8

Environmental and Nutritional Diseases

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Many diseases are caused or influenced by environmental factors. Broadly defined, the term ambient environment encompasses the various outdoor, indoor, and occupational settings in which humans live and work. In each of these settings, the air people breathe, the food and water they consume, and the toxic agents they are exposed to are major determinants of health. Other environmental factors pertain to the individual ("personal environment") and include tobacco use, alcohol ingestion, therapeutic and "recreational" drug consumption, diet, and the like. It is generally believed that factors in the personal environment have a larger effect on human health than that of the ambient environment, but new threats related to global warming (described later) may change this equation.

The term environmental disease refers to disorders caused by exposure to chemical or physical agents in the ambient, workplace, and personal environments, including diseases of nutritional origin. Environmental diseases are surprisingly common. The International Labor Organization has estimated that work-related injuries and illnesses kill more people per year globally than do road accidents and wars combined. Most of these work-related problems are caused by illnesses rather than accidents. The burden of disease in the general population created by nonoccupational exposures to toxic agents is much more difficult to estimate, mostly because of the diversity of agents and the difficulties in measuring the dose and duration of exposures. Whatever the precise numbers, environmental diseases are major causes of disability and suffering and constitute a heavy financial burden, particularly in developing countries.

Environmental diseases are sometimes the consequence of major disasters, such as the methyl mercury contamination of Minamata Bay in Japan in the 1960s, the leakage of methyl isocyanate gas in Bhopal, India, in 1984, the Chernobyl nuclear accident in 1986, the Fukushima nuclear meltdown following the tsunami in 2011, and lead poisoning resulting from contaminated drinking water in the city of Flint in the United States in 2016. Fortunately, these are unusual and infrequent occurrences. Less dramatic, but much more common, are diseases and injury produced by chronic exposure to relatively low levels of contaminants.

It should be noted that a host of factors, including complex interactions between pollutants producing multiplicative effects, as well as the age, genetic predisposition, and different tissue sensitivities of exposed persons, create wide variations in individual sensitivity. Disease related to malnutrition is even more pervasive. In 2010, it was estimated that 925 million people were malnourished—one in every seven persons worldwide. Children are disproportionately affected by undernutrition, which accounts for more than 50% of childhood mortality worldwide.

In this chapter, we first consider the emerging problem of the health effects of climate change. We then discuss the mechanisms of toxicity of chemical and physical agents, and address specific environmental disorders, including those of nutritional origin.

HEALTH EFFECTS OF CLIMATE CHANGE

Global temperature measurements show that the earth has warmed significantly since the early 20th century, and especially since the mid-1960s. Record-breaking global temperatures have become common, with 2005, 2010, and 2014,
and 2015 each setting successive high-temperature records. Of note, 15 of the 16 warmest years since 1880 have occurred during the 21st century. During 2015, the global land temperature was 0.9° C warmer than the 20th century average. Mean global ocean temperatures also set new records in 2015, with an annual average temperature 0.74° C above the 20th century average. As of this writing, 2016 is on track to approach or exceed the records just set in 2015.

The rising atmospheric and ocean temperatures have led to a large number of effects that include changes in storm frequency, drought, and flood, as well as large-scale ice losses in Greenland, Antarctica, and the vast majority of the other glaciated regions on earth, as well as dramatic thinning or disappearance of Arctic ocean sea ice. The melting of land-based glacial ice and the thermal expansion of the warming oceans has produced approximately 80 mm of global average sea level rise since 1993, and the sea level currently is rising at a global average rate of 3.5 ± 0.4 mm/year.

Although politicians quibble, among scientists there is a general acceptance that climate change is, at least in part, man-made. The culprit is the rising atmospheric level of greenhouse gases, particularly carbon dioxide (CO₂) released through the burning of fossil fuels (Fig. 8.1A), as well as ozone (an important air pollutant, discussed later), and methane. These gases, along with water vapor, produce the so-called “greenhouse effect” by absorbing energy radiated from Earth’s surface that otherwise would be lost into space. The annual average level of atmospheric CO₂ (about 401 ppm) in 2015 was higher than at any point in approximately 650,000 years and, without changes in human behavior, is expected to increase to 500 to 1200 ppm by the end of this century—levels not experienced for tens of millions of years. This increase stems not only from increased CO₂ production but also from deforestation and the attendant decrease in carbon fixation by plants. Depending on the computer model used, increased levels of greenhouse gases are projected to cause the global temperature to rise by 2°C to 5°C by the year 2100 (Fig. 8.1B). The health consequences of climate change will depend on its extent and rapidity, the severity of the ensuing consequences, and humankind’s ability to mitigate the damaging effects. Even in the best-case scenario, however, climate change is expected to have a serious negative impact on human health by increasing the incidence of a number of diseases, including the following:

- Cardiovascular, cerebrovascular, and respiratory diseases, all of which will be exacerbated by heat waves and air pollution.
- Gastroenteritis, cholera, and other food- and waterborne infectious diseases, caused by contamination as a consequence of floods and disruption of clean water supplies and sewage treatment, after heavy rains and other environmental disasters.
- Vector-borne infectious diseases, such as malaria and dengue fever, resulting from changes in vector number and geographic distribution related to increased temperatures, crop failures, and more extreme weather variation (e.g., more frequent and severe El Niño events).
- Malnutrition, caused by changes in local climate that disrupt crop production. Such changes are anticipated to be most severe in tropical locations, in which average temperatures may already be near or above crop tolerance levels; it is estimated that by 2080, agricultural productivity may decline by 10% to 25% in some developing countries as a consequence of climate change.

Beyond these disease-specific effects, it is estimated that the melting of glacial ice, particularly in Greenland and other parts of the Northern Hemisphere, combined with the thermal expansion of warming oceans, will raise sea levels by 2 to 6 feet by 2100. Approximately 10% of the world’s population—roughly 600 million people—live in low-lying areas that are at risk for flooding even if the rise in ocean levels is at the low end of these estimates. For example, a rise in sea level by 1.5 feet will submerge 70% of the land mass of Maldive islands by 2100 and a 3-foot rise will inundate 100% all of the islands by 2085. The resulting displacement of people will disrupt lives and commerce, creating conditions ripe for political
unrest, war, and poverty, the “vectors” of malnutrition, sickness, and death. Worldwide recognition of the catastrophic effects of climate change led in late 2015 to a historic meeting of 196 countries in Paris, France, at which the participating countries agreed to the following objective:

*Holding the increase in the global average temperature to well below 2°C above preindustrial levels and to pursue efforts to limit the temperature increase to 1.5°C above preindustrial levels, recognizing that this would significantly reduce the risks and impacts of climate change.*

**TOXICITY OF CHEMICAL AND PHYSICAL AGENTS**

Toxicology is defined as the science of poisons. It studies the distribution, effects, and mechanisms of action of toxic agents. More broadly, it also includes the study of the effects of physical agents such as radiation and heat. Approximately 4 billion pounds of toxic chemicals, including 72 million pounds of known carcinogens, are produced each year in the United States. In general, however, little is known about the potential health effects of chemicals. Of the approximately 100,000 chemicals in use in the United States, less than 1% have been tested experimentally for health effects.

We now consider some basic principles regarding the toxicity of exogenous chemicals and drugs.

- The definition of a poison is not straightforward. It is a quantitative concept strictly dependent on dosage. The quote from Paracelsus in the 16th century that “all substances are poisons; the right dosage differentiates a poison from a remedy” is perhaps even more valid today, in view of the proliferation of therapeutic drugs with potentially harmful effects.
- Xenobiotics are exogenous chemicals in the environment that may be absorbed by the body through inhalation, ingestion, or skin contact (Fig. 8.2).
- Chemicals may be excreted in urine or feces or eliminated in expired air, or they may accumulate in bone, fat, brain, or other tissues.
- Chemicals may act at the site of entry, or they may be transported to other sites. Some agents are not modified on entry in the body, but most solvents and drugs are metabolized to form water-soluble products (detoxification) or are activated to form toxic metabolites.
- Most solvents and drugs are lipophilic, which facilitates their transport in the blood by lipoproteins and penetration through lipid components of cell membranes.
- The reactions that metabolize xenobiotics into nontoxic products, or activate xenobiotics to generate toxic compounds (Fig. 8.3; see also Fig. 8.2), occur in two phases. In phase I reactions, chemicals can undergo hydrolysis, oxidation, or reduction. Products of phase I reactions often are metabolized into water-soluble compounds through phase II reactions of glucuronidation, sulfation, methylation, and conjugation with glutathione (GSH). Water-soluble compounds are readily excreted.
- The most important cellular enzyme system involved in phase I reactions is the cytochrome P-450 system. The P-450 system is present in organs throughout the body, but it is most active in the endoplasmic reticulum (ER) of the liver. The system catalyzes reactions that may either detoxify xenobiotics or convert xenobiotics into active compounds that cause cellular injury. Both types of reactions may produce, as a byproduct, reactive oxygen species (ROS), which can cause cellular damage (discussed in Chapter 2). Examples of metabolic activation of chemicals through the P-450 system are the conversion of carbon tetrachloride to the toxic trichloromethyl free radical, and the generation of a DNA-binding
Effects on cellular molecules (enzymes, receptors, membranes, DNA)

Toxicity (short- and long-term effects)

Fig. 8.3 Xenobiotic metabolism. Xenobiotics can be metabolized to nontoxic metabolites and eliminated from the body (detoxification). However, their metabolism also may result in formation of a reactive metabolite that is toxic to cellular components. If repair is not effective, short- and long-term effects develop. (Modified from Hodgson E: A textbook of modern toxicology, ed 3, Fig. 1–1. Hoboken, NJ, 2004, John Wiley & Sons.)

metabolite from benzo[a]pyrene, a carcinogen present in cigarette smoke. The cytochrome P-450 system also participates in the metabolism of a large number of common therapeutic drugs such as acetaminophen, barbiturates, and anti-convulsants, and in alcohol metabolism (discussed later).

