Applied Research Topics

The Application of Principles in Chemistry

Cells, tissues, organs, and organ systems are composed of chemicals. The survival of cells, tissues, organs, and systems depends on the control of chemical reactions, both within individual cells and in the extracellular fluids of the body. It is therefore not surprising that you cannot understand physiological principles without a familiarity with basic chemistry. As the understanding of physiological mechanisms has improved, physicians have become relatively adept at using chemical tests to diagnose disease. They have also developed ways of manipulating intracellular and extracellular chemical reactions to help restore homeostasis. In this section we will consider the practical application of some basic chemical principles introduced in Chapter 2.

THE MEDICAL IMPORTANCE OF RADIOISOTOPES  EAP p. 29

Many recent technological advances in medicine have involved the use of radioisotopes for diagnosis and the visualization of internal structures. This section will focus on two examples:

- The use of radioactive tracers in diagnosis: Radioisotopes can be attached to organic or inorganic molecules and injected into the body. Once within the body, these labeled compounds emit radiation energy that can be used to create images that provide information about tissue structure, tumorous growths, blocked or weakened blood vessels, or other abnormalities in the body.

- The use of radioactive compounds to treat disease: If a suitable radiation source can be accurately delivered to a target site, the radioactivity can be used to destroy abnormal cells or tissues.

Radioisotopes and Clinical Testing

Radioisotopes are isotopes having unstable nuclei that emit subatomic particles in measurable amounts. Alpha particles are generally released by the nuclei of large radioactive atoms, such as uranium. Each alpha particle consists of a helium nucleus: two protons and two neutrons. Beta particles are electrons, more often released by radioisotopes of lighter atoms. Gamma rays are very high-energy electromagnetic waves comparable to the X-rays used in clinical diagnosis. The half-life of any radioactive isotope is the time required for a 50 percent reduction in the amount of radiation it emits. The half-lives of radioisotopes range from fractions of a second to thousands of years.

Like X-rays, gamma rays, beta particles, and alpha particles can damage or destroy living tissues. The danger posed by radiation exposure varies, depending on the nature of the emission and the duration of exposure. But radiation also has a variety of beneficial uses in medical research and clinical diagnosis. Weakly radioactive isotopes with short half-lives can sometimes be used to check the structural and functional state of an organ.

Radioisotopes are useful because they can be incorporated into specific compounds normally found within the body. These labeled compounds, called tracers, can be introduced into the body and tracked by the radiation they release. After a labeled compound is swallowed, its uptake, distribution, and excretion can be determined by
monitoring the radioactivity of samples taken from the digestive tract, body fluids, and waste products. For example, compounds labeled with radioisotopes of cobalt are used to measure the intestinal absorption of vitamin B12. Usually cobalt-58, a radioisotope with a half-life of 71 days, is used.

Radioisotopes can also be injected into the blood or other body fluids to provide information on circulatory anatomy and the anatomy and function of specific target organs. In nuclear imaging, the radiation emitted by injected radioisotopes creates an image on a special detector. Such a procedure may be used to identify regions where particular radioactive materials are concentrated or to check the circulation through vital organs. Radioisotopes can also produce pictures of specific organs, such as the liver, spleen, or thyroid, where labeled compounds are removed from the circulation.

The thyroid gland sits below the larynx (voice box) on the anterior portion of the neck (Figure A-3a). A normal thyroid gland absorbs iodine, which is then used to produce thyroid hormones. As a result, the thyroid gland will actively absorb and concentrate radioactive iodine. The thyroid scan in Figure A-3b was taken following the injection of iodine-131, a radioisotope with an eight-day half-life. This procedure, called a thyroid radioactive iodine uptake measurement, or RAIU, can provide information on (1) the size and shape of the thyroid gland and (2) the amount of iodine absorption. Comparing the rate of iodine uptake with the level of circulating hormones allows us to evaluate the functional state of the gland.

Radioactive iodine is an obvious choice for imaging the thyroid gland. For most other tissues and organs a radioactive label must be attached to another compound. Technetium-99m, a versatile label, is the primary radioisotope used in nuclear imaging today. This isotope is artificially produced and has a half-life of six hours. This brief half-life significantly reduces the patient’s exposure to radiation. Technetium is used in more than 80 percent of all scanning procedures. The nature of the technetium-labeled compound varies, depending on the identity of the target organ. Technetium scans are performed to examine the thyroid gland, spleen, liver, kidneys, digestive tract, bone marrow, and a variety of other organs.

PET (Positron Emission Tomography) scans utilize the same principles as standard radioisotope scans, but the analyses are performed by computer. The scans are much more sensitive, and the computers can reconstruct sections through the body that permit extremely precise localization. Among other things, this procedure can analyze blood flow through organs and assess the metabolic activity within specific portions of an organ as complex as the human brain.

Figure A-3c is a PET scan of the brain showing activity at a single moment in time. The scan is dynamic, however, and changing patterns of activity can be followed in real time. PET scans can be used to analyze normal brain function as well as to diagnose brain disorders. To date, the technique has served primarily as a research tool. Because the equipment is expensive and bulky, it is unlikely to be available anywhere except in large regional

Figure A-3 Imaging techniques
(a) The position and contours of the normal thyroid gland as seen in dissection. (b) After it has been labeled with radioactive tracer, the thyroid can be examined by special imaging techniques. In this computer-enhanced image, different intensities indicate differing concentrations of the radioactive tracer. (c) A PET scan of the left cerebral hemisphere in lateral view. The light areas indicate regions of increased metabolic activity.
medical centers or universities. The research advantages of PET scans have diminished considerably since the advent of real-time CT analysis (cine-CT) and the realization that a rapid functional MRI (fMRI) can be used to monitor small changes in blood flow and tissue activity without the use of radioactive tracers.

**Radiopharmaceuticals**  
EAP p. 29

Nuclear medicine involving injected radioisotopes has been far more successful in producing useful images than in treating specific disorders. The problem is that relatively large doses of radiation must be used to destroy abnormal or cancerous tissues, and it is very difficult to control the distribution of these radioisotopes in the body with sufficient precision. As a result, both normal and abnormal tissues may be damaged by radiation exposure. For the same reason, it is difficult to control the radiation dosage administered to the target tissues. This is a problem because underexposure can have very little effect, whereas overexposure can cause the destruction of adjacent normal tissues.

Radioactive drugs, or radiopharmaceuticals, can be effective only if they are delivered precisely and selectively. One success story has been the treatment of hyperthyroidism, or thyroid oversecretion. As noted earlier, the thyroid gland selectively concentrates iodine. To treat hyperthyroidism, large doses of radioactive iodine-131 can be administered. The radiation released destroys the abnormal thyroid tissue and stops the excessive production of thyroid hormones. (Following this treatment, most individuals eventually become hypothyroid—deficient in thyroid hormone—but this condition can be treated by taking thyroid hormones in tablet form.) This is now the preferred treatment method for hyperthyroid patients over 40 years of age.

A relatively new application of nuclear medicine involves attaching a radioactive isotope to a monoclonal antibody (MoAb). Antibodies are proteins produced in the body to provide a selective defense against foreign proteins, toxins, or pathogens. Monoclonal antibodies are produced by immune cells cultured under laboratory conditions. The antibodies these cells manufacture can be extracted, labeled with radioactive materials, and concentrated. If injected into the body, the antibodies will bind to their targets and expose the surrounding tissues to radiation. MoAbs specific for certain types of tumor cells have already been approved by the FDA. The amount of radiation emitted is low, however, and the procedure is used to produce images rather than to treat the disease. This technique is very sensitive and can detect small tumors for early diagnosis and treatment. Experiments continue, with the eventual goal of using radiolabeled MoAbs to destroy tumor cells.

