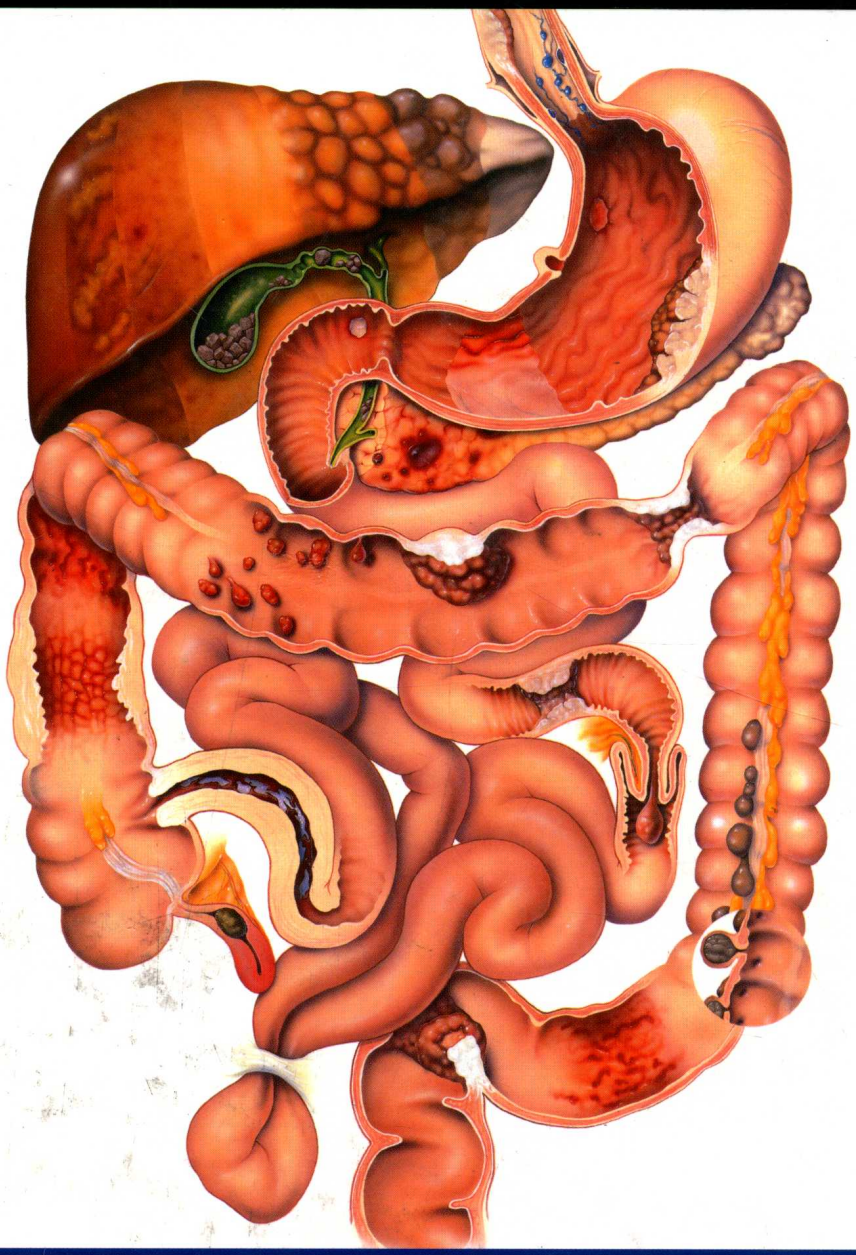
ANATOMICAL CHART COMPANY

ATLAS of PATHOPHYSIOLOGY

THIRD EDITION



Wolters Kluwer Health | Lippincott Williams & Wilkins

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I dedicate this book to my wife Sheena, my son Wyatt, and my new baby girl Adree. I hope that my work someday inspires my children because they inspire me every day. I would also like to thank Steve Bassett for being a positive role model in the field of teaching anatomy and physiology and encouraging me to get involved with reviewing textbooks and publishing my own work. Lastly, I would like to thank Jeff Downing for giving me the opportunity to work on this project (hopefully this is the first of many) and also Karen Turner for all her help and patience walking me through the process. I hope the students find this helpful.