- P-450 enzymes vary widely in activity among different people, owing to both polymorphisms in the genes encoding the enzymes and interactions with drugs that are metabolized through the system. The activity of the enzymes also may be decreased by fasting or starvation, and increased by alcohol consumption and smoking.

**ENVIRONMENTAL POLLUTION**

**Air Pollution**

Air pollution is a significant cause of morbidity and mortality worldwide, particularly among at-risk individuals with preexisting pulmonary or cardiac disease. The life-giving air that we breathe is also often laden with many potential causes of disease. Airborne microorganisms have long been major causes of morbidity and death. More widespread are the chemical and particulate pollutants found in the air, both in so-called “developed” and “under-developed” countries. Specific hazards have been recognized for both outdoor and indoor air.

**Outdoor Air Pollution**

The ambient air in industrialized nations is contaminated with an unsavory mixture of gaseous and particulate pollutants, more so in cities and in proximity to heavy industry. In the United States, the Environmental Protection Agency (EPA) monitors and sets allowable upper limits for six pollutants: sulfur dioxide, CO, ozone, nitrogen dioxide, lead, and particulate matter. Together, some of these agents produce the well-known smog that sometimes stifes major cities such as Cairo, Los Angeles, Houston, Mexico City, and São Paulo. It may seem that air pollution is a modern phenomenon. This is not the case; Seneca wrote in AD 61 that he felt an alteration of his disposition as soon as he left the “pestilential vapors, soot, and heavy air of Rome.” The first environmental-control law was proclaimed by Edward I in 1306 and was straightforward in its simplicity: “Whoever should be found guilty of burning coal shall suffer the loss of his head.” What has changed in modern times is the nature and sources of air pollutants, and the types of regulations that control their emission. It could be argued that modern man has lost his head to drown himself in pollution!

The lungs bear the brunt of the adverse consequences of air pollution, but air pollutants affect many organ systems (as with the effects of lead poisoning and CO, discussed later). More detailed discussion of pollutant-caused lung diseases is found in Chapter 13. Here we consider the major health effects of ozone, sulfur dioxide, particulates, and CO (Table 8.1).

**Table 8.1 Health Effects of Outdoor Air Pollutants**

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Populations at Risk</th>
<th>Effect(s)</th>
</tr>
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<tbody>
<tr>
<td>Ozone</td>
<td>Healthy adults and children</td>
<td>Decreased lung function Increased airway reactivity Lung inflammation Decreased exercise capacity</td>
</tr>
<tr>
<td></td>
<td>Athletes, outdoor workers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthmatics</td>
<td>Increased hospitalizations</td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
<td>Healthy adults Asthmatics Children</td>
<td>Increased airway reactivity Decreased lung function Increased respiratory infections</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>Healthy adults Asthmatics</td>
<td>Increased respiratory symptoms Increased mortality</td>
</tr>
<tr>
<td></td>
<td>Patients with chronic lung disease Asthmatics</td>
<td>Increased hospitalization Decreased lung function</td>
</tr>
<tr>
<td>Acid aerosols</td>
<td>Healthy adults Asthmatics</td>
<td>Altered mucociliary clearance Increased respiratory infections Decreased lung function Increased hospitalizations</td>
</tr>
<tr>
<td>Particulates</td>
<td>Children Asthmatics</td>
<td>Increased respiratory infections Decreased lung function Excess mortality</td>
</tr>
<tr>
<td></td>
<td>Patients with chronic lung or heart disease Asthmatics</td>
<td>Increased attacks</td>
</tr>
</tbody>
</table>

Ozone is one of the most pervasive air pollutants, with levels in many cities exceeding EPA standards. It is a gas formed by sunlight-driven reactions involving nitrogen oxides, which are released mostly by automobile exhaust. Together with oxides and fine particulate matter, ozone forms the familiar smog (from the words smoke and fog). Its toxicity stems from its participation in chemical reactions that generate free radicals, which injure the lining cells of the respiratory tract and the alveoli. Low levels of ozone may be tolerated by healthy persons but are detrimental to lung function, especially in those with asthma or emphysema, and when present along with particulate pollution. Unfortunately, pollutants rarely occur singly but combine to create a veritable “witches’ brew.”

Sulfur dioxide, particles, and acid aerosols are emitted by coal- and oil-fired power plants and industrial processes burning these fuels. Of these, particles appear to be the main cause of morbidity and death. Particles less than 10 µm in diameter are particularly harmful, because when inhaled they are carried by the airstream all the way to the alveoli. Here, they are phagocytosed by macrophages and neutrophils, causing the release of mediators (possibly by activating inflamasomes, Chapter 2) and inciting an inflammatory reaction. By contrast, larger particles are removed in the nose or are trapped by the mucociliary “escalator” and as a result are less dangerous.

Carbon monoxide (CO) is a nonirritating, colorless, tasteless, odorless gas. It is produced by the incomplete oxidation of carbonaceous materials. Its sources include automotive engines, industries using fossil fuels, home oil burners, and cigarette smoke. The low levels often found in ambient air may contribute to impaired respiratory function but usually are not life threatening. However, persons working in confined environments with high exposure to fumes, such as tunnel and underground garage workers, may develop chronic poisoning. CO is included here as an air pollutant, but it also is an important cause of accidental and suicidal death. In a small, closed garage, exhaust from a running car engine can induce a lethal coma within 5 minutes. CO is a systemic asphyxiant that kills by binding to hemoglobin and preventing oxygen transport. Hemoglobin has a 200-fold greater affinity for CO than for O₂. The carboxyhemoglobin, that is formed by binding of CO is incapable of carrying oxygen. Hypoxia leads to central nervous system (CNS) depression, which develops so insidiously that victims often are unaware of their plight and are unable to help themselves. Systemic hypoxia appears when the hemoglobin is 20% to 30% saturated with CO, and unconsciousness and death are probable with 60% to 70% saturation. The diagnosis of CO poisoning is based on detection of high levels of carboxyhemoglobin in the blood.

**SUMMARY**

**ENVIRONMENTAL DISEASES AND ENVIRONMENTAL POLLUTION**

- Environmental diseases are conditions caused by exposure to chemical or physical agents in the ambient, workplace, and personal environments.
- Exogenous chemicals, known as xenobiotics, enter the body through inhalation, ingestion, and skin contact, and can either be eliminated or accumulate in fat, bone, brain, and other tissues.
- Xenobiotics can be converted into nontoxic products or toxic compounds through a two-phase reaction process that involves the cytochrome P-450 system.
• The most common air pollutants are ozone (which in combination with oxides and particulate matter forms smog), sulfur dioxide, acid aerosols, and particles less than 10 µm in diameter.
• CO is an air pollutant and an important cause of death from accidents and suicide; it binds hemoglobin with high affinity, leading to systemic asphyxiation resulting in CNS depression.

Metals as Environmental Pollutants

Lead, mercury, arsenic, and cadmium, the heavy metals most commonly associated with harmful effects in human populations, are considered here.

Lead

Lead is a readily absorbed metal that binds to sulfhydryl groups in proteins and interferes with calcium metabolism, leading to hematologic, skeletal, neurologic, GI, and renal toxicities. Lead exposure occurs through contaminated air, food, and water. For most of the 20th century the major sources of lead in the environment were house paints and gasoline. Although the use of lead-based paints and leaded gas has greatly diminished, many sources of lead persist in the environment, such as mines, foundries, batteries, and spray paints, all of which constitute occupational hazards. However, flaking lead paint in older houses and soil contamination pose the major hazards for youngsters. Blood levels of lead in children living in older homes containing lead-based paint or lead-contaminated dust often exceed 5 µg/dL, the level at which the Centers for Disease Control and Prevention (CDC) recommends that measures be taken to limit further exposure. A dramatic case of lead contamination of drinking water occurred in the U.S. city of Flint, Michigan, in 2014–2016. The so-called “Flint water crisis” occurred when the source of water supply to the city was changed from Lake Huron to the Flint River. Because water from the Flint River had a higher chloride concentration than the lake waters, it leached lead from century-old lead pipes. This caused an increase in lead levels in tap water above the acceptable limit of 15 parts per billion (ppb), as a result 6000 to 12,000 residents developed lead poisoning in about 25% of the homes and in some cases as high as 13,200 ppb. As a result 6000 to 12,000 residents developed very high lead levels in their blood. Ingested lead is particularly harmful to children because they absorb more than 50% of lead from food, whereas adults absorb approximately 15%. A more permeable blood–brain barrier in children creates a high susceptibility to brain damage. The clinical features of lead poisoning are shown in Fig. 8.4.