**SOLUTIONS AND CONCENTRATIONS**  
EAP p. 36

Physiologists and clinicians pay particular attention to the electrolyte composition of blood fluids. Standard values for physiological tests are provided throughout the text and summarized in Appendix IV. Data must be analyzed from several different perspectives, and physiological values may be reported in several different ways. One method is to report the concentration of atoms, ions, or molecules in terms of weight per unit volume of solution. Although grams per liter (g/l) may be used, values are most often expressed in grams (g), milligrams (mg), or micrograms (µg) per 100 ml. Since 100 ml is 0.1 liter, or 1 deciliter (dl), the abbreviations most often used in this text are g/dl and mg/dl.

Osmotic concentration, or osmolarity, depends on the total number of individual atoms, ions, and molecules in solution, without regard to molecular weight, electrical charge, or molecular identity. As a result, if fluid balance and osmolarity are being monitored, concentrations are usually reported in moles per liter (mol/l or M) or millimoles per liter (mmol/l or mM) rather than in g/dl or mg/dl. To convert from g/dl to mol/l, multiply by 10 and divide by the atomic weight of the element. For example, a sample of plasma (blood with the cells removed) contains sodium ions at a concentration of roughly 0.32 g/dl (320 mg/dl). This value can be converted to mmol/l as follows:

\[
g/dl \times \frac{10}{atomic \ weight} = \frac{0.32 \times 10}{22.99} = 0.140 \text{ mol/l (} \approx 140 \text{ mmol/l)}
\]

Moles or millimoles per liter can also be used to indicate the concentration of molecules in solution: the same conversion can be performed by substituting molecular weight for atomic weight in the above equation.

Because electrolyte concentrations have profound effects on living cells, it is often important to know how many positive and negative charges are present in a biological solution. In this case the important question is not just how many ions or molecules are present, but how many positive or negative charges they bear. For example, a single ion of calcium (Ca\(^{2+}\)) has twice the electrical charge of a single sodium atom (Na\(^{+}\)), although the two are identical in terms of their effects on osmolarity. One equivalent (Eq) represents a mole of positive or negative charges; physiological concentrations are often reported in terms of milliequivalents per liter (mEq/l). You should become familiar with both methods of expression, and fortunately, the conversion from millimoles to milliequivalents is relatively easy to perform. For monovalent ions, those with a +1 or –1 charge, millimole and milli-
equivalent values are identical, and no calculation is needed. For **divalent ions**, with +2 or −2 charges, the number of charges (mEq) is twice the number of ions (mmol); if an ion had a +3 or −3 charge, the number of milliequivalents would be 3 times the number of millimoles. To reverse the process and convert mEq to mmol, simply divide by the ionic valence (number of charges).

Table A-6 compares the different methods of reporting the concentration of major electrolytes in plasma in terms of weight, moles, and equivalents; the tables in Appendix IV of Essentials of Anatomy and Physiology provide data in terms currently accepted for clinical laboratory reports.

There is no doubt that physiologists and clinicians would benefit from the use of standardized reporting procedures; it can be very frustrating to consult three references and find that the first reports electrolyte concentrations in mg/dl, the second in mM/l, and the third in mEq/l. In 1984, the American Medical Association House of Delegates endorsed a plan to standardize clinical test results through the use of metric SI (Systeme Internationale) units, with a target date of July 1, 1987, for the switchover. Unfortunately, there was no mechanism for enforcing compliance, and the plan may not prove any more successful than the ill-fated attempt to drop the U.S. system of measurement in favor of the metric system.

The major problem is that the relationships to current normal values are difficult to remember. Electrolyte concentrations, now most often indicated in mEq/l, will be reported in SI units that represent mM/l. That means the values for sodium or potassium concentrations remain unchanged, but the normal values for calcium or magnesium are reduced by 50 percent. The situation becomes more confusing when metabolite concentrations are considered. Cholesterol and glucose concentrations are now reported in terms of mg/dl, but the SI units represent mM/l (mmol/l). However, total lipid concentrations, also currently listed as mg/dl, and total protein concentrations, now shown as g/dl, will be reported in terms of g/l. To be useful in a clinical setting, physicians must not only remember the definition of each SI unit but convert and relearn the normal ranges. As a result, it appears unlikely that the conversion to SI units will be completed in the immediate future.

### Topics in Metabolism

**Metabolism** is the sum of all the biochemical reactions proceeding in the body. There are hundreds of thousands of reactions occurring in each cell, and at any given moment biochemical pathways may be producing phospholipids for the cell membrane or peptide hormones for secretion while breaking down carbohydrates to generate ATP. This section will consider three aspects of metabolism:

1. Many disease processes are the result of a faulty biochemical pathway. For example, an enzyme may be missing or nonfunctional, or the necessary enzymatic substrates may be unavailable. *Phenyketonuria* and *albinism* are metabolic disorders that we will consider shortly.

2. Enzymes play a pivotal role in controlling metabolic processes in our cells. The mechanisms responsible for controlling enzymatic reactions are therefore important, and problems with enzymatic regulation can cause severe metabolic disorders.

3. Diet and nutrition have an obvious impact on metabolic operations within the body. A substantial research effort is under way to manipulate metabolic operations by dietary changes—the control of cholesterol in the diet is only one of several pertinent examples.

<table>
<thead>
<tr>
<th>Solute</th>
<th>mg/dl</th>
<th>mM/l</th>
<th>mEq/l</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (Na⁺)</td>
<td>320</td>
<td>140</td>
<td>140</td>
<td>140 mmol/l</td>
</tr>
<tr>
<td>Potassium (K⁺)</td>
<td>16.4</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2 mmol/l</td>
</tr>
<tr>
<td>Calcium (Ca²⁺)</td>
<td>9.5</td>
<td>2.4</td>
<td>4.8</td>
<td>2.4 mmol/l</td>
</tr>
<tr>
<td>Chloride (Cl⁻)</td>
<td>354</td>
<td>100</td>
<td>100</td>
<td>100 mmol/l</td>
</tr>
<tr>
<td><strong>Metabolites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>90</td>
<td>5</td>
<td>nr</td>
<td>5 mmol/l</td>
</tr>
<tr>
<td>Lipids, total</td>
<td>600</td>
<td>nr</td>
<td>nr</td>
<td>0.6 g/l</td>
</tr>
<tr>
<td>Proteins, total</td>
<td>7 g/dl</td>
<td>nr</td>
<td>nr</td>
<td>70 g/l</td>
</tr>
</tbody>
</table>

**Artificial Sweeteners**

Some people cannot tolerate sugar for medical reasons; others avoid it because recent dietary guidelines call for reduced sugar consumption or they are trying to lose weight. Thus many people today use artificial sweeteners in their foods and beverages.

Artificial sweeteners are organic molecules that can stimulate taste buds and provide a sweet taste to foods without adding substantial amounts of calories to the diet. These molecules have a much greater effect on the taste receptors than natural sweeteners, such as fructose or sucrose, so they can be used in minute quantities. For example, *saccharin* is about 300 times sweeter than sucrose. The popularity of this sweetener has declined since it was reported that saccharin may promote bladder cancer in rats. The risk is very small, however, and saccharin continues to be used. Several other artificial sweeteners are currently on the market, including *aspartame* (*NutraSweet®*), *sucralose*, and *acesulfame potassium* (*Ace-K, or Surette®*). The market success of an artificial sweetener ultimately depends on its taste and its chemical properties. Stability in high temperatures (as in baking) and resistance to breakdown in an acidic pH (as in carbonated drinks) are important properties for any artificial sweetener.
Molecules of artificial sweeteners do not resemble those of natural sugars. Saccharin, acesulfame potassium, and sucralose cannot be broken down by the body and have no nutritional value. Aspartame consists of a pair of amino acids. Amino acids are the building blocks of proteins (as discussed later in this chapter), and they can be broken down in the body to provide energy. However, because aspartame is 200 times sweeter than sucrose, very small quantities are needed, so the sweetener adds few calories to a meal. Aspartame does not produce the bitter aftertaste sometimes attributed to saccharin and thus is used in many diet drinks and low-calorie desserts.