Drew Case

Introduction

This Study Guide was designed to help you learn, review, and most importantly, prepare for exams for Essentials of Anatomy & Physiology. Prior to using this Study Guide, it is my strong recommendation that you have had the content in lecture, read the corresponding chapters in the text, and that you have studied the material. The best way to check your knowledge and preparedness prior to taking an exam is by taking a practice exam. I have designed this Study Guide so that you can quickly, efficiently, and effectively check your level of comprehension of the material prior to exams. The Study Guide is set up in such a manner that you will be able to quickly go back to the textbook and study or review more should you have difficulty answering the questions. I based the format of this guide on what would be most likely encountered on course exams. The exam is the final test of our efforts and success of learning the material.

I will give you study tips, hints, and suggestions throughout the Study Guide. They are based on years of teaching and student feedback and are worth reading and giving a try. You may not find all of them helpful. Learning is a "trial-and-error" process. Be open to new ways of studying and try different methods and you will find the way that works best for you.

I have organized the questions of each chapter in the same pattern to simplify studying and create predictability in the Study Guide. Below is a list and description of the questions in the order that will be encountered throughout the guide. Not all of the question types will always be used for each section.

Fill in the Blanks

Fill in the blank questions are the highest level of difficulty and require you to recall the answer from memory. They are very similar many times to multiple-choice questions simply without the choices, thus the higher level of difficulty. They make excellent questions to put on flash cards for studying.

Matching

Matching questions are one of the lowest levels of difficulty of the questions provided and may contain some of the more difficult definitions to increase the challenge. Match the term on the left with the definition on the right and write in the letter of the term in the answer blank next to the term. Each term can only be used once unless noted otherwise. I have tried to make the answers short and to the point. Sometimes I use words or phrases that I found helpful in learning the material.

Multiple Choice

Multiple-choice questions are a moderate difficulty level and are the most frequently encountered type of question on exams and more importantly, board and certification exams. Multiple-choice questions are short answer or fill in the blank questions with choices. If you have difficulty with multiple-choice questions because you "talk yourself out of the right answer," cover the choices and answer it like a fill in the blank and then see if your answer is one of the choices. If so, pick that answer and move on.

Labeling

Labeling questions are a completely different way of testing your knowledge from all the other question types presented. This is referred to as "visual learning" and is an excellent method of testing what is "memorized." I recommend using a scrap piece of paper to record your answers so that you may label the pictures/diagrams over and over till you can consistently get a 100%.

Short Answer

Short answers are similar to fill in the blank in difficulty and style. These questions usually require listing out multiple answers and often in order. These too also make excellent flash card questions. The majority of the short answer questions cover critical material that is very likely to show up on exams.

Study Tips

Every chapter will have study tips that include things like mnemonics and other ideas on how to memorize and learn the material. The study tips will have an icon next to them to help identify them and make them stand out. These study tips are based on years of teaching and positive student feedback, so be sure to read them.

Sample Flash Cards

FC This symbol, used throughout the Study Guide, indicates questions or information that would be helpful to include in making flash cards. It does not suggest making a flash card with the same question or format but rather that the term, concept, structure(s), or definition has been frequently included on exams covering this material.

Flash cards can be one of the most effective methods of putting vast amounts of material to memory. The great advantage of using flash cards is that you are testing yourself just as though you had your own personal tutor sitting there asking you questions. Think about what you would want someone to ask you to help you prepare for an exam, and that is what you put on the flash card. If you make flash cards correctly, you remove the doubt or question, "do I really know the material?" You either answer the question right or wrong. Here are just a few quick tips for making flash cards:

1. Keep them simple; use as few words as possible
2. Question on one side (be sure to ask a question), answer on the other
3. DO NOT make flash cards on material that you already know or have memorized
4. Make a flash card on everything you think will be on the exam that you DO NOT have memorized
5. Limit the number of questions to only a couple per card based on the complexity of the answer. The questions and answers should be short and to the point like fill in the blank or multiple-choice questions without the choices. AVOID long answer questions that take more than one sentence to answer.
6. List questions are excellent flash card questions as are matching questions.

Here are a couple of sample flash cards from Chapter 1:

1. Study of human body's structures?
2. Standing with feet and head facing forward and the arms at the sides with the palms facing forward?
3. Study of body's functions?
4. Study of body's dysfunction?