Most absorbed lead (80% to 85%) is taken up into developing teeth and into bone, where it competes with calcium, binds phosphates, and has a half-life of 20 to 30 years. About 5% to 10% of the absorbed lead remains in the blood, and the remainder is distributed throughout soft tissues. Excess lead is toxic to nervous tissues in adults and children; peripheral neuropathies predominate in adults, whereas central effects are more common in children. The effects of chronic lead exposure in children may be subtle, producing mild dysfunction, or they may be massive and lethal. In young children, sensory, motor, intellectual, and psychologic impairments have been described, including reduced IQ, learning disabilities, retarded psychomotor development, and, in more severe cases, blindness, psychoses, seizures, and coma. Lead-induced peripheral neuropathies in adults generally remit with the elimination of exposure, but both peripheral and CNS abnormalities in children usually are irreversible. Other effects of lead exposure include the following.

Excess lead interferes with the normal remodeling of calcified cartilage and primary bone trabeculae in the epiphyses in children, causing increased bone density detected as radiodense “lead lines” (Fig. 8.5). Lead lines of a different sort also may occur in the gums, where excess lead stimulates hyperpigmentation. Lead inhibits the healing of fractures by increasing chondrogenesis and delaying cartilage mineralization. Excretion of lead occurs by way of the kidneys, and acute exposures may cause damage to proximal tubules.

Lead has a high affinity for sulphydryl groups and interferes with two enzymes involved in heme synthesis:
Lead also inhibits sodium- and potassium-dependent ATPases in cell membranes, an effect that may increase the fragility of red cells, causing hemolysis. The diagnosis of lead poisoning requires constant vigilance. It may be suspected on the basis of neurologic changes in children or unexplained anemia with basophilic stippling in red cells in adults and children. Elevated blood lead and red cell free protoporphyrin levels (greater than 50 µg/dL) or, alternatively, zinc-protoporphyrin levels, are required for definitive diagnosis. In milder cases of lead exposure, anemia may be the only obvious abnormality.

Mercury

Mercury, like lead, binds to sulfhydryl groups in certain proteins with high affinity, leading to damage in the CNS and several other organs such as the GI tract and the kidneys. Humans have used mercury in many ways throughout history, including as a pigment in cave paintings, a cosmetic, a remedy for syphilis, and a component of diuretics. Poisoning from inhalation of mercury vapors has long been recognized and is associated with tremor, gingivitis, and bizarre behavior, such as that of the “Mad Hatter” in Lewis Carroll’s Alice in Wonderland (mercury formerly was used in hat-making).

Today, the main sources of exposure to mercury are contaminated fish and dental amalgams, which release mercury vapors. In some areas of the world, mercury used in gold mining has contaminated rivers and streams. Inorganic mercury from the natural degassing of the earth’s crust or from industrial contamination is converted to organic compounds such as methyl mercury by bacteria. Methyl mercury enters the food chain, and in carnivorous fish such as swordfish, shark, and bluefish, mercury levels may be 1 million times higher than in the surrounding water. Almost 90% of the ingested mercury is absorbed in the GI tract. The consumption of contaminated fish from the release of methyl mercury in Minamata Bay and the Agano River in Japan, and the consumption of bread containing grain treated with contaminated fish and dental amalgams, which release mercury vapors. In some areas of the world, mercury used in gold mining has contaminated rivers and streams. 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and Medici families in Renaissance Italy. Today, arsenic exposure is an important health problem in many areas of the world. Arsenic is found naturally in soil and water and is used in wood preservatives, herbicides, and other agricultural products. It may be released into the environment by the mining and smelting industries. Arsenic is present in Chinese and Indian herbal medicine, and arsenic trioxide is a frontline treatment for acute promyelocytic leukemia (Chapter 6). Large concentrations of inorganic arsenic are present in ground water in countries such as Bangladesh, Chile, and China. Between 35 and 77 million people in Bangladesh drink water contaminated with arsenic, constituting one of the greatest environmental cancer risks yet uncovered.

If ingested in large quantities, arsenic causes acute toxicity manifesting as severe abdominal pain, diarrhea; cardiac arrhythmias, shock and respiratory distress syndrome; and acute encephalopathy. GI, cardiovascular and CNS toxicity may be severe enough to cause death. These effects may be attributed to the interference with mitochondrial oxidative phosphorylation. Chronic exposure to arsenic causes hyperpigmentation and hyperkeratosis of the skin, which may be followed by the development of basal and squamous cell carcinomas (but not melanomas). A symmetrical sensorimotor polyneuropathy can also develop. Arsenic-induced skin tumors differ from those induced by sunlight by appearing on palms and soles, and by occurring as multiple lesions. Arsenic exposure also is associated with an increased risk of lung carcinoma. The mechanisms of arsenic carcinogenesis in the skin and the lung are uncertain.

**Cadmium**

Cadmium is preferentially toxic to the kidneys and the lungs through uncertain mechanisms that may involve increased production of ROS. In contrast with the metals already discussed, cadmium is a relatively modern toxic agent. It is used mainly in nickel-cadmium batteries, which generally are disposed of as household waste. Cadmium can contaminate soil and plants directly or through fertilizers and irrigation water. Food is the most important source of exposure for the general population. Excessive cadmium intake can lead to obstructive lung disease and renal toxicity, initially as tubular damage that may progress to end-stage renal disease. Cadmium exposure can also cause skeletal abnormalities associated with calcium loss. Cadmium-contaminated water used to irrigate rice fields in Japan caused a disease in postmenopausal women known as “itai-itai” (ouch-ouch), a combination of osteoporosis and osteomalacia associated with renal disease. A survey showed that 5% of persons aged 20 years and older in the U.S. population have urinary cadmium levels that, according to research data, may produce subtle kidney injury and increased calcium loss.

**SUMMARY**

**TOXIC EFFECTS OF HEAVY METALS**

- Lead, mercury, arsenic, and cadmium are the heavy metals most commonly associated with toxic effects in humans.
- Children absorb more ingested lead than adults; the main source of exposure for children is lead-containing paint.
- Excess lead causes CNS defects in children and peripheral neuropathy in adults. Excess lead competes with calcium in bones and interferes with the remodeling of cartilage; it also causes anemia.
- The major source of mercury is contaminated fish. The developing brain is highly sensitive to methyl mercury, which accumulates in the brain and blocks ion channels.
- Exposure of the fetus to high levels of mercury in utero may lead to Minamata disease, characterized by cerebral palsy, deafness, and blindness.
- Arsenic is naturally found in soil and water and is a component of some wood preservatives and herbicides. Excess arsenic interferes with mitochondrial oxidative phosphorylation and causes toxic effects in the GI tract, CNS, and cardiovascular system; long-term exposure causes polyneuropathy, skin lesions and carcinomas.
- Cadmium from nickel-cadmium batteries and chemical fertilizers can contaminate soil. Excess cadmium causes obstructive lung disease and kidney damage.

**Industrial and Agricultural Exposures**

More than 10 million occupational injuries occur annually in the United States, and approximately 65,000 people die as a consequence of occupational injuries and illnesses. Industrial exposures to toxic agents are as varied as the industries themselves. They range from merely annoying irritations of respiratory airways by formaldehyde or ammonia fumes, to lung cancers arising from exposure to asbestos, arsenic, or uranium. Human diseases associated with occupational exposures are listed in Table 8.2. In addition to toxic metals (already discussed), other important agents that contribute to environmental diseases include the following:

- **Organic solvents** are widely used in huge quantities worldwide. Some, such as chloroform and carbon tetrachloride, are found in degreasing and dry cleaning agents and paint removers. Acute exposure to high levels of vapors from these agents can cause dizziness and confusion, leading to CNS depression and even coma. Lower levels may cause liver and kidney toxicity. Occupational exposure of rubber workers to benzene and 1,3-butadiene increases the risk of leukemia. Benzene is oxidized to an epoxide through hepatic CYP2E1, a component of the P-450 enzyme system already mentioned. The epoxide and other metabolites disrupt progenitor cell differentiation in the bone marrow, and may lead to marrow aplasia and acute myeloid leukemia.
- **Polycyclic hydrocarbons** are released during the combustion of coal and gas, particularly at the high temperatures used in steel foundries, and also are present in tar and soot. (Pott identified soot as the cause of scrotal cancers in chimney sweeps in 1775, as mentioned in Chapter 6). Polycyclic hydrocarbons are among the most potent carcinogens, and industrial exposures have been implicated in the causation of lung and bladder cancer.
- **Organochlorines** (and halogenated organic compounds in general) are synthetic products that resist degradation and are lipophilic. Important organochlorines used...
as pesticides are DDT (dichlorodiphenyltrichloroethane) and its metabolites, and agents such as lindane, aldrin, and dieldrin. Nonpesticide organochlorines include polychlorinated biphenyls (PCBs) and dioxin (TCDD [2,3,7,8-tetrachlorodibenzo-p-dioxin]). DDT was banned in the United States in 1973, but more than half of the population have detectable serum levels of p,p'-DDE, a long-lasting DDT metabolite, including those born after the ban on DDT went into effect. PCB and TCDD also are present in the blood of most of the U.S. population. Acute DDT poisoning in humans causes neurologic toxicity. Most organochlorines are endocrine disruptors and have anti-estrogenic or anti-androgenic activity in laboratory animals, but long-term health effects in humans have not been firmly established.