Two new sweeteners, thaumatin-1 and monellin, are proteins extracted from African berries. Thaumatin, roughly 100,000 times sweeter than sucrose, has been approved by the Food and Drug Administration for use in chewing gums.

Fat Substitutes

Although the average American diet is not as rich in fats as that of Eskimos, we still consume more fat than do people in many other parts of the world. Diets high in fat have been linked not only to heart disease but also to certain forms of cancer, and recent recommendations suggest that lowering the percentage of calories we derive from fat would benefit our health. This suggestion has led to an increased interest in the development of possible substitutes for fat.

Fat substitutes provide the texture, taste, and cooking properties of natural fats. Two fat substitutes, Simplesse® and Olestra®, have been approved by the Food and Drug Administration: a third, Trailblazer®, is currently under review. Simplesse and Trailblazer are made from proteins of egg white and skim milk or whey. The heated proteins are treated to form small spherical masses that have the taste and texture of fats. Simplesse can be used in place of fats in any application other than baking; it is found in low-calorie can be used in place of fats in any application other than baking; it is found in low-calorie

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Olestra is made by chemically combining sucrose and fatty acids. The resulting compounds cannot be used by the body, and so contribute no calories at all. Olestra has been approved as an ingredient in margarines, baked goods, and other snack foods; its use as a shortening and cooking oil is under review. One problem is that Olestra droplets in the digestive tract collect lipid-soluble materials, including fat-soluble vitamins, and prevent their absorption. In addition, if eaten in large quantities, Olestra can cause diarrhea. These side effects pose a serious threat—a combination of fluid loss and vitamin deficiency. To prevent vitamin deficiencies, manufacturers now fortify Olestra-containing foods with fat-soluble vitamins.

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Anomalies in Amino Acid Metabolism

1. Phenylketonuria (PKU): Persons with phenylketonuria (PKU) lack the enzyme that converts the amino acid phenylalanine to another amino acid, tyrosine. Without this enzyme, phenylalanine accumulates in the blood and tissues. If this condition is not detected shortly after birth, mental retardation may occur. Newborn infants usually undergo a blood test for PKU 48 hours after nursing begins, because milk is a major source of phenylalanine. Abnormally high circulating levels of phenylalanine may indicate PKU. Once a diagnosis of PKU is made, the diet is controlled to avoid foods high in phenylalanine.

2. Albinism: Albinism is a genetic disorder that results in a lack of pigment production in the skin. The cause is a defective enzyme involved in the metabolism of the amino acid tyrosine. Because this enzyme is abnormal, the protein pigment melanin cannot be synthesized. The skin is white, and the hair and eyes are also affected. Among its other functions, melanin helps protect the skin from the effects of ultraviolet (UV) radiation. When outdoors, individuals with albinism must be careful to avoid skin damage from the UV radiation in sunlight.


Topics in Cellular Biology and Histology

Cells are the smallest living units in the body, but they are not the only forms of life. Discussions throughout the text and the Applications Manual assume that you are familiar with the basic properties of cells and with the characteristics of potential pathogens (disease-causing organisms). This section begins with a review of the important distinctions among types of pathogens and then proceeds to a discussion of other topics at the cellular level of organization.

THE NATURE OF PATHOGENS

Chapter 3 of the text presented the structure of a "representative" cell. The cellular organization described there and shown in Figure 3-2 is that of a eukaryotic (iُ-kar-ëh-OT-ik; eu, "true" + karyon, "nucleus") cell. The defining characteristic of eukaryotic cells is the presence of a nucleus. All eukaryotic cells have similar membranes, organelles, and methods of cell division. All multicellular animals and plants (as well as some single-celled organisms) are composed of eukaryotic cells.

The eukaryotic plan of organization is not the only one found in the living world, however. There are organisms that do not consist of eukaryotic cells. These organisms that do not consist of eukaryotic cells. These organisms are of great interest to us because they include most of the pathogens that can cause human diseases.

Table A-7 Examples of Bacterial Diseases and Primary Organ Systems Affected

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
<th>Affected Organ System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacilli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>Anthrax</td>
<td>Integumentary, respiratory systems</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Tuberculosis</td>
<td>Respiratory system</td>
</tr>
<tr>
<td>Corynebacterium diphtheriae</td>
<td>Diphtheria</td>
<td>Respiratory system</td>
</tr>
<tr>
<td>Cocci</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Various skin infections</td>
<td>Integumentary system</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Pharyngitis (strep throat)</td>
<td>Respiratory system</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Gonorrhea</td>
<td>Reproductive system</td>
</tr>
<tr>
<td>Vibrios</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>Cholera</td>
<td>Digestive system</td>
</tr>
<tr>
<td>Spirochetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Syphilis</td>
<td>Reproductive, nervous systems</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>Lyme disease</td>
<td>Skeletal system (joints)</td>
</tr>
<tr>
<td>Rickettsias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rickettsia prowazekii</td>
<td>Epidemic typhus fever</td>
<td>Cardiovascular system</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>Q fever</td>
<td>Respiratory system</td>
</tr>
<tr>
<td>Chlamydiias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Trachoma (eye infections)</td>
<td>Nervous system</td>
</tr>
<tr>
<td>&quot;</td>
<td></td>
<td>Lymphogranuloma-venereum (LGV)</td>
</tr>
</tbody>
</table>
Some cocci and bacilli may form groupings of cells. The Latin names used to describe these groupings are also used to identify specific bacteria. For instance, pairs of cocci bacteria are called diplococci (diplo- means double). Streptococci and streptobacilli form twisted chains of cells (strepto- means twisted), and, staphylococci look like a bunch of grapes (staphylo-, grapelike).

Viruses

Another type of pathogen conforms neither to the prokaryotic nor the eukaryotic organizational plan. These tiny pathogens, called viruses, are not cells at all. In fact, when free in the environment, they do not show any of the characteristics of living organisms. They are classified as infectious agents because they can enter cells (either prokaryotic or eukaryotic) and replicate themselves.

Viruses consist of a core of nucleic acid (DNA or RNA) surrounded by a protein coat. (Some varieties have a membranous outer covering as well.) The structure of a representative virus is shown in Figures A-4b and A-6. Important viral diseases include influenza (flu), yellow fever, some leukemias, AIDS, hepatitis, polio, measles, mumps, rabies, and the common cold (Table A-8).

To enter a cell, a virus must first attach to the cell membrane. This attachment occurs at one of the normal membrane proteins. Once it has penetrated the cell membrane, the viral nucleic acid takes over the cell’s metabolic machinery. In the

---

**Figure A-4 Representative Pathogens**

(a) A bacterium, with prokaryotic characteristics indicated. Compare with Figure 3-2 (EAP p. 55), which shows a representative eukaryotic cell. (b) A typical virus. Each virus has an inner chamber containing nucleic acid, surrounded by a protein capsid or an inner capsid and an outer membranous envelope. The herpes viruses are enveloped DNA viruses; they cause chicken pox, shingles, and herpes. (c) Protozoan pathogens. Protozoa are eukaryotic, single-celled organisms, common in soil and water. (d) Multicellular parasites. Several different groups of organisms are human parasites and many have complex life histories. Note: These illustrations are not drawn to a common scale.

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In the case of an RNA virus, the story is somewhat more complicated (Figure A-7b). In the simplest RNA viruses, the viral RNA entering the cell functions as an mRNA strand that carries the information needed to direct the cell’s ribosomes to synthesize viral proteins. These proteins include enzymes that perform the duplication of the viral RNA. When the cell is packed with new viruses, the cell membrane ruptures and the RNA viruses are released into the interstitial fluid.

