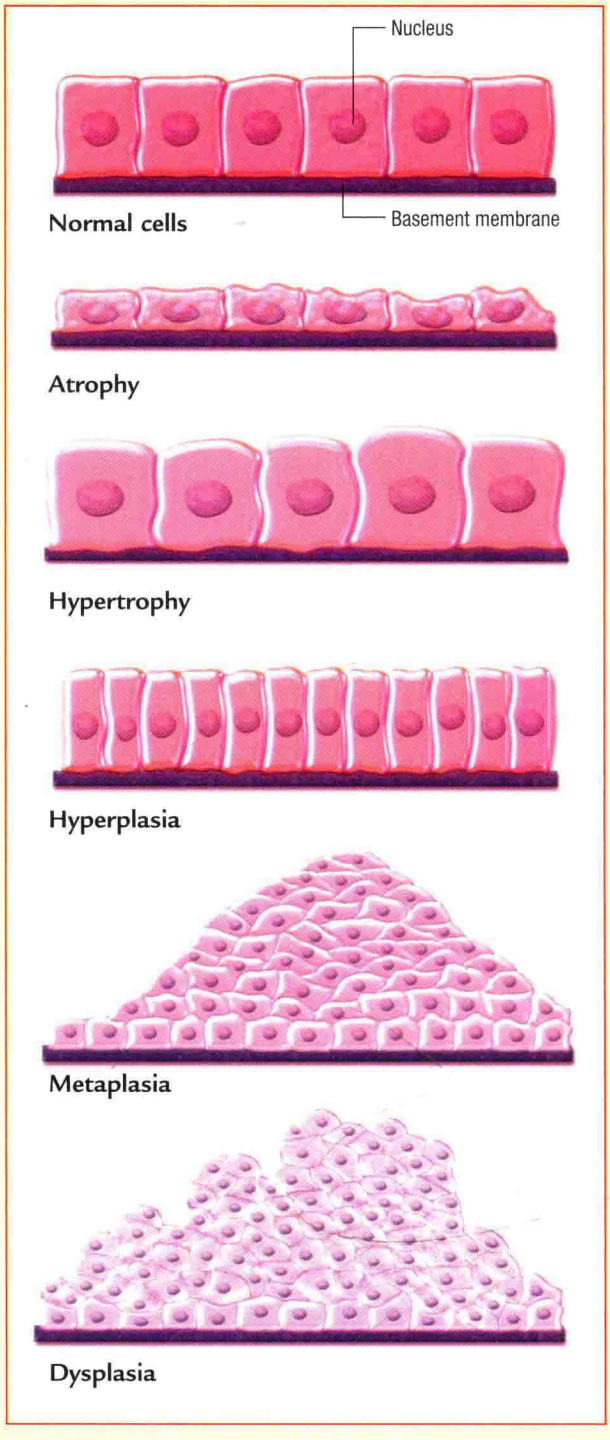
Hypertrophy is an increase in the size of a cell or organ due to an increase in workload. There are three types:

- *physiologic hypertrophy* — reflects an increase in workload that is not caused by disease; for example, the increase in muscle size caused by hard physical labor or weight training
- *compensatory hypertrophy* — increase in cell size to take over for nonfunctioning cells; for example, enlargement of one kidney when the other is not functioning or is absent
- *pathologic hypertrophy* — response to disease; for example, thickening of heart muscle as it pumps against increasing resistance in patients with hypertension.

Hyperplasia

Hyperplasia is an increase in the number of cells caused by increased workload, hormonal stimulation, or decreased tissue

ADAPTIVE CELL CHANGES



density. Like hypertrophy, hyperplasia may be *physiologic*, *compensatory*, or *pathologic*.

- *Physiologic hyperplasia* is an adaptive response to normal changes; for example, monthly increase in the number of uterine cells in response to estrogen stimulation after ovulation.
- *Compensatory hyperplasia* occurs in some organs to replace tissue that has been removed or destroyed; for example, regeneration of liver cells when part of the liver is surgically removed.
- *Pathologic hyperplasia* is a response to either excessive hormonal stimulation or abnormal production of hormonal growth factors; for example, acromegaly, in which excessive growth hormone production causes bones to enlarge.

Metaplasia

Metaplasia is the replacement of one cell type with another cell type that can better endure the change or stressor.

- *Physiologic metaplasia* is a normal response to changing conditions and is generally transient. For example, in the body's normal response to inflammation, monocytes migrate to inflamed tissues and transform into macrophages.
- *Pathologic metaplasia* is a response to an extrinsic toxin or stressor and is generally irreversible. For example, after years of exposure to cigarette smoke, stratified squamous epithelial cells replace the normal ciliated columnar epithelial cells of the bronchi. Although the new cells can better withstand smoke, they don't secrete mucus or have cilia to protect the airway. If exposure to cigarette smoke continues, the squamous cells can become cancerous.