- **Nonpesticide organochlorines** include polychlorinated biphenyls (PCBs) and dioxin (TCDD [2,3,7,8-tetrachlorodibenzo-p-dioxin]). Dioxins and PCBs can cause skin disorders such as folliculitis and acneiform dermatosis known as chloracne, which consists of acne, cyst formation, hyperpigmentation, and hyperkeratosis, generally around the face and behind the ears. It can be accompanied by abnormalities in the liver and CNS. Because PCBs induce the P-450 enzyme system, workers exposed to these substances may show altered drug metabolism. Environmental disasters in Japan and China in the late 1960s caused by the consumption of rice oil contaminated by PCBs poisoned about 2000 people in each episode. The primary manifestations of the disease (yusho in Japan, yu-cheng in China) were chloracne and hyperpigmentation of the skin and nails.

- **Bisphenol A (BPA)** is used in the synthesis of polycarbonate food and water containers and of epoxy resins that line almost all food bottles and cans; as a result, exposure to BPA is virtually ubiquitous in humans. BPA has long been known as a potential endocrine disruptor. Several large retrospective studies have linked elevated urinary BPA levels to heart disease in adult populations. In addition, infants who drink from BPA-containing containers may be particularly susceptible to BPA’s endocrine effects. In 2010, Canada was the first country to list BPA as a toxic substance, and the largest makers of baby bottles and “sippy” cups have stopped using BPA in the manufacturing process. The extent of the human health risks associated with BPA remains uncertain, however, and requires further study.

  - **Vinyl chloride**, used in the synthesis of polyvinyl resins, can cause angiosarcoma of the liver, a rare type of liver tumor.

  - **Inhalation of mineral dusts** causes chronic, nonneoplastic lung diseases called pneumoconioses. This group of disorders includes diseases induced by organic and inorganic particulates as well as chemical fume- and vapor-induced nonneoplastic lung diseases. The most common pneumoconioses are caused by exposures to coal dust (in mining of hard coal), silica (in sandblasting and stone cutting), asbestos (in mining, fabrication, and insulation work), and beryllium (in mining and fabrication). Exposure to these agents nearly always occurs in the workplace. The increased risk of cancer as a result of asbestos exposure, however, extends to family members of asbestos workers and to other persons exposed outside the workplace. Pneumoconioses and their pathogenesis are discussed in Chapter 13.

### EFFECTS OF TOBACCO

Tobacco is the most common exogenous cause of human cancers, being responsible for 90% of lung cancers. The
main culprit is cigarette smoking, but smokeless tobacco in its various forms (snuff, chewing tobacco) also is harmful to health and is an important cause of oral cancer. Not only does the use of tobacco products create personal risk, but also passive tobacco inhalation from the environment (“second-hand smoke”) can cause lung cancer in non-smokers. From 1998 to 2007 in the United States, the incidence of smoking declined modestly, but this trend failed to continue, and approximately 20% of adults remain smokers. In recent years, China has become the world’s largest producer and consumer of cigarettes. China has approximately 350 million smokers who in aggregate consume about 33% of all cigarettes smoked worldwide. Cigarette smoking causes, worldwide, more than 4 million deaths annually, mostly from cardiovascular disease, various types of cancers, and chronic respiratory problems. It is expected that there will be 8 million tobacco-related deaths yearly by 2020, the major increase occurring in developing countries. Of people alive today, an estimated 500 million will die from tobacco-related illnesses. In the United States alone, tobacco is responsible for more than 400,000 deaths per year, with one-third of these attributable to lung cancer.

Smoking is the most important cause of preventable human death. It reduces overall survival in a dose-dependent fashion. Whereas 80% of nonsmokers are alive at age 70, only about 50% of smokers survive to this age (Fig. 8.6). Cessation of smoking greatly reduces the risk of death from lung cancer, and it even has an effect, albeit reduced, on people who stop smoking at age 60. Discussed next are some of the agents contained in tobacco and diseases associated with tobacco consumption. Adverse effects of smoking in various organ systems are shown in Fig. 8.7.

The number of potentially noxious chemicals in tobacco smoke is vast; Table 8.3 presents only a partial list and includes the type of injury produced by these agents. Nicotine, an alkaloid present in tobacco leaves, is not a direct cause of tobacco-related diseases, but it is highly addictive. Nicotine binds to receptors in the brain and, through the

### Table 8.3 Effects of Selected Tobacco Smoke Constituents

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tar</td>
<td>Carcinogenesis</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>Carcinogenesis</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Ganglionic stimulation and depression, tumor promotion</td>
</tr>
<tr>
<td>Phenol</td>
<td>Tumor promotion; mucosal irritation</td>
</tr>
<tr>
<td>Benzopyrene</td>
<td>Carcinogenesis</td>
</tr>
<tr>
<td>CO</td>
<td>Impaired oxygen transport and use</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Toxicity to cilia; mucosal irritation</td>
</tr>
<tr>
<td>Oxides of nitrogen</td>
<td>Toxicity to cilia; mucosal irritation</td>
</tr>
<tr>
<td>Nitrosamine</td>
<td>Carcinogenesis</td>
</tr>
</tbody>
</table>
Effects of Tobacco

contributes to the development of cancers of the oral cavity, esophagus, pancreas, and bladder. Table 8.4 lists organ-specific carcinogens contained in tobacco smoke. Moreover, smoking multiplies the risk of disease associated with other carcinogens; well-recognized examples are the 10-fold increased incidence of lung carcinomas in asbestos workers and uranium miners who smoke than in those who do not. The combination of tobacco (chewed or smoked) and alcohol consumption has multiplicative effects on the risks of oral, laryngeal, and esophageal cancers. An example of the carcinogenic interaction of these all-too-common vices is shown for laryngeal cancer (Fig. 8.9).

- Atherosclerosis and its major complication, myocardial infarction, are strongly linked to cigarette smoking. The causal mechanisms probably relate to several factors, including increased platelet aggregation, decreased myocardial oxygen supply (because of lung disease coupled with hypoxia related to CO in cigarette smoke) accompanied by increased oxygen demand, and a decreased threshold for ventricular fibrillation. Almost one-third of all heart attacks are associated with cigarette smoking. Smoking has a multiplicative effect on risk when combined with hypertension and hypercholesterolemia.

- Maternal smoking increases the risk of spontaneous abortions and preterm births and results in intrauterine growth retardation (Chapter 7); however, birth weights of infants born to mothers who stopped smoking before pregnancy are normal.

### Table 8.4 Organ-Specific Carcinogens in Tobacco Smoke

<table>
<thead>
<tr>
<th>Organ</th>
<th>Carcinogen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung, larynx</td>
<td>Polycyclic aromatic hydrocarbons, 4-(Methyl nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK), 210Polonium</td>
</tr>
<tr>
<td>Esophagus</td>
<td>N′-Nitrosonornicotine (NNN)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>NNK (?), Polycyclic aromatic hydrocarbons, NNN, 210polonium</td>
</tr>
<tr>
<td>Bladder</td>
<td>4-Aminobiphenyl, 2-naphthylamine</td>
</tr>
<tr>
<td>Oral cavity: smoking</td>
<td>Polycyclic aromatic hydrocarbons, NNN, 210polonium</td>
</tr>
<tr>
<td>Oral cavity: snuff</td>
<td>NNK, NNN, 210polonium</td>
</tr>
</tbody>
</table>


- Direct irritant effect on the tracheobronchial mucosa, producing inflammation and increased mucus production (bronchitis). Cigarette smoke also causes the recruitment of leukocytes to the lung, increasing local elastase production and subsequent injury to lung tissue that leads to emphysema.

- Carcinogenesis. Components of cigarette smoke, particularly polycyclic hydrocarbons and nitrosamines (Table 8.4), are potent carcinogens in animals and probably are involved in the causation of lung carcinomas in humans (see Chapter 13). The mechanisms responsible for some tobacco-induced diseases include the following:

### Fig. 8.8

The risk of lung cancer is determined by the number of cigarettes smoked. (Data from Stewart BW, Kleihues P, editors: World cancer report, Lyon, 2003, IARC Press.)