In the retroviruses, a group that includes HIV (the virus that causes AIDS), the replication process is more complex. These RNA viruses carry an enzyme called reverse transcriptase that directs “reverse transcription”: the assembly of DNA based on the nucleotide sequence of an RNA strand. DNA created in this way is inserted into the infected cell’s chromosomes. The viral genes are then activated, and the cell begins producing RNA through normal transcription. The RNA produced includes viral RNA, mRNA carrying the information for the synthesis of reverse transcriptase, and mRNA controlling the synthesis of viral proteins. These components combine in the cytoplasm, which gradually becomes filled with viruses. The new RNA viruses are shed at the cell surface.

Even if the host cell is not destroyed outright by these events, normal cell function is usually disrupted. In effect, the metabolic activity of the cell is diverted to create viral components, rather than performing tasks needed for cell maintenance and survival. Some viruses, however, can lie dormant within infected cells for long periods of time before initiating this process of replication.
Viruses are now becoming important as benefactors, as well as adversaries. In genetic engineering procedures, viruses whose nucleic acid structure has been intentionally altered can be used to transfer copies of normal human genes into the cells of individuals with inherited enzymatic disorders. This was the method used to insert the gene for the enzyme missing in ADA patients (p. 32). Attempts are now planned to treat cystic fibrosis (CF) in the same way. Cystic fibrosis is a debilitating genetic defect whose most obvious—and potentially deadly—symptoms involve the respiratory system. The underlying problem is an abnormal gene that carries instructions for a chloride ion channel found in cell membranes throughout the body. Researchers have recently treated CF in laboratory animals by inserting the normal gene into a virus that infects cells lining the respiratory passageways. The virus could be given to human patients via an inhalant.

Table A-8 Examples of Viral Diseases and Primary Organ Systems Affected

<table>
<thead>
<tr>
<th>Nucleic Acid</th>
<th>Virus</th>
<th>Disease</th>
<th>Affected Organ System</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNA</td>
<td>Influenza A, B, C</td>
<td>Flu</td>
<td>Respiratory, reproductive systems</td>
</tr>
<tr>
<td></td>
<td>Paromyxovirus</td>
<td>Mumps</td>
<td>Digestive system</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A, C, D, E, G</td>
<td>Hepatitis</td>
<td>Digestive system (liver)</td>
</tr>
<tr>
<td></td>
<td>Rhinovirus</td>
<td>Common cold</td>
<td>Respiratory system</td>
</tr>
<tr>
<td></td>
<td>Human immunodeficiency virus (HIV)</td>
<td>AIDS</td>
<td>Lymphatic system</td>
</tr>
<tr>
<td>DNA</td>
<td>Herpesvirus</td>
<td>Cold sore/fever blister</td>
<td>Integumentary system</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex 1</td>
<td>Genital herpes</td>
<td>Reproductive system</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex 2</td>
<td>Chickenpox</td>
<td>Integumentary system</td>
</tr>
<tr>
<td></td>
<td>Varicella-zoster</td>
<td>Shingles</td>
<td>Nervous system</td>
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<tr>
<td></td>
<td>Varicella-zoster</td>
<td>Hepatitis</td>
<td>Digestive system (liver)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td>Mononucleosis</td>
<td>Respiratory system</td>
</tr>
</tbody>
</table>

Figure A-7 Viral Replication
(a) Replication of a typical DNA virus.

Examples: smallpox, herpes, hepatitis, common cold
Prion Diseases

Prions (PR-ions) are controversial proteins that are either infectious agents or the result of infection by an as-yet unidentified virus. (Current evidence suggests that the proteins are themselves infectious.) Normal neurons produce a very similar protein that exists as individual molecules. They are located in the cell membrane and exposed to the extracellular fluid. When exposed to a prion, this protein changes shape, and the individual molecules interact to form large insoluble complexes that are released into the extracellular fluid. These complexes are called amyloid plaques.

Either the presence of the amyloid plaques or the absence of the normal protein then disrupts neural function.

The first prion disease described was kuru, a deadly disease affecting members of a ritually cannibalistic society in New Guinea. The prions were passed from person to person when uninfected individuals ate infected brains. The infection, which led to death within a year, caused half of all childhood and adult deaths in parts of New Guinea. Other known prion diseases include Cruetzfeldt–Jakob disease and fatal familial insomnia. Most cases of prion disease (kuru excepted) are the result of mutations in the normal gene that produce amyloid plaques. However, if a normal person becomes exposed to these abnormal proteins, a prion disease will result.

Prion infection also occurs in domesticated animals. In sheep, the condition is called scrapie; in cows, it is called bovine spongiform encephalopathy (BSE). BSE was apparently spread by the use of cattle feed containing “beef byproducts.” Infected cows ultimately develop an assortment of strange neurological symptoms (such as pawing at the ground and difficulty in walking), giving the condition the common name of “mad cow disease.” In 1995, European researchers attributed an upsurge in the incidence of Cruetzfeldt–Jakob disease (CJD) in humans to the consumption of meat products from prion-infected cows. The incident has focused significant public interest and research attention on prion diseases, and stopped the practice of adding “beef byproducts” to cattle feed.
Unicellular Pathogens and Multicellular Parasites

Bacteria and viruses are the best-known human pathogens, but there are eukaryotic pathogens as well. Examples of the most important types are included in Figure A-4c. **Protozoa** are unicellular eukaryotic organisms that are abundant in soil and water. They are responsible for a variety of serious human diseases, including *amoebic dysentery* and *malaria*. **Fungi** (singular *fungus*) are eukaryotic organisms that absorb organic materials from the remains of dead cells. Mushrooms are familiar examples of very large fungi. In a fungal infection, a microscopic fungus spreads through living tissues, killing cells and absorbing nutrients. Several relatively common skin conditions (*athlete’s foot*) and a few more serious diseases (*histoplasmosis*) are the result of fungal infections.

Larger multicellular organisms such as *flukes* or *nematodes*, generally referred to as *parasites*, can also invade the human body and cause diseases (Figure A-4d). These organisms, which range from microscopic flatworms to tapeworms a meter or more in length, usually cause weakness and discomfort, but do not by themselves kill their host. However, complications resulting from the parasitic infection, such as chronic bleeding or secondary infections by bacterial or viral pathogens, can ultimately prove fatal.

**CELL STRUCTURE AND FUNCTION**

Each cell in the body has a particular role to play in maintaining the integrity of the individual as a whole. Some conduct nerve impulses, while others manufacture hormones, build bones, or contract to produce body movements. When any of these cells malfunction, whether due to genetic abnormalities affecting enzyme function, a viral or bacterial infection, trauma, or cancer, homeostasis is threatened. The next section introduces clinical and practical applications of basic principles of cellular function and discusses representative disorders resulting from problems at the cellular level of organization.

**Lysosomal Storage Diseases**

Problems with lysosomal enzyme production cause more than 30 storage diseases affecting children. In these conditions the lack of a specific lysosomal enzyme results in the buildup of materials normally removed and recycled by lysosomes. Eventually the cell cannot continue to function. Three important examples will be considered here: **Gaucher’s disease**, **Tay-Sachs disease**, and **glycogen storage disease**.

**Gaucher’s disease** is caused by the buildup of cerebrosides, glycolipids found in cell membranes. This is probably the most common type of lysosomal storage disease. There are two forms of this disease: (1) an infantile form, marked by severe neurological symptoms ending in death, and (2) a juvenile form, with enlargement of the spleen, anemia, pain, and relatively mild neurological symptoms. Gaucher’s disease is most common among the Ashkenazic Jewish population, where it occurs at a frequency of approximately 1 in 1000 births.

**Tay-Sachs disease** is another hereditary disorder caused by the inability to break down glycolipids. In this case the glycolipids are *gangliosides*, which are most abundant in neural tissue. Individuals with this condition develop seizures, blindness, dementia, and death, usually by age 3–4. Tay-Sachs disease is most common among the Ashkenazic Jewish population, where it occurs at a frequency of 0.3 per 1000 births.