(Notice how short and simple the questions are? Answer all the questions on this side in your head or out loud and turn the card over.)

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 are the sites of cellular respiration — the metabolic use of oxygen to produce energy, carbon dioxide, and water (They produce most of the body's adenosine triphosphate, which contains high-energy phosphate chemical bonds that fuel many cellular activities.)
- *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; and 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, obsolete, 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 [WBCs] by a similar process, *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 and enable cell division and migration
- *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 include:

- *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 these 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 include:
– *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. The three types include:
– *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* — 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.

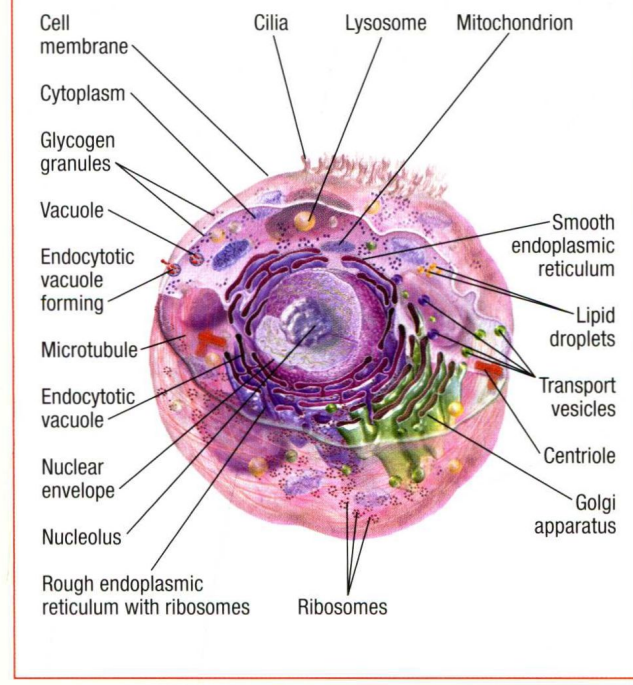
PATHOPHYSIOLOGIC CONCEPTS

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 alter 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.)