Dysplasia

In dysplasia, abnormal differentiation of dividing cells results in abnormal size, shape, or appearance. Although dysplastic cell changes aren't cancerous, they can precede cancerous changes. Common examples include dysplasia of epithelial cells of the cervix or the respiratory tract.

Cell injury

Injury to any cellular component can lead to disease as the cells lose their ability to adapt. Cell injury may result from any of several intrinsic or extrinsic causes:

- *toxins* — may be endogenous or exogenous (Common endogenous toxins include products of genetically determined metabolic errors and hypersensitivity reactions. Exogenous toxins include alcohol, lead, carbon monoxide, and drugs that alter cellular function.)
- *infection* — may be caused by viruses, fungi, protozoa, or bacteria
- *physical injury* — disruption of a cell's structure or the relationships among the organelles. For example, two types of physical injury are thermal and mechanical
- *deficit injury* — loss of normal cellular metabolism caused by inadequate water, oxygen, or nutrients.

Injury becomes irreversible when the cell membrane or the organelles can no longer function.

Cell degeneration

Degeneration is a type of sublethal cell damage that generally occurs in the cytoplasm and that doesn't affect the nucleus. Degeneration usually affects organs with metabolically active cells, such as the liver, heart, and kidneys. When changes in cells are identified, prompt health care can slow degeneration and prevent cell death. Unfortunately, many cell changes are unidentifiable, even with the use of a microscope, and early detection of disease is then impossible. An example of reversible degenerative change is cervical dysplasia. Examples of irreversible degenerative diseases include Huntington's disease and amyotrophic lateral sclerosis.

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Cell aging

During the normal process of aging, cells lose both structure and function. Atrophy may reflect loss of cell structure; hypertrophy or hyperplasia; or lost function. Signs of aging occur in all body systems. Aging can proceed at different rates depending on the number and extent of injuries and the amount of wear and tear on the cell.

Cell death

Cell death may be caused by internal (intrinsic) factors that limit the cell's life span or external (extrinsic) factors that contribute to cell damage and aging. When stress is severe or prolonged, the cell can no longer adapt and it dies. Cell death, or necrosis, may manifest in different ways, depending on the tissues or organs involved.

- *Apoptosis* — genetically programmed cell death — accounts for the constant cell turnover in the skin's outer keratin layer and the lens of the eye.
- *Liquefactive necrosis* occurs when a lytic (dissolving) enzyme liquefies necrotic cells. This type of necrosis is common in the brain, which has a rich supply of lytic enzymes.
- *Caseous necrosis* occurs when necrotic cells disintegrate but the cellular pieces remain undigested for months or years. Its name derives from the resulting tissue's crumbly, cheeselike (caseous) appearance. It commonly occurs in pulmonary tuberculosis.
- *Fat necrosis* occurs when lipase enzymes break down intracellular triglycerides into free fatty acids. These free fatty acids combine with sodium, magnesium, or calcium ions to form soaps. The tissue becomes opaque and chalky white.
- *Coagulative necrosis* commonly follows interruption of blood supply to any organ — generally the kidneys, heart, or adrenal glands — except the brain. It inhibits activity of lysosomal lytic enzymes in the cells, so that the necrotic cells maintain their shape, at least temporarily.
- *Gangrenous necrosis*, a form of coagulative necrosis, typically results from a lack of blood flow and is complicated by an overgrowth and invasion of bacteria. It commonly occurs in the lower limbs as a result of arteriosclerosis or in the GI tract. Gangrene can occur in one of three forms:

- *dry gangrene* — occurs when bacterial invasion is minimal. It's marked by dry, wrinkled, dark brown or blackened tissue on an extremity.
- *moist (or wet) gangrene* — is accompanied by liquifactive necrosis — extensive lytic activity from bacteria and white blood cells that produces a liquid center in affected area. It can occur in the internal organs as well as the extremities.
- *gas gangrene* — develops when anaerobic bacteria of the genus *Clostridium* infect tissue. It's more likely to follow severe trauma and may be fatal. The bacteria release toxins that kill nearby cells and the gas gangrene rapidly spreads. Release of gas bubbles from affected muscle cells indicates that gas gangrene is present.

Cell death releases intracellular enzymes, which start to dissolve cellular components, and triggers an acute inflammatory reaction in which white blood cells migrate to the necrotic area and begin to digest the dead cells.