### Fig. 8.9

Multiplicative increase in the risk of laryngeal cancer from the interaction between cigarette smoking and alcohol consumption. (Data from Stewart BW, Kleihues P, editors: World cancer report, Lyon, 2003, IARC Press.)
• Passive smoke inhalation is also associated with detrimental effects. It is estimated that the relative risk of lung cancer in nonsmokers exposed to environmental smoke is about 1.3 times that in nonsmokers who are not exposed to smoke. In the United States, approximately 3000 lung cancer deaths in nonsmokers older than 35 years can be attributed each year to environmental tobacco smoke. Even more striking is the increased risk of coronary atherosclerosis and fatal myocardial infarction. Studies report that 30,000 to 60,000 cardiac deaths annually in the United States are associated with passive exposure to smoke. Children living in a household with an adult who smokes have an increased frequency of respiratory illnesses and asthma. Passive smoke inhalation in nonsmokers can be estimated by measuring the blood levels of cotinine, a metabolite of nicotine. In the United States, median cotinine levels in nonsmokers have decreased by more than 60% since around 2000 because of the adoption of nonsmoking policies in public places. However, passive exposure to tobacco smoke in the home remains a major public health concern, particularly for children. It is clear that the transient pleasure a puff may provide comes with a heavy long-term price.

**SUMMARY**

**HEALTH EFFECTS OF TOBACCO**

- Smoking is the most preventable cause of human death.
- Tobacco smoke contains more than 2000 compounds. Among these are nicotine, which is responsible for tobacco addiction, and strong carcinogens—mainly, polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines.
- Approximately 90% of lung cancers occur in smokers. Smoking is also associated with an increased risk of cancers of the oral cavity, larynx, esophagus, stomach, bladder, and kidney, as well as some forms of leukemia. Cessation of smoking reduces the risk of lung cancer.
- Smokeless tobacco use is an important cause of oral cancers. Tobacco interacts with alcohol in multiplying the risk of oral, laryngeal, and esophageal cancer and increases the risk of lung cancers from occupational exposures to asbestos, uranium, and other agents.
- Tobacco consumption is an important risk factor for development of atherosclerosis and myocardial infarction, peripheral vascular disease, and cerebrovascular disease. In the lungs, in addition to cancer, it predisposes to emphysema, chronic bronchitis, and chronic obstructive disease.
- Maternal smoking increases the risk of abortion, premature birth, and intrauterine growth retardation.

**EFFECTS OF ALCOHOL**

Ethanol is consumed, at least partly, for its mood-altering properties, but when used in moderation its effects are socially acceptable and not injurious. When excessive amounts are used, alcohol can cause marked physical and psychologic damage. Here we describe the lesions that are directly associated with the abuse of alcohol.

Despite all the attention given to illegal drugs, alcohol abuse is a more widespread hazard and claims many more lives. Fifty percent of adults in the Western world drink alcohol, and approximately 5% to 10% have chronic alcoholism. It is estimated that there are more than 10 million chronic alcoholics in the United States and that alcohol consumption is responsible for more than 100,000 deaths annually. Almost 50% of these deaths result from accidents caused by drunken driving and alcohol-related homicides and suicides, and about 15% are a consequence of cirrhosis of the liver.

After consumption, ethanol is absorbed unaltered in the stomach and small intestine and then distributes to all of the tissues and fluids of the body in direct proportion to the blood level. Less than 10% is excreted unchanged in the urine, sweat, and breath. The amount exhaled is proportional to the blood level and forms the basis for the breath test used by law enforcement agencies. A concentration of 80 mg/dL in the blood constitutes the legal definition of drunk driving in most states. For an average individual, this alcohol concentration may be reached after consumption of three standard drinks, about three (12 ounce) bottles of beer, 15 ounces of wine, or 4 to 5 ounces of 80-proof distilled spirits. Drowsiness occurs at 200 mg/dL, stupor at 300 mg/dL, and coma, with possible respiratory arrest, at higher levels. The rate of metabolism affects the blood alcohol level. Chronic alcoholics develop tolerance to alcohol. They metabolize alcohol at a higher rate than normal and hence show lower peak levels of alcohol than average for the same about of alcohol consumed. Most of the alcohol in the blood is metabolized to acetaldehyde in the liver by three enzyme systems: alcohol dehydrogenase; cytochrome P-450 isoenzymes; and catalase (Fig. 8.10). Of these, the main enzyme involved in alcohol metabolism is alcohol dehydrogenase, located in the cytosol of hepatocytes. At high blood alcohol levels, however, the microsomal ethanol-oxidizing system also plays an important role. This system involves cytochrome P-450 enzymes, particularly the CYP2E1 isof orm, located in the smooth ER. Induction of P-450 enzymes by alcohol explains the increased susceptibility of alcoholics to other compounds metabolized by the same enzyme system, which include drugs (acetaminophen, cocaine), anesthetics, carcinogens, and industrial solvents. Of note, however, when alcohol is present in the blood at high concentrations, it competes with other CYP2E1 substrates and may delay the catabolism of other drugs, thereby potentiating their effects. Catalase is of minor importance, being responsible for only about 5% of alcohol metabolism. Acetaldehyde produced by these systems is in turn converted by acetaldehyde dehydrogenase to acetate, which is used in the mitochondrial respiratory chain.

Several toxic effects result from ethanol metabolism. Listed here are only the most important of these:

- **Alcohol oxidation** by alcohol dehydrogenase causes a decrease in nicotinamide adenine dinucleotide (NAD+) and an increase in NADH (the reduced form of NAD+). NAD+ is required for fatty acid oxidation in the liver. Its deficiency is a main cause of fat accumulation in the liver of alcoholics. The increase in the NADH/NAD+ ratio in alcoholics also causes lactic acidosis.
Effects of Alcohol

Fig. 8.10 Metabolism of ethanol: oxidation of ethanol to acetaldehyde by three different routes, and the generation of acetic acid. Note that oxidation by alcohol dehydrogenase (ADH) takes place in the cytosol; the cytochrome P-450 system and its CYP2E1 isoform are located in the ER (microsomes), and catalase is located in peroxisomes. Oxidation of acetaldehyde by aldehyde dehydrogenase (ALDH) occurs in mitochondria. (Data from Parkinson A: Biotransformation of xenobiotics. In Klassen CD, editor: Casarett and Doull's toxicology: The basic science of poisons, ed 6, New York, 2001, McGraw-Hill, pp 133.)

- **Acetaldehyde toxicity** may be responsible for some of the acute effects of alcohol. Acetaldehyde metabolism differs between populations because of genetic variation. Most notably, about 50% of Asians express a defective form of acetaldehyde dehydrogenase. After ingesting alcohol, such persons experience flushing, tachycardia, and hyperventilation owing to the accumulation of acetaldehyde.

- **ROS generation.** Metabolism of ethanol in the liver by CYP2E1 produces ROS and causes lipid peroxidation of cell membranes. Nevertheless, the precise mechanisms that account for alcohol-induced cellular injury have not been well defined.

- **Endotoxin release.** Alcohol may cause the release of endotoxin (lipopolysaccharide), a product of gram-negative bacteria, from the intestinal flora. Endotoxin stimulates the release of tumor necrosis factor (TNF) and other cytokines from circulating macrophages and from Kupffer cells in the liver, causing cell injury.

Acute alcoholism exerts its effects mainly on the CNS but also may induce reversible hepatic and gastric injuries. Even with moderate intake of alcohol, multiple fat droplets accumulate in the cytoplasm of hepatocytes (fatty change or hepatic steatosis). Gastric damage occurs in the form of acute gastritis and ulceration. In the CNS, alcohol is a depressant, first affecting subcortical structures that modulate cerebral cortical activity. Consequently there is stimulation and disordered cortical, motor, and intellectual behavior. At progressively higher blood levels, cortical neurons and then lower medullary centers are depressed, including those that regulate respiration. Respiratory arrest may follow.

**Chronic alcoholism** affects not only the liver and stomach but virtually all other organs and tissues as well. Chronic alcoholics suffer significant morbidity and have a shortened life span, related principally to damage to the liver, GI tract, CNS, cardiovascular system, and pancreas.

- **The liver** is the main site of chronic injury. In addition to fatty change, mentioned earlier, chronic alcoholism causes alcoholic hepatitis and cirrhosis (described in Chapter 16). Cirrhosis is associated with portal hypertension and an increased risk of hepatocellular carcinoma.

- **In the GI tract,** chronic alcoholism can cause massive bleeding from gastritis, gastric ulcer, or esophageal varices (associated with cirrhosis), which may prove fatal.

- **Neurologic effects.** Thiamine deficiency is common in chronic alcoholics; the principal lesions resulting from this deficiency are peripheral neuropathies and the Wernicke-Korsakoff syndrome (see Table 8.9 and Chapter 23). Cerebral atrophy, cerebellar degeneration, and optic neuropathy may also occur.
• **Cardiovascular effects.** Alcohol has diverse effects on the cardiovascular system. Injury to the myocardium may produce dilated congestive cardiomyopathy (*alcoholic cardiomyopathy*), discussed in Chapter 11. Moderate amounts of alcohol (one drink per day) have been reported to increase serum levels of high-density lipoproteins (HDLs) and inhibit platelet aggregation, thus protecting against coronary artery disease. However, heavy consumption, with attendant liver injury, results in decreased levels of HDL, increasing the likelihood of heart disease. Chronic alcoholism also is associated with an increased incidence of hypertension.