**Glycogen storage disease** (Type II) primarily affects skeletal muscle, cardiac muscle, and liver cells—the cells that synthesize and store glycogen. In this condition the cells are unable to mobilize glycogen normally, and large numbers of insoluble glycogen granules accumulate in the cytoplasm. These granules disrupt the organization of the cytoskeleton, interfering with transport operations and the synthesis of materials. In skeletal and heart muscle cells, the buildup leads to muscular weakness and potentially fatal heart problems.

**Mitochondrial DNA, Disease, and Evolution**

There are several inheritable disorders that result from abnormal mitochondrial activity. The mitochondria involved have defective enzymes that reduce their ability to generate ATP. Cells throughout the body may be affected, but symptoms involving muscle cells, neurons, and the receptor cells in the eye are most commonly seen because these cells have especially high energy demands. Disorders caused by defective mitochondria are called *mitochondrial cytopathies*. In several instances, the disorders have been linked to inherited abnormalities in mitochondrial DNA. In some cases, the problem appears in one population of cells only. For example, abnormal mitochondrial DNA has been found in the motor neurons whose degeneration is responsible for the condition of *Parkinson's disease*, a neurological disorder characterized by a shuffling gait and uncontrollable tremors.

More often, mitochondria in cells throughout the body are involved. Examples of conditions caused by mitochondrial dysfunction include one class of epilepsies (*myoclonic epilepsy*) and a type of blindness (*Leber’s hereditary optic neuropathy*). These are inherited conditions, but the pattern of inheritance is very unusual. Although men or women may have the disease, only affected women can pass the condition on to their children. The explanation for this pattern is that the disorder results from an abnormality in the DNA of mitochondria, not in the DNA of cell nuclei. All the mitochondria in the body are produced through
the replication of mitochondria present in the fertilized ovum. Few if any of those mitochondria were provided by the father; most of the mitochondria of the sperm do not remain intact after fertilization takes place. As a result, children can usually inherit these conditions only from their mothers.

This brings us to an interesting concept. Virtually all your mitochondria were inherited from your mother, and hers from her mother, and so on back through time. The same is true for every other human being. Now, it is known that over long periods of time small changes in DNA nucleotide sequences accumulate. Mitochondrial DNA, or mtDNA, can therefore be used to estimate the degree of relationship between individuals. The greater the difference between the mtDNA of two individuals, the more time has passed since the lifetime of their most recent common ancestor, and the more distant their relationship. On this basis it has been estimated that all human beings now alive shared a common female ancestor roughly 350,000 years ago. Appropriately enough, that individual has been called a “Mitochondrial Eve.” The existence and history of Mitochondrial Eve remain controversial.

**TISSUE STRUCTURE AND DISEASE**

**Pathologists** (pa-THOL-o-jists) are physicians who specialize in the study of disease processes. Diagnosis, rather than treatment, is usually the main focus of their activities. In their analyses, pathologists integrate anatomical and histological observations to determine the nature and severity of the disease. Because disease processes affect the histological organization of tissues and organs, tissue samples, or biopsies, often play a key role in their diagnoses.

Figure A-8 diagrams the histological changes induced by one relatively common irritating stimulus, cigarette smoke. The first abnormality to be observed is dysplasia (dis-PLÄ-zë-uh), a change in the normal shape, size, and organization of tissue cells. It is usually a response to chronic irritation or inflammation, and the changes are reversible. The normal trachea (windpipe) is lined by a pseudostratified, ciliated columnar epithelium. The cilia move a mucous layer that traps foreign particles and moistens incoming air. The drying and chemical effects of smoking first paralyze the cilia, halting the movement of mucus (Figure A-8a). As mucus builds up, the individual coughs to dislodge it (the well-known “smoker’s cough”).

Epithelia and connective tissues may undergo more radical changes in structure, caused by the division and differentiation of stem cells. **Metaplasia** (me-tuh-PLÄ-zë-uh) is a structural change that dramatically alters the character of the tissue. In our example, heavy smoking first paralyzes the cilia, and over time the epithelial cells lose their cilia altogether. As metaplasia occurs, the epithelial cells produced by stem cell divisions no longer differentiate into ciliated columnar cells. Instead, they form a stratified squamous epithelium that provides a greater resistance to drying and chemical irritation (Figure A-8b). This epithelium protects the underlying tissues more effectively, but it completely eliminates the moisturization and cleaning properties of the epithelium. The cigarette smoke will now have an even greater effect on more delicate portions of the respiratory tract. Fortunately, metaplasia is reversible, and the epithelium gradually returns to normal once the individual quits smoking.

During anaplasia (a-nuh-PLÄ-zë-uh) tissue organization breaks down. Tissue cells change size and shape, often becoming unusually large or abnormally small. In anaplasia, which is the primary hallmark (or sign) of cancer, the cells divide.

![Figure A-8 Changes in a Tissue under Stress](image-url)
more frequently, but not all divisions proceed in the normal way, and many of the tumor cells have abnormal chromosomes (Figure A-8c). Unlike dysplasia and metaplasia, anaplasia is irreversible.

**Topics in Molecular Biology**

*Molecular biology* is the division of science that studies the synthesis, structure, and function of macromolecules important to life, such as proteins and nucleic acids. Deciphering the genetic code and relating the intricate structure of a protein to its particular functions are major goals of molecular biology. Research in this area has greatly enhanced our understanding of normal functions as well as disease processes.

The field of molecular biology has revolutionized the study of medicine by uncovering a clear biochemical basis for many complex diseases. For example, in sickle-cell anemia red blood cells undergo changes in shape that result in blocked vessels and tissue damage due to oxygen starvation. It is now known that this condition results when an individual carries two copies of a defective gene that determines the structure of *hemoglobin*, the oxygen-binding protein found within red blood cells. The genetic defect is small and changes just 2 of the 574 amino acids in this protein. That one change is enough to alter the functional properties of the hemoglobin molecule, leading to changes in the properties of the red blood cells. This type of disorder is often called a *molecular disease* because it results from abnormalities at the molecular level of organization.

Roughly 2500 inherited disorders have now been identified, and researchers have located the defective genes responsible for cystic fibrosis, Duchenne’s muscular dystrophy, and Huntington’s and Tay-Sachs diseases. Identifying the genetic defect is the vital first step toward the development of an effective gene therapy or other treatment. The treatments that are now evolving make use of the principles of *genetic engineering*.

**GENETIC ENGINEERING AND GENE THERAPY**  EAP p. 71

Once the mechanics of the genetic code were understood, everyone realized that it would be theoretically possible to change the genetic makeup of organisms—perhaps even of a human being. The popular term for activities related to this goal is *genetic engineering*.

What are some of the key problems confronting genetic engineers? Genes code for proteins—the makeup of each protein is determined by the sequence of codons (nucleotide triplets) in a stretch of DNA. A human cell has 46 chromosomes, 2 meters of DNA, and roughly $10^9$ triplets. If all the DNA in the human body were extracted and strung together, the resulting strand would be long enough to make several hundred round-trips between the earth and the sun. Simply finding a particular gene among the approximately 35,000 that each of us carries is an imposing task. Yet before a specific gene can be modified, its location must be determined with great precision. This involves preparing a map of the appropriate chromosome.

**Mapping the Human Genome**

Several techniques can be used to create a general map of the chromosomes. *Karyotyping* (KAR-é-ó-ti-ping: *karyon*, nucleus + *typos*, a mark) is the determination of an individual’s chromosome complement. Figure A-9a shows a complete set (46) of normal human chromosomes. Each chromosome has characteristic banding patterns, and segments can be stained with special dyes. Unusual banding patterns can indicate structural abnormalities. These abnormalities are sometimes linked to specific inherited conditions, including a form of leukemia. *Down syndrome* results from the presence of an extra chromosome, a copy of chromosome 21 (Figure A-9b).