Homeostasis: maintaining balance

Every cell in the body participates in maintaining a dynamic, steady state of internal balance, called *homeostasis*. Pathophysiology results from changes or disruption in normal cellular function. Three structures in the brain are primarily responsible for maintaining homeostasis of the entire body:

- *medulla oblongata* — the part of the brain stem associated with vital functions such as respiration and circulation
- *pituitary gland* — regulates the function of other glands and, thereby, the body's growth, maturation, and reproduction
- *reticular formation* — a network of nerve cells and fibers in the brain stem and spinal cord that helps control vital reflexes such as cardiovascular function and respiration.

Each structure that maintains homeostasis through self-regulating feedback mechanisms has three components:

- *sensors* — cells that detect disruptions in homeostasis reflected by nerve impulses or changes in hormone levels
- *CNS control center* — receives signals from the sensor and regulates the body's response to those disruptions by initiating the effector mechanism
- *effector* — acts to restore homeostasis.

Feedback mechanisms exist in two varieties:

- *positive* — moves the system away from homeostasis by enhancing a change in the system
- *negative* — works to restore homeostasis by correcting a deficit in the system. Negative feedback mechanisms produce adaptive responses.

Disease

Although *disease* and *illness* are often used interchangeably, they aren't synonyms. *Disease* occurs when homeostasis isn't maintained. *Illness* occurs when a person is no longer in a state of perceived "normal" health. A person may have a disease, but not be ill all the time because his body has adapted to the disease.

The cause of disease may be intrinsic or extrinsic. Genetic factors, age, gender, infectious agents, or behaviors (such as inactivity, smoking, or abusing illegal drugs) can all cause disease. Diseases that have no known cause are called *idiopathic*.

The way a disease develops is called its *pathogenesis*. A disease is usually detected when it causes a change in metabolism or cell division that causes signs and symptoms. How the cells respond to disease depends on the causative agent and the affected cells, tissues, and organs. In the absence of intervention, resolution of the disease depends on many factors functioning over a period of time, such as extent of disease and the presence of other diseases. Manifestations of disease may include hypofunction, hyperfunction, or increased mechanical function.

Typically, diseases progress through the following stages:

- *exposure or injury* — target tissue exposed to a causative agent or injury
- *latency or incubation period* — no signs or symptoms are evident
- *prodromal period* — signs and symptoms are generally mild and nonspecific
- *acute phase* — disease reaches its full intensity, possibly with complications; called the *subclinical acute phase* if the patient can still function as though the disease weren't present
- *remission* — a second latency phase that occurs in some diseases and is commonly followed by another acute phase
- *convalescence* — patient progresses toward recovery
- *recovery* — return of health or normal functioning; no signs or symptoms of disease remain.

Cancer

Cancer refers to a group of more than 100 different diseases characterized by DNA damage that causes abnormal cell growth and development. Malignant cells have two defining characteristics: first, they can no longer divide and differentiate normally, and, secondly, they can invade surrounding tissues and travel to distant sites. In the United States, cancer accounts for more than half a million deaths each year, second only to cardiovascular disease.

Causes

The healthy body is well equipped to defend itself against cancer. Only when the immune system and other defenses fail does cancer prevail. Current evidence suggests that cancer develops from a complex interaction of exposure to carcinogens and accumulated mutations in several genes. Researchers have identified approximately 100 cancer genes, most of which fall into one of two categories:

- *oncogenes* — activate cell division and influence embryonic development
- *tumor-suppressor genes* — halt cell division.

Most normal human cells contain proto-oncogenes (oncogene precursors) and tumor-suppressor genes, which remain dormant unless they are transformed by genetic or acquired mutation. Common causes of acquired genetic damage are viruses, radiation, environmental and dietary carcinogens, and hormones. Other factors that interact to increase a person's likelihood of developing cancer are age, nutritional status, hormonal balance, and response to stress.

Risk factors

Many cancers are related to specific environmental and lifestyle factors that predispose a person to develop cancer. Accumulating data suggest that some of these risk factors initiate carcinogenesis, others act as promoters, and some both initiate and promote the disease process.

Air pollution

Air pollution has been linked to the development of cancer, particularly lung cancer. Many outdoor air pollutants — such as arsenic, benzene, hydrocarbons, polyvinyl chlorides, and other industrial emissions as well as vehicle exhaust — have been studied for their carcinogenic properties. Indoor air pollution, such as cigarette smoke and radon gas, also poses an increased risk of cancer. In fact, indoor air pollution is considered to be more carcinogenic than outdoor air pollution.

Tobacco and alcohol

A cigarette smoker's risk of lung cancer is more than ten times greater than that of a nonsmoker's by late middle age. Tobacco smoke contains carcinogens that are known to cause mutations. The risk of lung cancer from cigarette smoking correlates directly with the duration of smoking and the number of cigarettes smoked per day. Research also shows that a person who stops smoking decreases his or her risk of lung cancer.