• **Pancreatitis.** Excess alcohol intake increases the risk of acute and chronic pancreatitis (Chapter 16).

• **Effects on fetus.** The use of ethanol during pregnancy—reportedly even in low amounts—can cause fetal alcohol syndrome. It consists of microcephaly, growth retardation and facial abnormalities in the newborn, and a reduction of mental functions in older children. It is difficult to establish the amount of alcohol consumption that can cause fetal alcohol syndrome, but consumption during the first trimester of pregnancy is particularly harmful.

• **Carcinogenesis.** Chronic alcohol consumption is associated with an increased incidence of cancers of the oral cavity, esophagus, liver, and, possibly, breast in females. The mechanisms of the carcinogenic effect are uncertain.

• **Malnutrition.** Ethanol is a substantial source of energy, but is often consumed at the expense of food (empty calories). Chronic alcoholism is thus associated with malnutrition and deficiencies, particularly of the B vitamins.

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**SUMMARY**

**ALCOHOL—METABOLISM AND HEALTH EFFECTS**

- Acute alcohol abuse causes drowsiness at blood levels of approximately 200 mg/dL. Stupor and coma develop at higher levels.
- Alcohol is oxidized to acetaldehyde in the liver primarily by alcohol dehydrogenase, and to a lesser extent by the cytochrome P-450 system, and by catalase. Acetaldehyde is converted to acetate in mitochondria and is used in the respiratory chain.
- Alcohol oxidation by alcohol dehydrogenase depletes NAD, leading to accumulation of fat in the liver and to metabolic acidosis.
- The main effects of chronic alcoholism are fatty liver, alcoholic hepatitis, and cirrhosis, which leads to portal hypertension and increases the risk for development of hepatocellular carcinoma.
- Chronic alcoholism can cause bleeding from gastritis and gastric ulcers, peripheral neuropathy associated with thiamine deficiency, and alcoholic cardiomyopathy, and it increases the risk for development of acute and chronic pancreatitis.
- Chronic alcoholism is a major risk factor for cancers of the oral cavity, larynx, and esophagus. The risk is greatly increased by concurrent smoking or the use of smokeless tobacco.

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**INJURY BY THERAPEUTIC DRUGS AND DRUGS OF ABUSE**

**Injury by Therapeutic Drugs: Adverse Drug Reactions**

Adverse drug reactions (ADRs) are untoward effects of drugs that are administered in conventional therapeutic settings. These reactions are extremely common in the practice of medicine and are believed to affect 7% to 8% of patients admitted to a hospital. About 10% of such reactions prove fatal. Table 8.5 lists common pathologic findings in ADRs and the drugs most frequently involved. As can be seen, many of the drugs involved in ADRs, such as the anti-neoplastic agents, are highly potent, and the ADR is a calculated risk for the dosage assumed to achieve the maximum therapeutic effect. Commonly used drugs such as long-acting tetracyclines, which are used to treat diverse conditions, including acne, may produce localized or systemic reactions (Fig. 8.11). Because they are widely used, estrogens and oral contraceptives (OCs) are discussed next in more detail. In addition, acetaminophen and aspirin, which are nonprescription drugs but are important

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**Fig. 8.11** Adverse reaction to minocycline, a long-acting tetracycline derivative. (A) Diffuse blue-gray pigmentation of the forearm, secondary to minocycline administration. (B) Deposition of drug metabolite/iron/melanin pigment particles in the dermis. (A and B, Courtesy of Dr. Zsolt Argenyi, Department of Pathology, University of Washington, Seattle, Washington.)
Table 8.5 Some Common Adverse Drug Reactions and Their Agents

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Major Offenders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Dyscrasias</strong></td>
<td></td>
</tr>
<tr>
<td>Granulocytopenia, aplastic anemia, pancytopenia</td>
<td>Anti-neoplastic agents, immunosuppressives, and chloramphenicol</td>
</tr>
<tr>
<td>Hemolytic anemia, thrombocytopenia</td>
<td>Penicillin, methyldopa, quinidine</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Urticaria, macules, papules, vesicles, petechiae, exfoliative dermatitis, fixed drug eruptions, abnormal pigmentation</td>
<td>Anti-neoplastic agents, sulfonamides, hydantoin, some antibiotics, and many other agents</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Theophylline, hydantoin</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Doxorubicin, daunorubicin</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Penicillamine</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>Aminoglycoside antibiotics, cyclosporine, amphotericin B</td>
</tr>
<tr>
<td>Tubulointerstitial disease with papillary necrosis</td>
<td>Phenacetin, salicylates</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Acute pneumonitis</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>Busulfan, nitrofurantoin, bleomycin</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
</tr>
<tr>
<td>Fatty change</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Diffuse hepatocellular damage</td>
<td>Halothane, isoniazid, acetaminophen</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Chlorpromazine, estrogens, contraceptive agents</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Lupus erythematosus syndrome (drug-induced lupus)</td>
<td>Hydralazine, procainamide</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
</tr>
<tr>
<td>Tinnitus and dizziness</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Acute dystonic reactions and parkinsonian syndrome</td>
<td>Phenothiazine anti-psychotics</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Sedatives</td>
</tr>
</tbody>
</table>

*Feature in almost half of all drug-related deaths.

causes of accidental or intentional overdose, merit special comment.

**Exogenous Estrogens and Oral Contraceptives**

*Menopausal Hormone Therapy (MHT)*

The most common type of MHT (previously referred to as hormone replacement therapy, or HRT) consists of the administration of estrogens together with a progestogen. Because of the risk of uterine cancer, estrogen therapy alone is used only in hysterectomized women. Initially used to counteract “hot flashes” and other symptoms of menopause, early clinical studies suggested that MHT use in postmenopausal women could prevent or slow the progression of osteoporosis (Chapter 21) and reduce the likelihood of myocardial infarction. However, subsequent randomized clinical trials have produced decidedly mixed results. According to these, although MHT did reduce the number of fractures in women on treatment, it was also reported that after 5 years of treatment, combination MHT increased the risk of breast cancer (Chapter 19), stroke, and venous thromboembolism and had no effect on the incidence of coronary heart disease. But during the past few years there has been a reappraisal of the risks and benefits of MHT. These newer analyses showed that MHT effects depend on the type of hormone therapy regimen used (combination estrogen-progestin versus estrogen alone), the age and risk factor status of the woman at the start of treatment, the duration of the treatment, and possibly the hormone dose, formulation, and route of administration. The current risk:benefit consensus can be summarized as follows:

- **Combination estrogen-progestin** increases the risk of breast cancer after a median time of 5 to 6 years. In contrast, estrogen alone in women with hysterectomy is associated with a borderline reduction in the risk of breast cancer.
- **MHT may have a protective effect on the development of atherosclerosis and coronary disease** in women younger than 60 years of age, but there is no protection in women who started MHT at an older age. These data support the notion that there may be a critical therapeutic window for MHT effects on the cardiovascular system. Protective effects in younger women depend in part on the response of estrogen receptors in healthy vascular endothelium. However, MHT should not be used for the
prevention of cardiovascular disease or other chronic diseases.

• **MHT increases the risk of stroke and venous thromboembolism (VTE),** including deep vein thrombosis and pulmonary embolism. The increase in VTE is more pronounced during the first 2 years of treatment and in women who have other risk factors, such as immobilization and hypercoagulable states caused by prothrombin or factor V Leiden mutations (Chapter 4). Whether risks of VTE and stroke are lower with transdermal than oral routes of estrogen administration warrants further study.

As can be appreciated from these associations, assessment of risks and benefits when considering the use of MHT in women is complex. The current feeling is that these agents have a role in the management of menopausal symptoms in early menopause but should not be used long term for chronic disease prevention.

**Oral Contraceptives**

Although OCs have been used for several decades, disagreement continues about their safety and adverse effects. They nearly always contain a synthetic estradiol and a variable amount of a progestin (“combination OCs”), but a few preparations contain only progestins. Currently prescribed OCs contain a smaller amount of estrogens (less than 50 µg/day) and clearly have fewer side effects than those reported for earlier formulations. Hence, the results of epidemiologic studies must be interpreted in the context of the dosage. Nevertheless, there is reasonable evidence to support the following conclusions:

• **Breast carcinoma:** The prevailing opinion is that OCs do not cause an increase in breast cancer risk.

• **Endometrial cancer and ovarian cancers:** OCs have a protective effect against these tumors.

• **Cervical cancer:** OCs may increase the risk of cervical carcinomas in women infected with human papillomavirus.

• **Thromboembolism:** Most studies indicate that OCs, including the newer low-dose (less than 50 µg of estrogen) preparations, are associated with a threefold to sixfold increased risk of venous thrombosis and pulmonary thromboembolism resulting from increased hepatic synthesis of coagulation factors. This risk may be even higher with newer “third-generation” OCs that contain synthetic progestins, particularly in women who are carriers of the factor V Leiden mutation. To put this complication into context, however, the risk of thromboembolism associated with OC use is two to six times lower than the risk of thromboembolism associated with pregnancy.