In December 1993, French researchers at the Centre d’Etude de Polymorphism Humaine (CEPH; “Center for the Study of Human Polymorphism”) completed the first preliminary mapping of the entire human genome. This provided the landmarks and reference points needed to make more precise maps that indicate the locations of specific genes. More detailed maps have now been prepared for the Y chromosome and chromosome 21—the two smallest chromosomes—and work continues on the others.

Mapping is useful in itself, but it is only an intermediate step on the way to the ultimate goal: the determination of the nucleotide sequence of every gene in the human genome. In 2002, the Human Genome Project reported a “working draft” of the entire human genome, with high-quality sequencing of 97.8% of the genome complete. It is expected that all of the sequencing will be complete by 2003. To paraphrase Winston Churchill, the accurate sequencing of the human genome may be “the end of the beginning” in understanding our genetic selves.

**Gene Manipulation and Modification**

Suppose that the location of a defective gene has been pinpointed. Before attempting to remedy the defect, one would have to determine the nature of the genetic abnormality. For example, the gene could be inactive or overactive or producing an abnormal protein. It could even be missing entirely.

Finally, it would be necessary to decide how to remedy the defect. Can the gene be turned on, turned off, modified, or replaced?

*What’s the problem?* This can be a particularly difficult question to answer. Many of the 2500
Inheritable genetic disorders are classified according to general patterns of symptoms rather than any specific protein or enzyme deficiency. In some cases the approximate location of the gene has been determined, but the identity of the protein responsible for the clinical symptoms remains a mystery. In cystic fibrosis, many different abnormalities in the gene and the resulting protein result in different patterns of clinical disease.

What can be done? If the gene is present but overproducing or underproducing, its activity might be controlled by introducing chemical repressors or inducers. Another approach relies on gene splicing to produce a protein missing or present in inadequate quantities in the abnormal individual. Gene splicing begins with the localization of the gene, followed by its isolation (Figure A-10). That gene is then “spliced” into the relatively simple DNA strand of a bacterium, creating recombinant DNA. Bacteria grow and reproduce rapidly under laboratory conditions, and before long there is a colony of identical bacteria. All the members of the colony will carry the introduced gene and manufacture the corresponding protein. The protein can be extracted, concentrated, and administered to individuals whose diseases represent deficiencies in the activity of that particular gene. Hemophilia, a deficiency of blood clotting factors, and a form of diabetes caused by an insulin deficiency can be treated in this way.

Gene splicing is also used to obtain large quantities of proteins normally found in very small concentrations. Interferon, an antiviral protein, and human growth hormone are examples of compounds now being produced commercially using gene-splicing technology.

The most revolutionary strategies involve “fixing” abnormal cells by giving them copies of normal genes. In general, this method poses significant targeting problems, for the gene must be introduced into the right kind of cell. For example, placing liver enzymes in fingernails would not correct a metabolic disorder. But when the target cells can be removed and isolated, as in the case of bone marrow, the technique is promising. Actual removal of a defective gene does not appear to be a practical approach, and the focus has been on adding genes that can take over normal functions.
In September 1990, the first gene therapy trials were initiated. The procedure was used to treat a 4-year-old girl afflicted with adenosine deaminase deficiency (ADA). A rare condition, ADA affects only about 20 children worldwide each year. Without this enzyme, toxic chemicals build up in cells of the immune system. As these cells die, the body’s defenses break down.

ADA results in a complex of symptoms known as severe combined immunodeficiency disease, or SCID. SCID can also be caused by other enzyme disorders affecting cells of the immune system. Symptoms include chronic respiratory infections, diarrhea, and a low resistance to viral or bacterial infections. Most children with ADA die from infections that would pose no threat to normal children. A new drug called PEG-ADA, an altered form of the missing enzyme, can prolong life, but it does not cure the condition.

In the 1990 clinical trial, blood cells were collected, and lymphocytes, the primary cells of the immune system were removed. Short segments of DNA containing the normal gene for adenosine deaminase were then inserted into the nuclei of these cells, and the modified immune cells were returned to the body. Roughly a billion modified cells were reintroduced. Over time these modified cells divided to produce a large population of normal immune cells. The experiment was successful, and this method has been used to treat several other children with ADA deficiency. Each has regained and retained apparently normal immune function, although the treatment must be repeated every few years.

This procedure attempts to relieve the symptoms of disease by inserting genes into defective somatic cells. They do not change the genetic structure of reproductive cells; because the eggs or sperm retain the original genetic pattern, the genetic defect will be passed to future generations. Researchers are much further away from practical methods of changing the genetic characteristics of reproductive cells. Mouse eggs fertilized outside the body have been treated and transplanted into the uterus of a second mouse for development. The gene added was one for a growth hormone obtained from a rat, and the large "supermouse" that resulted demonstrated that such manipulations can be performed. The possibilities for manipulating the characteristics of valuable animal stocks,
such as cattle, sheep, or chickens, are quite exciting. The potential for altering the genetic characteristics of human beings is intimidating. Before any clinical variations on this theme are tested, our society will have to come to grips with a number of difficult ethical issues.

To get a sense of the kinds of problems we might have to deal with, discuss the following questions with your friends and classmates.

**Genetic Engineering—Questions to Think About**

1. Your 51-year-old father has recently been diagnosed with a hereditary disorder affecting the brain. The prognosis is poor, and there is currently no cure for the disorder. The physician advises that you can be tested for the presence of the faulty gene.
   - Would you be tested? Would you want to know if you had the defective gene?
   - If you were tested, who should have access to the results:
     - Your insurance company?
     - Your family, spouse, or fiancé?
     - Your employer?

2. Eugenics is the control of the hereditary characteristics of individuals to improve the species. The science of eugenics became distorted through the work of scientists under Adolf Hitler’s control. Prenatal testing now permits the diagnosis of a variety of inherited disorders before birth. This information could be used to “improve the species” by selectively terminating pregnancies. Is this advisable or ethical?

3. Many scientists today, such as Nobel laureate James Watson, consider the human genome to be the blueprint for a human being. If an individual’s genetic code affects every characteristic of that person, can people accused of crimes be held legally responsible for their actions?

4. Studies in the past have seemed to show that men with an extra Y chromosome (XYY) are more violent and predisposed to crime than are men with the XY genotype. More recent studies have revealed no greater tendency toward violence among XYY individuals than among XY males. A prejudice against XYY males still exists due to the original study, now known to be seriously flawed.
   - What type of controls are needed to ensure that new information concerning genetic abnormalities is not released before it is confirmed? Not every person with a specific genotype will develop the same characteristics to the same degree. How can possible stereotypes be avoided when information is released?

5. You are an airline employer trying to offer your employees the least expensive health insurance available. The insurance company requires a blood test on each new potential employee to determine genetic abnormalities. Somehow you learn that a potential candidate for a job as a pilot has a genetic predisposition for a heart attack. Would this information affect your decision to hire that individual?

**CANCER**

Twenty-five percent of all Americans develop cancer at some point in their lives. It has been estimated that 70–80 percent of these cases involve chemical exposure, environmental factors, or both, and almost 40 percent of these are due to a single stimulus: cigarette smoke. During 2002, an estimated 555,000 Americans will die of some form of cancer, making it second only to heart disease.

**Cancer Causes**

Relatively few cancers are actually inherited: 18 types have been identified to date, including two forms of leukemia. Most cancers develop through the interaction of genetic and environmental factors, and it is difficult to separate the two completely.

**Genetic Factors:** Two related genetic factors are involved in the development of cancer: hereditary predisposition and oncogene activation.