Although the risk associated with pipe and cigar smoking is similar to that of cigarette smoking, some evidence suggests that the effects are less severe. Smoke from cigars and pipes is more alkaline. This alkalinity decreases nicotine absorption in the lungs and also is more irritating to the lungs, so that the smoker doesn't inhale as readily.

Inhalation of "secondhand" smoke, or passive smoking, by nonsmokers also increases the risk of lung and other cancers. Use of smokeless tobacco, in which the oral tissue directly absorbs nicotine and other carcinogens, is linked to an increase in oral cancers that seldom occur in persons who don't use the product.

Alcohol consumption is commonly associated with cirrhosis of the liver, a precursor to hepatocellular cancer. The risk of breast and colorectal cancers also increases with alcohol consumption. Heavy use of alcohol and cigarette smoking synergistically increase the incidence of cancers of the mouth, larynx, pharynx, and esophagus. It's likely that alcohol acts as a solvent for the carcinogenic substances in smoke, thus enhancing their absorption.

Sexual factors

Sexual practices have been linked to specific types of cancer. The age of first sexual intercourse and the number of sexual partners are positively correlated with a woman's risk of cervical cancer. Furthermore, a woman who has had only one sexual partner is at higher risk if that partner has had multiple partners. The suspected underlying mechanism here involves virus transmission, most likely human papilloma virus (HPV).

Hormones — specifically the sex steroid hormones estrogen, progesterone, and testosterone — have been implicated as promoters of breast, endometrial, ovarian, or prostate cancer.

Occupation

Certain occupations, by exposing workers to specific substances, increase the risk of cancer. For example, persons exposed to asbestos are at risk of a specific type of lung cancer, called mesothelioma. Asbestos also may act as a promoter for other carcinogens. Workers involved in the production of dyes, rubber, paint, and beta-naphthylamine are at increased risk of bladder cancer.

Radiation

Exposure to ultraviolet radiation, or sunlight, causes genetic mutation in the P53 control gene. Sunlight also releases tumor necrosis factor alpha in exposed skin, possibly diminishing the immune response. Ultraviolet sunlight is a direct cause of basal and squamous cell cancers of the skin. The amount of exposure to ultraviolet radiation also correlates with the type of cancer that develops. For example, cumulative exposure to ultraviolet sunlight is associated with basal and squamous cell skin cancer, and severe episodes of burning and blistering at a young age are associated with melanoma.

Ionizing radiation (such as X-rays) is associated with acute leukemia, thyroid, breast, lung, stomach, colon, and urinary tract cancers as well as multiple myeloma. Low doses can cause DNA mutations and chromosomal abnormalities, and large doses can inhibit cell division. Ionizing radiation also can en-

hance the effects of genetic abnormalities. Other compounding variables include the part and percentage of the body exposed, the person's age, hormonal balance, prescribed drugs and preexisting or concurrent conditions.

Diet

Numerous aspects of diet are linked to an increase in cancer, including:

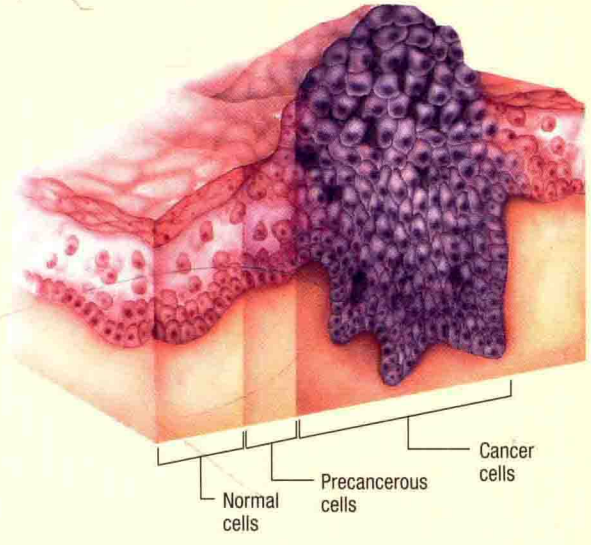
- obesity
- high consumption of dietary fat
- high consumption of smoked foods and salted fish or meats and foods containing nitrites
- naturally occurring carcinogens (such as hydrazines and aflatoxin) in foods
- carcinogens produced by microorganisms stored in foods
- diet low in fiber.

Pathophysiologic concepts

The characteristic features of cancer are rapid, uncontrollable proliferation of cells and independent spread from a primary site (site of origin) to other tissues where it establishes secondary foci (metastases). (See *Histologic characteristics of cancer cells.*) This spread occurs through circulation in the blood or lymphatic fluid, by unintentional transplantation from one site to another during surgery, and by local extension. Thus, cancer cells differ from normal cells in terms of cell size, shape, number, differentiation, function, and ability to travel to distant tissues and organ systems.