CELL COMPONENTS



Atrophy

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

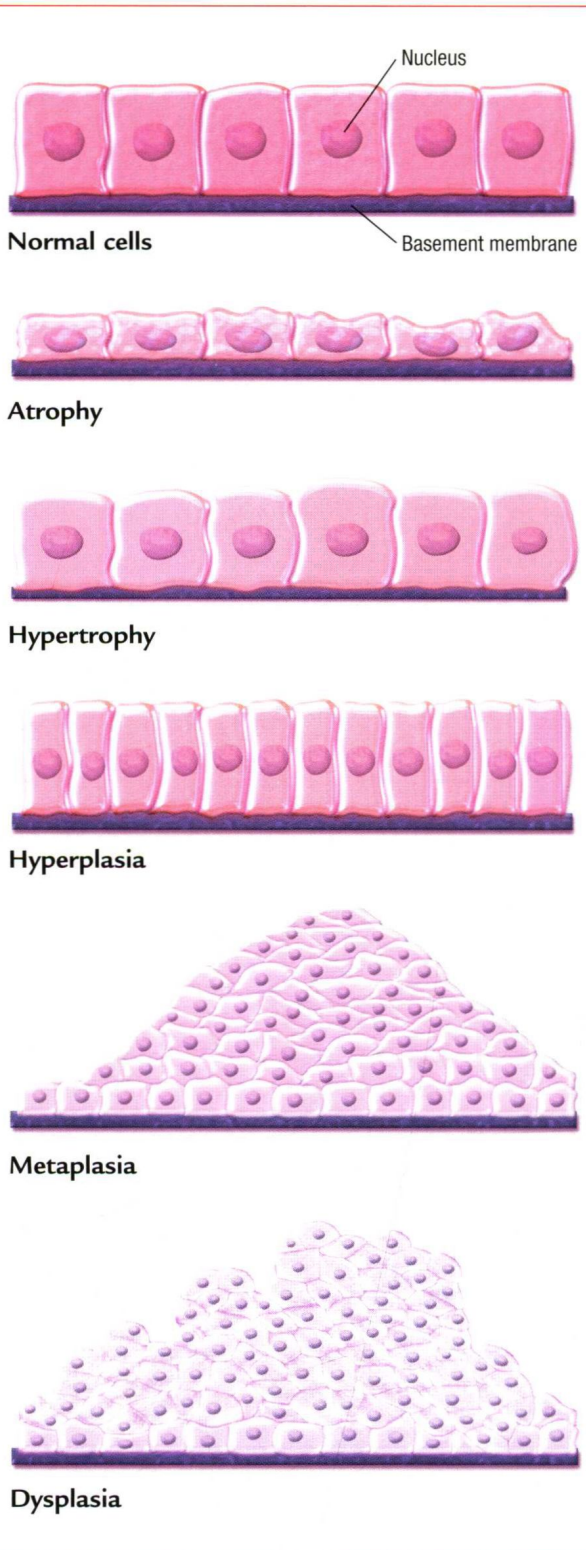
Hypertrophy

Hypertrophy is an increase in the size of a cell or organ due to an increase in workload. It may result from normal physiologic conditions or abnormal pathologic conditions. Types include:
• *physiologic hypertrophy* — reflects an increase in workload that isn't caused by disease (for example, the increase in muscle size caused by hard physical labor or weight training)
• *pathologic hypertrophy* — an adaptive or compensatory response to disease; for example, an adaptive response is thickening of heart muscle as it pumps against increasing resistance in patients with hypertension. An example of a compensatory response is when one kidney enlarges if the other isn't functioning or present.

Hyperplasia

Hyperplasia is an increase in the number of cells caused by increased workload, hormonal stimulation, or decreased tissue. Hypertrophy and hyperplasia may occur together and are commonly triggered by the same mechanism. 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.

Adaptive cell changes



factors — for example, acromegaly, in which excessive growth hormone production causes bones to enlarge.

Metaplasia

Metaplasia is the replacement of one mature cell type with another differentiated cell type that can better endure the change or stressor. It's usually a response to chronic inflammation or irritation.

- *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, deranged cell growth of specific tissue results in abnormal size, shape, and appearance. Although dysplastic cell changes are adaptive and potentially reversible, 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.

Clinical tip

Oxygen deficiency is the most common cause of irreversible cell injury and cell death.

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 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. Examples of reversible degenerative changes are cervical dysplasia and fatty changes in the liver. Examples of irreversible degenerative diseases include Huntington's chorea and amyotrophic lateral sclerosis.

- *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

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 may manifest in different ways, depending on the tissues or organs involved. It can involve apoptosis or necrosis.

- *Apoptosis* — genetically programmed cell death — accounts for the constant cell turnover in the skin's outer keratin layer and the lens of the eye. It's characterized by a series of events including chromatin condensation, membrane blebbing, cell shrinkage, and DNA degradation. It's controlled by autodigestion.

There are five types of necrosis:

- *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 liquefactive necrosis, which is extensive lytic activity from bacteria and WBCs 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.

Necrotic cells release intracellular enzymes, which start to dissolve cellular components, and trigger an acute inflammatory reaction in which WBCs 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 and producing 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 isn't 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. Without 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 these stages:

- *exposure or injury* — target tissue exposed to a causative agent or injury
- *latency or incubation period* — no signs or symptoms evident
- *prodromal period* — signs and symptoms generally mild and nonspecific
- *acute phase* — disease reaches 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 development and growth. Malignant cells have two defining characteristics: first, they can no longer divide and differentiate normally and, second, they can invade surrounding tissues and travel to distant sites within the body. In the United States, cancer is the number one cause of death in people younger than age 85 and accounts for more than half a million deaths each year.

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-related genes: oncogenes or tumor suppressor genes.

Oncogenes provide growth-promoting signals, thereby causing one or more characteristics of cancer cells when overexpressed or mutated.

Proto-oncogenes are genes that can be converted to oncogenes by transforming cells or contributing to tumor formation. *Tumor suppressor genes* are growth-suppressing genes that inhibit tumor development.

Both types of these cancer-related genes can be inherited or acquired. 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, genetics, nutritional status, hormonal balance, and response to stress.

Risk factors

Cancer is recognized as a multistage disease involving multiple, distinct changes in cell genotype and phenotype.

Many cancers are related to specific environmental factors (air pollution, tobacco and alcohol, occupation, and radiation) and lifestyle factors (sexual practices and diet) 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. In addition, age and genetics can also determine a person's risk of cancer.