An individual born with genes that increase the likelihood of cancer is said to have a hereditary predisposition for the disease. Under these conditions a cancer is not guaranteed, but it is a lot more likely. The inherited genes usually affect tissue abilities to metabolize toxins, control mitosis and growth, perform repairs after injury, or identify and destroy abnormal tissue cells. As a result, body cells become more sensitive to local or environmental factors that would have little effect on normal tissues.

Cancers may also result from somatic mutations that modify genes involved with cell growth, differentiation, or mitosis. As a result, an ordinary cell is converted into a cancer cell. The modified genes are called oncogenes (ON-kó-jenz); the normal genes are called proto-oncogenes. Oncogene activation occurs by alteration of normal somatic genes. Because these mutations do not affect reproductive cells, the cancers caused by active oncogenes are not inherited.

A proto-oncogene, like other genes, has a regulatory component that turns the gene “on” and “off” and a structural component that contains the triplets that determine protein structure. Mutations in either portion of the gene may convert it to an active oncogene. A small mutation can accomplish this; changing 1 nucleotide out of a chain of 5000 can convert a normal proto-oncogene to an active oncogene. In some cases, a viral
infection can trigger activation of an oncogene. For example, one of the papilloma “wart” viruses appears to be responsible for many cases of cancer of the cervix.

More than 50 proto-oncogenes have been identified. In addition, a group of anticancer genes has been discovered. These genes, called tumor-suppressing genes (TSG), or anti-oncogenes, suppress division and growth in normal cells. Mutations that alter TSGs make oncogene activation more likely. TSG mutation has been suggested as important in promoting several cancers, including several blood cell cancers, breast cancer, and ovarian cancer. Examples of important suppressor genes include the genes p53 and p16. Mutations affecting the p53 gene are responsible for the majority of cancers of the colon, breast, and liver. Abnormal p16 gene activity may be involved in as many as half of all cancer cases.

Environmental Factors: Many cancers can be directly or indirectly attributed to environmental factors called carcinogens (kar-SIN-o-jenz). Carcinogens stimulate the conversion of a normal cell to a cancer cell. Some carcinogens are mutagens (MU-ta-jenz)—that is, they damage DNA strands and sometimes cause chromosomal breakage. Radiation is an example of a mutagen that has carcinogenic effects.

There are many different chemical carcinogens in the environment. Plants manufacture poisons that protect them from insects and other predators, and although their carcinogenic activities are often relatively weak, many common spices, vegetables, and beverages contain compounds that can be carcinogenic if consumed in large quantities. Animal tissues may also store or concentrate toxins, and hazardous compounds of many kinds can be swallowed in contaminated food. A variety of laboratory and industrial chemicals, such as coal tar derivatives and synthetic pesticides, have been shown to be carcinogenic. Cosmic radiation, X-rays, UV radiation, and other radiation sources can also cause cancer. It has been estimated that 70–80 percent of all cancers are the result of chemical and/or environmental factors, and almost half (40 percent) are due to a single stimulus: cigarette smoke.

Specific carcinogens will affect only those cells capable of responding to that particular physical or chemical stimulus. The responses vary because differentiation produces cell types with specific sensitivities. For example, benzene can produce a cancer of the blood, cigarette smoke a lung cancer, and vinyl chloride a liver cancer. Very few stimuli can produce cancers throughout the body; radiation exposure is a notable exception. In general, cells undergoing mitosis are most likely to be vulnerable to chemical or radiational carcinogens. As a result, the cancer rates are highest in epithelial tissues, where stem cell divisions occur rapidly and relatively low in nervous and muscle tissues, where divisions do not normally occur.

### Cancer Formation and Growth

Physicians who specialize in the identification and treatment of cancers are called oncologists (on-KOL-o-jists; onkos, “mass”). Pathologists and oncologists classify cancers according to their cellular appearance and their sites of origin. Over a hundred kinds have been described, but broad categories are usually used to indicate the location of the primary tumor. Table A-9 summarizes information concerning benign and malignant tumors (cancers) associated with the major tissues of the body.

Cancer develops in a series of steps diagrammed in Figure A-11. Initially the cancer cells are restricted to a single location, called the primary tumor or primary neoplasm. All the cells in the

<table>
<thead>
<tr>
<th>Table A-9: Benign and Malignant Tumors in the Major Tissue Types</th>
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<tbody>
<tr>
<td><strong>Tissue</strong></td>
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<tr>
<td><strong>Epithelia</strong></td>
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<td>Carcinoma</td>
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<tr>
<td>Adenocarcinoma</td>
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<tr>
<td>Angiosarcomas</td>
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<tr>
<td>Mesotheliomas</td>
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<td><strong>Connective tissues</strong></td>
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<td>Fibromas</td>
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<td>Lipomas</td>
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<td>Liposarcomas</td>
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<td>Leukemias</td>
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<td>Chondromas</td>
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<td>Chondrosarcomas</td>
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<td>Osteosarcomas</td>
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<tr>
<td><strong>Muscle tissues</strong></td>
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<td>Myxomas; myomas</td>
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<td>Cardiac sarcomas</td>
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<tr>
<td>Leiomyomas</td>
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<td>Leiomyosarcomas</td>
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<td><strong>Neural tissues</strong></td>
</tr>
<tr>
<td>Gliomas</td>
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<tr>
<td>Neuromas</td>
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</table>
tumor are usually the daughter cells of a single malignant cell. At first the growth of the primary tumor simply distorts the tissue, and the basic tissue organization remains intact. Metastasis begins as tumor cells “break out” of the primary tumor and invade the surrounding tissue. They may then enter the lymphatic system and accumulate in nearby lymph nodes. When this invasion is followed by penetration of nearby blood vessels, the cancer cells begin circulating throughout the body. The growth of blood vessels into the tumor is a vital step in the development and spread of the cancer. Without those vessels, the growth of the cancer cells will be limited by the availability of oxygen and nutrients. A chemical called \textit{antiangiogenesis factor} can prevent the growth of blood vessels and slow the growth of cancers. This chemical, a peptide, is produced in normal human cartilage and can be extracted in large quantities from sharks, whose skeletons are entirely cartilaginous.

Cancer cells within the circulatory system, responding to cues that are as yet unknown, ultimately migrate out of the blood vessels to establish \textit{secondary tumors} at other sites. These tumors are extremely active metabolically, and their presence stimulates the growth of blood vessels into the area. The increased circulatory supply provides additional nutrients and further accelerates tumor growth and metastasis. Death may occur as a result of compression of vital organs, because nonfunctional cancer cells have killed or replaced the normal cells in vital organs, or because the cancer cells have starved normal tissues of essential nutrients.

\textbf{Detection and Incidence of Cancer}

A statistical profile of cancer incidence and survival rates has been included as Table A-10. Interestingly, the picture changes when you look at data from other countries. For example, bladder cancer is common in Egypt, stomach cancer in Japan, and liver cancer in Africa. A combination of genetic, dietary, infectious, and environmental factors are thought to be responsible for these differences.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{ANATOMICAL SYSTEM} & \textbf{Estimated New cases (2002)} & \textbf{Estimated Deaths (2002)} & \textbf{Five-Year Survival Rates} & \\
\hline
\textbf{DIGESTIVE TRACT} & & & & \\
Esophagus & 13,100 & 12,600 & 5\% & 14\% \\
Stomach & 21,600 & 12,400 & 15\% & 22\% \\
Colon and rectum & 148,300 & 56,000 & 50\% & 61\% \\
\hline
\textbf{RESPIRATORY TRACT} & & & & \\
Lung and bronchus & 169,400 & 154,900 & 12\% & 15\% \\
\hline
\textbf{URINARY TRACT} & & & & \\
Kidney and Other Urinary Structures & 34,200 & 12,300 & 52\% & 62\% \\
Bladder & 56,500 & 12,000 & 73\% & 81\% \\
\hline
\textbf{REPRODUCTIVE SYSTEM} & & & & \\
Breast & 205,000 & 40,000 & 75\% & 86\% \\
Ovary & 23,300 & 13,900 & 37\% & 52\% \\
Testis & 7500 & 400 & 79\% & 95\% \\
Prostate gland & 189,000 & 30,200 & 67\% & 96\% \\
\hline
\textbf{NERVOUS SYSTEM} & & & & \\
SKIN (MELANOMA ONLY) & 17,000 & 13,100 & 22\% & 32\% \\
\hline
\end{tabular}
\caption{Cancer Incidence and Survival Rates in the United States}
\end{table}

Data courtesy of the American Cancer Society
Clinical Staging and Tumor Grading

Detection of a cancer often begins during a routine physical examination, when the physician detects an abnormal lump or growth. A tumor or neoplasm is defined as a “new growth” resulting from uncontrolled cell division. A tumor may be malignant or benign, metastasizing rapidly or spreading very slowly; only malignant tumors are called cancers.