Histologic characteristics of cancer cells

Cancer is a destructive (malignant) growth of cells, which invade nearby tissues and may metastasize to other areas of the body. Dividing rapidly, these cells tend to be very aggressive.



Cell growth

Typically, each of the billions of cells in the human body has an internal clock that tells the cell when it is time to reproduce. Mitotic reproduction occurs in a sequence called the *cell cycle.* Normal cell division occurs in direct proportion to cells lost, thus providing a mechanism for controlling growth and differentiation. These controls are absent in cancer cells, and cell production exceeds cell loss. The loss of control over normal growth is termed *autonomy.* This independence is further evidenced by the ability of cancer cells to break away and travel to other sites.

Normal cells reproduce at a rate controlled through the activity of specific control or regulator genes. These genes produce proteins that act as "on" and "off" switches. There is no generalized control gene; different cells respond to specific control genes. In cancer cells, the control genes fail to function normally. The actual control may be lost or the gene may become damaged. An imbalance of growth factors may occur, or the cells may fail to respond to the suppressive action of the growth factors. Any of these mechanisms may lead to uncontrolled cellular reproduction.

Hormones, growth factors, and chemicals released by neighboring cells or by immune or inflammatory cells can influence control gene activity. These substances bind to specific receptors on the cell membranes and send out signals causing the control genes to stimulate or suppress cell reproduction.

Substances released by nearby injured or infected cells or by cells of the immune system also affect cellular reproduction. For example, interleukin, released by immune cells, stimulates cell proliferation and differentiation, and interferon, released from virus-infected and immune cells, may affect the cell's rate of reproduction.

Additionally, cells that are close to one another appear to communicate with each other through gap junctions (channels through which ions and other small molecules pass). This communication provides information to the cell about the neighboring cell types and the amount of space available. The nearby cells send out physical and chemical signals that control the rate of reproduction. Cancer cells fail to recognize the signals about available tissue space. Instead of forming only a single layer, cancer cells continue to accumulate in a disorderly array.

Differentiation

Normally, during development, cells become specialized. That is, they develop highly individualized characteristics that reflect their specific structure and functions. As the cells become more specialized, their reproduction and development slow down. Eventually, highly differentiated cells become unable to reproduce and some, skin cells for example, are programmed to die and be replaced.

Cancer cells lose the ability to differentiate; that is, they enter a state, called *anaplasia*, in which they no longer appear or function like the original cell. Anaplasia occurs in varying degrees. The less the cells resemble the cell of origin, the more anaplastic they are said to be. As the anaplastic cells continue to reproduce, they lose the typical characteristics of the original cell. Some anaplastic cells begin functioning as another type of cell, possibly beginning to produce hormones. Anaplastic cells of the same type in the same site exhibit many different shapes and sizes. Mitosis is abnormal and chromosome defects are common.

Intracellular changes

The abnormal and uncontrolled proliferation of cancer cells is also associated with numerous changes within the cancer cell itself. These changes affect cell components as follows:

- *cell membrane* — affects the organization, structure, adhesion, and migration of the cells. Impaired intercellular communication, enhanced response to growth factors, and diminished recognition of other cells causes uncontrolled growth and greatly increases metabolic demand for nutrients.
- *cytoskeleton* — disrupts protein filament networks, including actin and microtubules. Normally, actin filaments exert a pull on the extracellular organic molecules that bind cells together. Microtubules control cell shape, movement, and division.
- *cytoplasm* — components fewer in number and abnormally shaped. Less cellular work occurs because of a decrease in endoplasmic reticulum and mitochondria.
- *nucleus* — becomes pleomorphic (enlarged and misshapen) and highly pigmented. Nucleoli are larger and more numerous than normal. The nuclear membrane is often irregular and commonly has projections, pouches, or blebs, and fewer pores. Chromatin may clump along the outer areas of the nucleus. Chromosomal breaks, deletions, translocations, and abnormal karyotypes are common and seem to stem from the increased mitotic rate in cancer cells.

Tumor development and growth

Typically, a long time passes between the initiating event and the onset of the disease. During this time, the cancer cells continue to grow, develop, and replicate, each time undergoing successive changes and further mutations.

For a tumor to grow, an initiating event or events must cause a mutation that will transform the normal cell into a cancer cell. After the initial event, the tumor continues to grow only if available nutrients, oxygen, and blood supply are adequate and the immune system fails to recognize or respond to the tumor.

Two important tumor characteristics affecting growth are location of the tumor and available blood supply. The location determines the originating cell type, which in turn determines the cell cycle time. For example, epithelial cells have a shorter cell cycle than connective tissue cells. Thus, tumors of epithelial cells grow more rapidly than do tumors of connective tissue cells.