Air pollution

Environmental factors such as air pollution have 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 motor 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 10 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 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 is also 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 increases 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.

Occupation

Certain occupations that expose workers to specific substances increase the risk of cancer. For example, persons exposed to asbestos are at risk for 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 for bladder cancer.

Radiation

Exposure to ultraviolet radiation, including sunlight (UVB) or tanning booths (UVA), 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 of radiation can cause DNA mutations and chromosomal abnormalities, and large doses can inhibit cell division. Ionizing radiation can also enhance the effects of genetic abnormalities. Other compounding variables include the part and percentage of the

body exposed, the person's age, hormonal balance, use of prescription drugs, and preexisting or concurrent conditions.

Sexual practices

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). Of the approximately 70 types of HPV, types 6 and 11 are associated with genital warts. HPV is the most common cause of abnormal Papanicolaou (Pap) tests, and cervical dysplasia is a direct precursor to squamous cell carcinoma of the cervix, both of which have been linked to HPV (especially types 16 and 31).

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

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
- low-fiber diet.

It's also important to note that childhood obesity may increase the risk of cancer development in later life. Obesity is a prominent risk factor for breast, colon, and prostate cancers. Because cancer is a disease of abnormal cell proliferation, the increased total number of cells in the body associated with obesity undergo a greater number of cell divisions, thereby increasing their susceptibility to abnormal changes and an increased risk of cancer development.

Age

Age is a major determinant in the development of cancer. The longer men and women live, the more likely they are to develop the disease. For example, because of the long natural history of common cancers, prostate cancer may take up to 60 years to become invasive, while colon cancer may take as long as 40 years to develop into an invasive stage. Possible explanations for the increased incidence of cancer with advancing age include:

- *altered hormonal levels,* which may stimulate cancer
- *ineffective immunosurveillance,* which fails to recognize and destroy abnormal cells
- *prolonged exposure to carcinogenic agents,* which is more likely to produce neoplastic transformation
- *inherent physiologic changes and functional impairments,* which decrease the body's ability to tolerate and survive stress.

Genetics

Genes, through the proteins they encode, are the chemical messages of heredity. Located at specific locations on the 46 chromosomes within the cell's nucleus, genes transmit specific hereditary traits.

Most cancers develop from a complex interplay among multiple genes and between genes and internal or external environmental factors. Phenomenal progress has been made in the fields of cancer genetics and cytogenetics that has established specific chromosomal changes as diagnostic and prognostic factors in acute and chronic leukemias, as diagnostic factors in various solid tumors, and as indicators for the localization and characterization of genes responsible for tumor development.

Moreover, in the past 25 years, research has identified and characterized many of the genetic alterations that lead to tumor transformation at the chromosomal and molecular cell level. The Human Genome Project, started in 1988 to identify the entire sequence of human DNA, has helped to increase knowledge about genetics and cancer carcinogenesis. The Philadelphia (Ph) chromosome was the first chromosomal anomaly caused by translocation implicated in a human disease (chronic myelocytic leukemia [CML]). However, it's important to note that not all mutated genes always lead to disease.

As previously discussed, two sets of genes, oncogenes and tumor suppressor genes, participate in the transformation of a normal cell into a malignant cell; however, because multiple, successive changes in distinct cellular genes are required to complete the entire process, the human cell rarely sustains the necessary number of changes needed for tumor transformation. Gene mutations are either *inherited* from a parent (hereditary or germline mutation) or *acquired* (somatic mutation). Inheritance accounts for about 10% of all cancers. Acquired mutations are changes in DNA that develop throughout a person's lifetime. Carcinogenic agents, such as radiation or toxins, commonly are able to damage cellular genes, which are present in the cancer cell genome, thereby triggering cancer development.