Many laboratory and diagnostic tests are necessary for the correct diagnosis of cancer. Information is usually obtained through examination of a tissue sample, or biopsy, often supplemented by medical imaging and blood studies. A biopsy is one of the most significant diagnostic procedures because it permits a direct look at the tumor cells. Not only do malignant cells have an abnormally high mitotic rate, but they are structurally distinct from normal body cells.

If the tissue appears cancerous, other important questions must be answered, including:

- What is the measurable size of the primary tumor?
- Has the tumor invaded surrounding tissues?
- Has the cancer already metastasized to develop secondary tumors?
- Are any regional lymph nodes affected?

The answers to these questions are combined with observations from the physical exam, the biopsy results, and information from any imaging procedures to develop an accurate diagnosis (an identification of the disease) and prognosis (the probable outcome of the disorder).

In an attempt to develop a standard system, national and international cancer organizations have developed the TNM system for staging cancers. The letters refer to tumor (T) size and invasion, lymph node (N) involvement, and degree of metastasis (M).

- Tumor size is graded on a scale of 0 to 4, with the largest dimensions and greatest amount of invasion categorized as T4. (T0 indicates the absence of a primary tumor.)
- Lymph node involvement is graded on a scale of 0 to 3. A designation of N0 indicates that no lymph nodes have been invaded by cancer cells. A classification of N1–3 indicates the involvement of increasing numbers of lymph nodes.

A classification of N1 involves involvement of a single lymph node less than 3 cm in diameter. A classification of N2 includes one medium-sized node (3–6 cm) or multiple nodes, all smaller than 6 cm. A classification of N3 indicates the presence of a single lymph node larger than 6 cm in diameter, whether or not other nodes are involved.

This categorization is important because lymph nodes filter the tissue fluids from nearby capillary beds. The fluid, called lymph, then returns to the general circulation. Once cancer cells have entered the lymphatic system, they can spread very quickly throughout the body.

- Metastasis is graded using a scale of 0 to 1. M0 indicates that there is no evidence of metastasis, whereas M1 indicates that the cancer cells have produced secondary tumors in other portions of the body.

This grading system provides a general overview of the progression of the disease. For example, a tumor classified as T1N1M0 obviously has a better prognosis than T4N2M1. The latter tumor will be much more difficult to treat. The grading system alone does not provide all the information needed to plan a treatment, however, because different types of cancer progress in different ways, and the therapies must vary as a result. Thus leukemia, a cancer of the blood-forming tissues, will be treated differently than colon cancer. Specific treatments will be considered in discussions dealing with cancers affecting individual body systems. The next section provides a general overview of the strategies used to treat cancer.

Cancer Treatment

It is unfortunate that the media tend to describe cancer as though it were one disease rather than many. This simplistic perspective fosters the belief that some dietary change, air ionizer, or wonder drug will be found that can prevent the affliction. There is no single, universally effective cure for cancer; there are too many separate causes, possible mechanisms, and individual differences.

The goal of cancer treatment is to achieve remission. A tumor in remission either ceases to grow or decreases in size. Basically the treatment of malignant tumors must accomplish one of the following to produce remission:

1. **Surgical removal or destruction of individual tumors:** Tumors containing malignant cells can be surgically removed or destroyed by radiation, heat, or freezing. These techniques are very effective if the treatment is undertaken before metastasis has occurred. For this reason early detection is important in improving survival rates for all forms of cancer.

2. **Killing metastatic cells throughout the body:** This is much more difficult and potentially dangerous, because healthy tissues are likely to be damaged at the same time. At present the most widely approved treatments are chemotherapy and radiation.

Traditional chemotherapy involves the administration of drugs that will either kill the cancerous tissues or prevent mitotic divisions. These drugs often affect stem cells in normal tissues, and the side
effects are usually unpleasant. For example, because chemotherapy slows the regeneration and maintenance of epithelia of the skin and digestive tract, patients lose their hair and experience nausea and vomiting. Several different drugs are often administered simultaneously, or in sequence, because over time cancer cells can develop a resistance to a single drug. Chemotherapy is often used in the treatment of many kinds of metastatic cancer.

Massive doses of radiation are sometimes used to treat advanced cases of lymphoma, a cancer of the immune system. In this rather drastic procedure enough radiation is administered to kill all the blood-forming cells in the body. After treatment, new blood cells must be provided by a bone marrow transplant. Later sections dealing with the lymphatic system contain additional information about marrow transplants, lymphomas, and other cancers of the blood.

An understanding of molecular mechanisms and cell biology is leading to new approaches that may revolutionize cancer treatment. One approach focuses attention on the fact that cancer cells are ignored by the immune system. In immunotherapy, chemicals are administered that help the immune system recognize and attack the cancer cells. More elaborate experimental procedures involve the creation of customized antibodies using the gene-splicing techniques discussed on p. 31. The resulting antibodies are specifically designed to attack the tumor cells in one patient; although this technique shows promise, it remains difficult, costly, and very labor intensive.

A second approach is targeted "designer" cancer drugs. One type of cancer, chronic myelogenous leukemia, involves the activity of an abnormal enzyme. Using the techniques of molecular biology, a molecule was designed and produced that specifically blocks the abnormal enzyme. In early trials of this drug (Gleevac), complete responses occurred in 53 of 54 patients.

A third approach is based on the observation that cartilage cells lack blood vessels (an avascular condition) and can survive cancer. In other tissues, when cells are crowded and active, blood vessels grow into the area and improve oxygen and nutrient delivery. Cartilage secretes a chemical (a peptide) that blocks the growth of blood vessels. This compound has been named antiangiogenesis factor (anti- against + angeion, vessel + gennan, to produce).

One reason cancers can grow so explosively is that blood vessels branch into the developing tumor, delivering supplies to the renegade cells. This growth could theoretically be prevented by antiangiogenesis factor, but the quantities produced in normal human cartilage are extremely small. Sharks have cartilaginous skeletons and are one source of antiangiogenesis factors, but production by techniques based on molecular biology is a more reliable source. Some mice with cancerous tumors have been cured through the use antiangiogenesis factor, but human trials are preliminary and have not been as successful.

**Cancer and Survival**

Advances in chemotherapy, radiation procedures, and molecular biology have produced significant improvements in the survival rates for several types of cancer. However, the improved survival rates indicated in Table A-10 not only reflect advances in therapy but in early detection. Much of the credit goes to increased public awareness and concern about cancer. In general, the odds of survival increase markedly if the cancer is detected early, especially before it undergoes metastasis. Despite the variety of possible cancers, the American Cancer Society has identified seven "warning signs" that mean it's time to consult a physician. These are presented in Table A-11.

### Table A-11  Seven Warning Signs of Cancer

| C | Change in bowel or bladder habits |
| A | A sore that does not heal         |
| U | Unusual bleeding or discharge    |
| T | Thickening or lump in breast or elsewhere |
| I | Indigestion or difficulty in swallowing |
| O | Obvious change in wart or mole   |
| N | Nagging cough or hoarseness      |