• **Cardiovascular disease:** There is considerable uncertainty about the risk of atherosclerosis and myocardial infarction in users of OCs. It seems that OCs do not increase the risk of coronary artery disease in women younger than 30 years or in older women who are nonsmokers, but the risk approximately doubles in women older than 35 years who smoke.

• **Hepatic adenoma:** There is a well-defined association between the use of OCs and this rare benign hepatic tumor, especially in older women who have used OCs for prolonged periods (Chapter 14).

Obviously, the pros and cons of OCs must be viewed in the context of their wide applicability and acceptance as a form of contraception that protects against unwanted pregnancies.

**Acetaminophen**

At therapeutic doses, acetaminophen, a widely used non-prescription analgesic and anti-pyretic, is mostly conjugated in the liver with glucuronide or sulfate. About 5% or less is metabolized to NAPQI (N-acetyl-p-benzoquinoneimine) through the hepatic P-450 system. With very large doses, however, NAPQI accumulates, leading to centrilobular hepatic necrosis. The mechanisms of injury produced by NAPQI include (1) covalent binding to hepatic proteins and (2) depletion of reduced GSH. The depletion of GSH makes the hepatocytes more susceptible to cell death caused by ROS. The window between the usual therapeutic dose (0.5 g) and the toxic dose (15 to 25 g) is large, and the drug ordinarily is very safe. Nevertheless, accidental overdoses occur in children, and suicide attempts using acetaminophen are not uncommon, particularly in the United Kingdom. In the United States, acetaminophen toxicity is causes about 50% of acute liver failure. Toxicity begins with nausea, vomiting, diarrhea, and sometimes shock, followed in a few days by the appearance of jaundice. Overdoses of acetaminophen can be treated in early stages by the administration of N-acetylcysteine, which restores GSH. With serious overdoses, liver failure ensues, and centrilobular necrosis may extend to involve entire lobules; such patients often require liver transplantation. Some patients also show evidence of concurrent renal damage.

**Aspirin (Acetylsalicylic Acid)**

Aspirin overdose may result from accidental ingestion in young children or suicide attempts in adults. The major untoward consequences are metabolic, with few morphologic changes. At first, respiratory alkalosis develops, followed by a metabolic acidosis that often proves fatal. Fatal doses may be as little as 2 to 4 g in children and 10 to 30 g in adults, but survival has been reported after doses five times larger.

**Chronic aspirin toxicity** (salicylism) may develop in persons who take 3 gm or more daily (the dose used to treat chronic inflammatory conditions). Chronic salicylism is manifested by headache, dizziness, ringing in the ears (tinnitus), difficulty in hearing, mental confusion, drowsiness, nausea, vomiting, and diarrhea. The CNS changes may progress to convulsions and coma. The morphologic consequences of chronic salicylism are varied. Most often, there is an acute erosive gastritis (Chapter 15), which may produce overt or covert GI bleeding and lead to gastric ulceration. A bleeding tendency may appear concurrently with chronic toxicity because aspirin irreversibly inhibits platelet cyclooxygenase and blocks the ability to make thromboxane A2, an activator of platelet aggregation (Chapter 4). Petechial hemorrhages may appear in the skin and internal viscera, and bleeding from gastric ulcerations may be exaggerated.

Proprietary analgesic mixtures of aspirin and phenacetin or its active metabolite, acetaminophen, when taken throughout several years, can cause tubulointerstitial
nephritis with renal papillary necrosis. This clinical entity is referred to as analgesic nephropathy (Chapter 14).

### Injury by Nontherapeutic Agents (Drug Abuse)

Drug abuse generally involves the use of mind-altering substances beyond therapeutic or social norms. Drug addiction and overdose are serious public health problems. Common drugs of abuse are listed in Table 8.6. Considered here are cocaine, opiates, and marijuana, with a brief mention of a few other drugs.

**Cocaine**

In 2014, it was estimated that there were 1.5 million users of cocaine in the United States, of which approximately 15% to 20% were users of “crack” cocaine. Use is highest among adults 18 to 25 years of age, of whom 1.4% reported taking cocaine within the past month. Extracted from the leaves of the coca plant, cocaine usually is prepared as a water-soluble powder, cocaine hydrochloride, but when sold on the street it is liberally diluted with talcum powder, lactose, or other look-alikes. Crystallization of the pure alkaloid from cocaine hydrochloride yields nuggets of crack (so called because of the popping sound it makes when heated). The pharmacologic actions of cocaine and crack are identical, but crack is far more potent. Both forms can be snorted, smoked after mixing with tobacco, ingested, or injected subcutaneously or intravenously.

Cocaine produces a sense of intense euphoria and mental alertness, making it one of the most addictive of all drugs. Experimental animals will press a lever more than 1000 times and will forgo food and drink to obtain the drug. In cocaine users, although physical dependence seems not to occur, the psychologic dependence is profound. Intense cravings are particularly severe in the first several months after abstinence and can recur for years. Acute overdose produces seizures, cardiac arrhythmias, and respiratory arrest. The following are the important manifestations of cocaine toxicity:

- **Cardiovascular effects.** The most serious physical effects of cocaine relate to its acute action on the cardiovascular system. Cocaine is a sympathomimetic agent (Fig. 8.12), both in the CNS, where it blocks the reuptake of dopamine, and at adrenergic nerve endings, where it blocks the reuptake of both epinephrine and norepinephrine while stimulating the presynaptic release of norepinephrine. The net effect is the accumulation of these products in synapses and excessive stimulation, manifested by tachycardia, hypertension, and peripheral vasoconstriction. Cocaine also induces myocardial ischemia, the basis for which is multifactorial. It causes coronary artery vasoconstriction and promotes thrombus formation by facilitating platelet aggregation. Cigarette smoking potentiates cocaine-induced coronary vasospasm. Thus, by increasing myocardial oxygen demand by its sympathomimetic action and, at the same time, reducing coronary blood flow, cocaine often triggers myocardial ischemia, which may lead to myocardial infarction. Cocaine also can precipitate lethal arrhythmias by enhanced sympathetic activity as well as by disrupting normal ion (K+, Ca2+, Na+) transport in the myocardium. These toxic effects are not necessarily dose related, and a fatal event may occur in a first-time user with what is a typical mood-altering dose.

- **CNS effects.** The most common CNS findings are hyperpyrexia (thought to be caused by aberrations of the dopaminergic pathways that control body temperature) and seizures.

- **Effects on the fetus.** In pregnant women, cocaine may cause decreased blood flow to the placenta, resulting in fetal hypoxia and spontaneous abortion. Neurologic development may be impaired in the fetuses of pregnant women who are chronic drug users.

### Table 8.6 Common Drugs of Abuse

<table>
<thead>
<tr>
<th>Class</th>
<th>Molecular Target</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid narcotics</td>
<td>Mu opioid receptor (agonist)</td>
<td>Heroin, hydromorphone (Dilaudid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxycodone</td>
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<tr>
<td></td>
<td></td>
<td>Methadone (Dolophine)</td>
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<tr>
<td>Sedative-hypnotics</td>
<td>GABA receptor (agonist)</td>
<td>Barbiturates</td>
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<td></td>
<td></td>
<td>Ethanol</td>
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<tr>
<td></td>
<td></td>
<td>Methaqualone (“Quaalude”)</td>
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<tr>
<td></td>
<td></td>
<td>Glutethimide (Doriden)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etchlorvynol (Placidyl)</td>
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<tr>
<td>Psychomotor stimulants</td>
<td>Dopamine transporter (antagonist)</td>
<td>Cocaine</td>
</tr>
<tr>
<td></td>
<td>Serotonin receptors (toxicity)</td>
<td>Amphetamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3,4-methylenedioxymethamphetamine (MDMA) (i.e., “ecstasy”)</td>
</tr>
<tr>
<td>Phencyclidine-like drugs</td>
<td>NMDA glutamate receptor channel (antagonist)</td>
<td>Phencyclidine (PCP) (i.e., “angel dust”)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ketamine</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>CB1 cannabinoid receptors (agonist)</td>
<td>Marijuana</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hashish</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicotine acetylcholine receptor (agonist)</td>
<td>Tobacco products</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Serotonin 5-HT2 receptors (agonist)</td>
<td>Lysergic acid diethylamide (LSD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mescaline</td>
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<tr>
<td></td>
<td></td>
<td>Psilocybin</td>
</tr>
</tbody>
</table>

CB1, Cannabinoid receptor type 1; GABA, gamma-aminobutyric acid; 5-HT2, 5-hydroxytryptamine; NMDA, N-methyl-D-aspartate; PCP, 1-(1-phenylcyclohexyl)piperidine. Data from Hyman SE: A 28-year-old man addicted to cocaine, JAMA 286:2586, 2001.
on the street, it is cut (diluted) with an agent (often talc or quinine); thus, the size of the dose not only is variable but also usually is unknown to the buyer. Heroin, along with any contaminating substances, usually is self-administered intravenously or subcutaneously. Effects are varied and include euphoria, hallucinations, somnolence, and sedation. Heroin has a wide range of adverse physical effects that can be categorized etiologically according to (1) the pharmacologic action of the agent, (2) reactions to the cutting agents or contaminants, (3) hypersensitivity reactions to the drug or its adulterants, and (4) diseases contracted through the sharing of needles. Some of the most important adverse effects of heroin are the following:

- **Sudden death.** Sudden death, usually related to overdose, is an ever-present risk, because drug purity generally is unknown and may range from 2% to 90%. The yearly incidence of sudden death among chronic users in the United States is estimated to be between 1% and 3%. Sudden death sometimes is due to a loss of tolerance for the drug, such as after a period of incarceration. The mechanisms of death include profound respiratory depression, arrhythmia and cardiac arrest, and pulmonary edema.