Tumors need an available blood supply to provide nutrients and oxygen for continued growth, and to remove wastes, but a tumor larger than 1 to 2 mm in size has typically outgrown its available blood supply. Some tumors secrete tumor angiogenesis factors, which stimulate the formation of new blood vessels, to meet the demand.

The degree of anaplasia also affects tumor growth. Remember that the more anaplastic the cells of the tumor, the less differentiated the cells and the more rapidly they divide.

Many cancer cells also produce their own growth factors. Numerous growth factor receptors are present on the cell membranes of rapidly growing cancer cells. This increase in receptors, in conjunction with the changes in the cell membranes, further enhances cancer cell proliferation.

Important characteristics of the host that affect tumor growth include age, sex, overall health status, and immune system function.

AGE ALERT

Age is an important factor affecting tumor growth. Relatively few cancers are found in children, and the incidence of cancer correlates directly to increasing age. This suggests that numerous or cumulative events are necessary for the initial mutation to continue, eventually forming a tumor.

Certain cancers are more prevalent in females, others in males. For example, sex hormones influence tumor growth in breast, endometrial, cervical, and prostate cancers. Researchers believe that the hormone sensitizes the cell to the initial precipitating factor, thus promoting carcinogenesis.

Overall health status is also an important characteristic. As tumors obtain nutrients for growth from the host, they can alter normal body processes and cause cachexia. Conversely, if the person is nutritionally depleted, tumor growth may slow. Chronic tissue trauma also has been linked with tumor growth because healing involves increased cell division. And the more rapidly cells divide, the greater the likelihood of mutations.

Spread

Between the initiating event and the emergence of a detectable tumor, some or all of the mutated cells may die. The survivors, if any, reproduce until the tumor reaches a diameter of 1 to 2 mm. New blood vessels form to support continued growth and proliferation. As the cells further mutate and divide more rapidly, they become more undifferentiated, and the number of cancerous cells soon begins to exceed the number of normal cells. Eventually, the tumor mass extends and invades the surrounding tissues. When the local tissue is blood or lymph, the tumor can gain access to the circulation. Once access is gained, tumor cells that detach may travel to distant sites in the body, where they can survive and form a new tumor in the secondary site. This process is called metastasis. (See *How cancer spreads.*)

Dysplasia

Not all cells that proliferate rapidly go on to become cancerous. Throughout a person's life span, various body tissues experience periods of benign rapid growth, such as during wound healing. In some cases, changes in the size, shape, and organization of the cells leads to a condition called dysplasia. Exposure to chemicals, viruses, radiation, or chronic inflammation causes dysplastic changes that may be reversed by removing the initiating stimulus or treating its effects. However, if the stimulus is not removed, precancerous or dysplastic lesions can progress and give rise to cancer.

Localized tumor

Initially, a tumor remains localized. Recall that cancer cells communicate poorly with nearby cells. As a result, the cells continue to grow and enlarge, forming a mass or clumps of cells. The mass exerts pressure on the neighboring cells, blocking their blood supply, and subsequently causing their death.