Hereditary genes

Genes implicated in hereditary cancer include:

- *mutation of the adenomatous polyposis coli (APC) suppressor gene,* which is altered by somatic mutations in colonic epithelial cells, permitting the outgrowth of early colonic polyps
- *familial adenomatous polyposis (FAP) or APC,* which acts as an autosomal dominant inherited condition in which hundreds of potentially cancerous polyps develop in the colon and rectum
- *familial cutaneous malignant melanoma gene,* on the distal short arm of chromosome 1
- *expression of the N-myc oncogene* in neuroblastoma, with amplification of this oncogene associated with rapid disease progression in children
- *loss of regulation of N-myc gene expression,* which is also a pivotal factor in the development of retinoblastoma, the most common pediatric intraocular tumor
- *germline mutation of the P53 gene,* which is mapped to the short arm of chromosome 17 and is associated with Li-Fraumeni syndrome, an extremely rare familial cancer syndrome that increases susceptibility to breast cancer, soft tissue sarcomas, brain tumors, bone cancer, leukemia, and adrenocortical carcinoma
- *human epidermal growth factor receptor-2 (HER-2)/neu proto-oncogene,* which is involved in regulation of normal cell growth. Gene amplification or HER-2/neu overexpression, which occurs in 25% to 30% of human breast cancers and to varying degrees in other tumor types, produces activated HER-2/neu receptors and stimulates cell growth. Tumors positive for the

HER-2/neu gene are associated with poor clinical outcomes, shortened disease-free survival, more rapid cancer progression, and poor response to standard clinical interventions.

Gene mutations

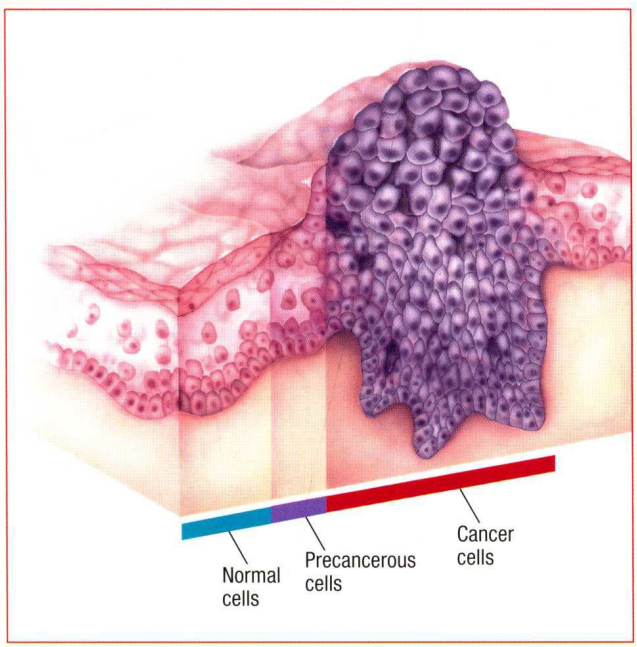
Gene mutations have also been linked to inherited tendencies toward common cancers, including colon cancer and breast cancer. The BRCA 1 gene normally helps to restrain cell growth. Researchers have found that families who carry inherited mutations of breast cancer susceptibility genes may also have an increased risk of other cancers, for example, women with an altered copy of the BRCA 1 breast cancer susceptibility gene (located on chromosome 17q21) have increased susceptibility to ovarian cancer as well. Moreover, BRCA 2, a second breast cancer susceptibility gene mapped to chromosome 13q, may account for a significant number of hereditary breast cancers not associated with BRCA 1.

PATHOPHYSIOLOGIC CONCEPTS

The characteristic features of cancer are rapid, uncontrollable proliferation of cells and independent spread from a primary site, the 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 invades nearby tissues and may metastasize to other areas of the body. Dividing rapidly, cancer cells tend to be extremely aggressive.



Cell growth

Typically, each of the billions of cells in the human body has an internal clock that tells the cell when it's 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 in the body.

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 one another 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.

Cell 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 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* — becomes 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, cancer cells continue to develop, grow, 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

A person's 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 sex hormones sensitize the cell to the initial precipitating factor, thus promoting carcinogenesis.

Overall health status is also an important characteristic affecting tumor growth. 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 down. Chronic tissue trauma has also been linked with tumor growth because healing involves increased cell division. Therefore, the more rapidly cells divide, the greater the likelihood of mutations.

Metastasis

Between the initiating event and the emergence of a detectable tumor, some or all of the mutated cancer 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. When 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 metastasizes,* page 10.)