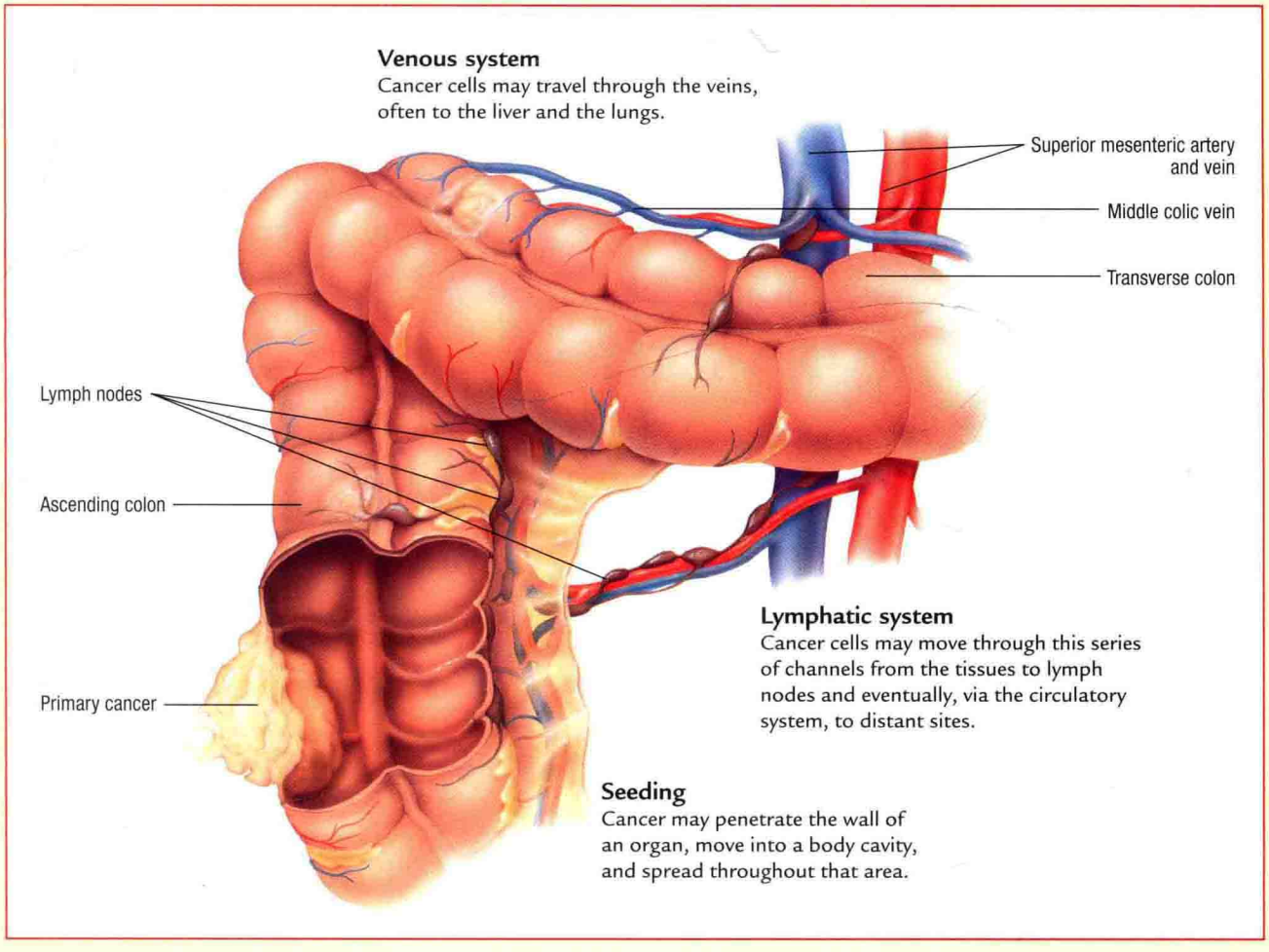
Invasive tumor

Invasion is growth of the tumor into surrounding tissues. It's actually the first step in metastasis. Five mechanisms are linked to invasion:

- *cellular multiplication* — By their very nature, cancer cells multiply rapidly.

How cancer spreads

Cancer cells may invade nearby tissues or metastasize (spread) to other organs. Cancer cells may move to other tissues by any or all of three routes:



• *mechanical pressure* — As they grow, they exert pressure on surrounding cells and tissues, which eventually die because their blood supply has been cut off or blocked. Loss of mechanical resistance opens the way for the cancer cells to spread along the lines of least resistance and occupy the space once filled by the dead cells.

• *lysis of nearby cells* — Vesicles on the cancer cell surface contain a rich supply of receptors for laminin, a complex glycoprotein that is a major component of the basement membrane. These receptors permit the cancer cells to attach to the basement membrane, forming a bridgelike connection. Some cancer cells produce and excrete powerful proteolytic enzymes; other cancer cells induce normal host cells to produce them. These enzymes, such as collagenases and proteases, destroy the normal cells and break through their basement membrane, enabling the cancer cells to enter.

• *reduced cell adhesion* — This is likely the result of damage to the cell membrane.

• *increased motility* — Cancer cells secrete a chemotactic factor that stimulates motility. Thus, they can move independently into adjacent tissues, and into the circulation, and then to a secondary site. Finally, cancer cells develop fingerlike projections called pseudopodia that facilitate cell movement. These projections injure and kill neighboring cells and attach to vessel walls, enabling the cancer cells to enter.

Metastatic tumor

Metastatic tumors are those in which the cancer cells have traveled from the original or primary site to a second or more distant site. Most commonly, metastasis occurs through the blood vessels and lymphatic system. Tumor cells also can be transported from one body location to another by external means, such as surgical instruments or gloves.

Invasive tumor cells break down the basement membrane and walls of blood vessels, and the tumor sheds malignant cells into the circulation. Most of the cells die, but a few escape the host defenses and the turbulent environment of the blood-

stream. From here, the surviving tumor mass of cells travels downstream and commonly lodges in the first capillary bed it encounters. Once lodged, the tumor cells develop a protective coat of fibrin, platelets, and clotting factors to evade detection by the immune system. Then they become attached to the epithelium, ultimately invading the vessel wall, interstitium, and the parenchyma of the target organ. To survive, the new tumor develops its own vascular network and, once established, may ultimately spread again.