Dysplasia

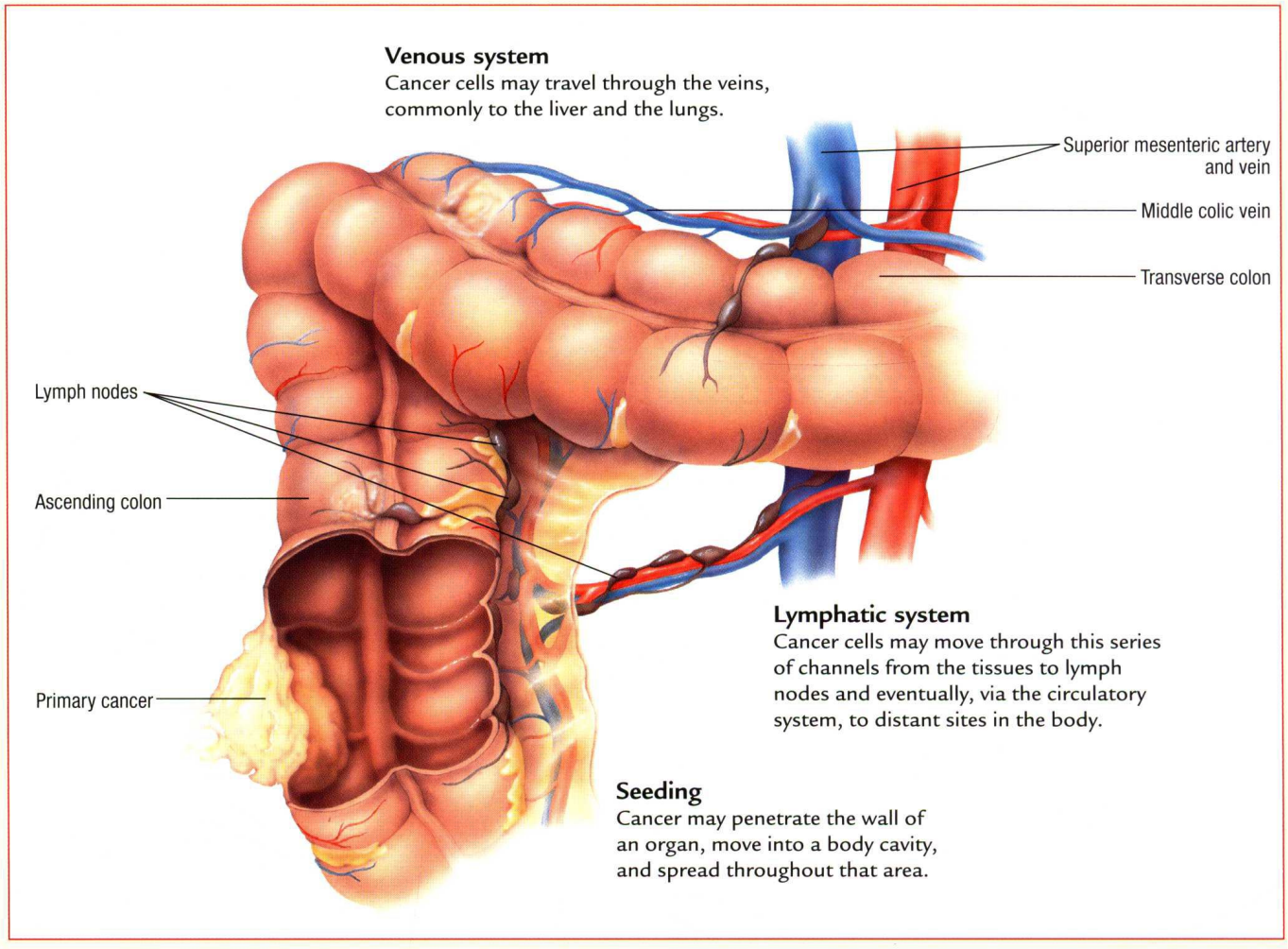
Not all cells that proliferate rapidly go on to become cancerous. Throughout a person's life span, various body tissues experience periods of benign rapid growth such as during wound healing. In some cases, changes in the size, shape, and organization of cells leads to a condition called *dysplasia.* 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 isn't 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.

How cancer metastasizes

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



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.
- *mechanical pressure* — As cancer cells 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 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's 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* — Cancer cells' adhesion decreases, likely the result of deregulation of cell adhesion receptors.
- *increased motility* — Cancer cells secrete chemotactic factors that stimulate motility. Thus, they can move 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.

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 can also be transported from one body location to another by external means, such as surgical instruments or gloves.