The lymphatic system is the most common route for distant metastasis. Tumor cells enter the lymphatic vessels through damaged basement membranes and are transported to regional lymph nodes. In this case, the tumor becomes trapped in the first lymph node it encounters. The consequent enlargement, possibly the first evidence of metastasis, may be due to the increased tumor growth within the node or a localized immune reaction to the tumor. The lymph node may filter out or contain some of the tumor cells, limiting their further spread. The cells that escape can enter the blood from the lymphatic circulation through plentiful connections between the venous and lymphatic systems.

Typically, the first capillary bed, whether lymphatic or vascular, encountered by the circulating tumor mass determines the location of the metastasis. For example, because the lungs receive all of the systemic venous return, they are a frequent site for metastasis.

Signs and symptoms

In most patients, the earlier the cancer is found, the more effective the treatment is likely to be and the better the prognosis. Some cancers may be diagnosed by a routine physical examination, even before the person develops any signs or symptoms. Others may display some early warning signals. (See *Cancer's seven warning signs.*)

Unfortunately, a person may not notice or heed the warning signs. These patients may present with some of the commoner signs and symptoms of advancing disease, such as fatigue, cachexia, pain, anemia, thrombocytopenia and leukopenia, and infection. Unfortunately, these signs and symptoms are nonspecific and can be attributed to many other disorders.

Cancer's seven warning signs

The American Cancer Society has developed an easy way to remember the seven warning signs of cancer. Each letter in the word *CAUTION* represents a possible warning sign that should spur an individual to see a doctor.

C hange in bowel or bladder habits
A sore that doesn't heal
U nusual bleeding or discharge
T hickening or lump in the breast or elsewhere
I ndigestion or difficulty swallowing
O bvious change in a wart or mole
N agging cough or hoarseness

Diagnostic tests

A thorough history and physical examination should precede sophisticated diagnostic tests. The choice of diagnostic tests is determined by the patient's presenting signs and symptoms and the suspected body system involved. Diagnostic tests serve several purposes, including:

- establishing tumor presence and extent of disease
- determining possible sites of metastasis
- evaluating affected and unaffected body systems
- identifying the stage and grade of tumor.

Useful tests for early detection and staging of tumors include screening tests, X-rays, radioactive isotope scanning (nuclear medicine imaging), computed tomography (CT) scanning, endoscopy, ultrasonography, and magnetic resonance imaging (MRI). The single most important diagnostic tool is the biopsy for direct histologic study of the tumor tissue.

- *Screening tests* are perhaps the most important diagnostic tools in the prevention and early detection of cancer. They may provide valuable information about the possibility of cancer even before the patient develops signs and symptoms.
- *X-rays* are most commonly ordered to identify and evaluate changes in tissue densities. The type and location of the X-ray is determined by the patient's signs and symptoms and the suspected location of the tumor or metastases.
- *Radioactive isotope scanning* involves the use of a specialized camera which detects radioactive isotopes that are injected into the blood stream or ingested. The radiologist evaluates their distribution (uptake) throughout tissues, organs, and organ systems. This type of scanning provides a view of organs and regions within an organ that cannot be seen with a simple X-ray.
- *CT scanning* evaluates successive layers of tissue by using narrow beam X-ray to provide a cross-sectional view of the structure. It also can reveal different characteristics of tissues within a solid organ.
- *Endoscopy* provides a direct view of a body cavity or passageway to detect abnormalities. During endoscopy, the physician can excise small tumors, aspirate fluid, or obtain tissue samples for histologic examination.
- *Ultrasonography* uses high-frequency sound waves to detect changes in the density of tissues that are difficult or impossible to observe by radiology or endoscopy. Ultrasound helps to differentiate cysts from solid tumors.
- *MRI* uses magnetic fields and radio frequencies to show a cross-sectional view of the body organs and structures.
- *Biopsy*, removing a portion of suspicious tissue, is the only definitive method to diagnose cancer. Biopsy tissue samples can be taken by curettage, fluid aspiration, fine-needle aspiration, dermal punch, endoscopy, and surgical excision. The specimen then undergoes laboratory analysis for cell type and characteristics to provide information about the grade and stage of the cancer.

Some cancer cells release substances that normally aren't present in the body or are present only in small quantities. These substances, called tumor markers or biologic markers, are produced either by the cancer cell's genetic material during growth and development or by other cells in response to the presence of cancer. Markers may be found on the cell membrane of the tumor or in the blood, cerebrospinal fluid, or urine. Tumor cell markers include hormones, enzymes, genes, antigens, and antibodies.

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