- **Pulmonary disease.** Pulmonary complications include edema, septic embolism, lung abscess, opportunistic infections, and foreign body granulomas from talc and other adulterants. Although granulomas occur principally in the lung, they also are sometimes found in the spleen, liver, and lymph nodes that drain the upper extremities. Examination under polarized light often highlights trapped talc crystals, sometimes enclosed within foreign body giant cells.

- **Infections.** Infectious complications are common. The sites most commonly affected are the skin and subcutaneous tissue, heart valves, liver, and lungs. In a series of addicted patients admitted to the hospital, more than 10% had endocarditis, which often takes a distinctive form involving right-sided heart valves, particularly the tricuspid. Most cases are caused by *Staphylococcus aureus*, but fungi and a multitude of other organisms have also been implicated. Viral hepatitis is the most common infection among addicts and is acquired by the sharing of dirty needles. In the United States, this practice has also led to a very high incidence of human immunodeficiency virus (HIV) infection in intravenous drug abusers.

- **Skin lesions.** Cutaneous lesions probably are the most frequent telltale sign of heroin addiction. Acute changes include abscesses, cellulitis, and ulcers resulting from subcutaneous injections. Scarring at injection sites, hyperpigmentation over commonly used veins, and thrombosed veins are the usual sequelae of repeated intravenous inoculations.

- **Renal problems.** Kidney disease is a relatively common hazard. The two forms most frequently encountered are amyloidosis (generally secondary to skin infections) and focal glomerulosclerosis; both induce heavy proteinuria and the nephrotic syndrome.

Tragically, more widespread availability of prescription opiates, such as hydrocodone and oxycodone, has fueled an epidemic of opioid abuse that surpasses that associated with
heroin. In 2014, it was estimated that 4.3 million Americans engaged in non-medical use of prescription opioids, and that prescription opioid overdoses led to approximately 19,000 deaths, mainly from respiratory failure. Moreover, an increasing number of heroin users start with prescription opioids, then switch to heroin because it is a substantially less expensive habit. This trend underlies a near doubling of heroin use in the United States between 2005 and 2012. Current efforts are focused on making opioid antagonists widely available to first responders, which has prevented many deaths, and tightening the use of prescription opioids to limit their potential for abuse.

Marijuana
Marijuana, or “pot,” is the most widely used illegal drug. As of 2014 in the United States, 22.2 million people (7.0% of the population) admitted use during the previous month. Several states in the United States have legalized the “recreational” use of marijuana, and more states appear poised to follow; thus, its status as an illicit drug is undergoing reevaluation.

Marijuana is made from the leaves of the Cannabis sativa plant, which contain the psychoactive substance Δ9-tetrahydrocannabinol (THC). When marijuana is smoked, about 5% to 10% of the THC content is absorbed. Despite numerous studies, whether the drug includes persistent adverse physical and functional effects remains unresolved. Some of the untoward anecdotal effects may be allergic or idiosyncratic reactions or are possibly related to contaminants in the preparations, rather than to marijuana’s pharmacologic effects. On the other hand, beneficial effects of THC include its capacity to decrease intraocular pressure in glaucoma and to combat intractable nausea secondary to cancer chemotherapy.

The functional and organic CNS consequences of marijuana have received great scrutiny. Marijuana use is well recognized to distort sensory perception and impair motor coordination, but these acute effects generally clear in 4 to 5 hours. With continued use, these changes may progress to cognitive and psychomotor impairments, such as the inability to judge time, speed, and distance. Among adolescents, such impairment often leads to automobile accidents. Marijuana increases the heart rate and sometimes blood pressure and it may cause angina in a person with coronary artery disease.

The lungs are affected by chronic marijuana smoking; laryngitis, pharyngitis, bronchitis, cough, hoarseness, and asthmalike symptoms all have been described, along with mild but significant airway obstruction. Smoking a marijuana cigarette, compared with a tobacco cigarette, is associated with a 3-fold increase in the amount of tar inhaled and retained in the lungs, as a consequence of deeper inhalation and longer breath holding.

Other Illicit Drugs
The variety of drugs that have been tried by those seeking “new experiences” (highs, lows, “out-of-body experiences”) defies belief. These drugs include various stimulants, depressants, analgesics, and hallucinogens. Among these are PCP (1-(1-phenylcyclohexyl) piperidine), or phencyclidine, and ketamine (related anesthetic agents); lysergic acid diethylamide (LSD), the most potent hallucinogen known; “ecstasy” (3,4-methylenedioxymethamphetamine [MDMA]); and “bat salts,” synthetic cathinones that are chemically related to khat, a widely used stimulant in East Africa. Not much is known about the long-term deleterious effects of any of these agents. Acutely, LSD has unpredictable effects on mood, affect, and thought, sometimes leading to bizarre and dangerous behaviors. Chronic use of ecstasy may deplete the CNS of serotonin, potentially leading to sleep disorders, depression, anxiety, and aggressive behavior.

**SUMMARY**

**INJURY BY PHYSICAL AGENTS**

Injury induced by physical agents is divided into the following categories: mechanical trauma, thermal injury, electrical injury, and injury produced by ionizing radiation. Each type is considered separately.

**Mechanical Trauma**

Mechanical forces may inflict a variety of forms of damage. The type of injury depends on the shape of the colliding object, the amount of energy discharged at impact, and the tissues or organs that bear the impact. Bone and head injuries result in unique damage and are discussed elsewhere (Chapter 23). All soft tissues react similarly to mechanical forces, and the patterns of injury can be divided into abrasions, contusions, lacerations, incised wounds, and puncture wounds (Fig. 8.13).

**MORPHOLOGY**

An abrasion is a wound produced by scraping or rubbing the skin surface, which damages the superficial layer. Typical skin abrasions remove only the epidermal layer. A contusion, or bruise, is a wound usually produced by a blunt trauma and is characterized by damage to a vessel and extravasation of blood.
MORPHOLOGY

On gross inspection, **full-thickness burns** are white or charred, dry, and anesthetic (as a result of the destruction of nerve endings), whereas **partial-thickness burns**, depending on the depth, are pink or mottled, blistered, and painful. Histologic examination of devitalized tissue shows coagulative necrosis adjacent to vital tissue, which quickly accumulates inflammatory cells and marked exudation.

Despite continuous improvement in therapy, any burn exceeding 50% of the total body surface, whether superficial or deep, is grave and potentially fatal. With burns of more than 20% of the body surface, there is a rapid shift of body fluids into the
interstitial compartments, both at the burn site and systemically, which can result in **hypovolemic shock** (Chapter 4). Because protein from the blood is lost into interstitial tissue, generalized edema, including pulmonary edema, may become severe.

Another important consideration is the degree of injury to the airways and lungs. **Inhalation injury** is frequent in persons trapped in burning buildings and may result from the direct effect of heat on the mouth, nose, and upper airways or from the inhalation of heated air and gases in the smoke. Water-soluble gases, such as chlorine, sulfur oxides, and ammonia, may react with water to form acids or alkalis, particularly in the upper airways, resulting in inflammation and swelling, which may lead to partial or complete airway obstruction. Lipid-soluble gases, such as nitrous oxide and products of burning plastics, are more likely to reach deeper airways, producing pneumonitis. Unlike in shock, which develops within hours, pulmonary manifestations may not develop for 24 to 48 hours.

**Organ system failure** resulting from sepsis continues to be the leading cause of death in burned patients. The burn site is ideal for the growth of microorganisms; the serum and debris provide nutrients, and the burn injury compromises blood flow, blocking effective inflammatory responses. The most common offender is the opportunistic *Pseudomonas aeruginosa*, but antibiotic-resistant strains of other common hospital-acquired bacteria, such as *S. aureus* and fungi, particularly *Candida* spp., also may be involved. Furthermore, cellular and humoral defenses against infections are compromised, and both lymphocyte and phagocyte functions are impaired. Direct bacteremic spread and release of toxic substances such as endotoxin from the local site have dire consequences. **Pneumonia or septic shock**, accompanied by renal failure and/or the acute respiratory distress syndrome (ARDS) (Chapter 13), are the most common serious sequelae.

Another very important pathophysiologic effect of burns is the development of a hypermetabolic state, with excess heat loss and an increased need for nutritional support. It is estimated that when more than 40% of the body surface is burned, the resting metabolic rate may approach twice normal.

### Hyperthermia

Prolonged exposure to elevated ambient temperatures can result in heat cramps, heat exhaustion, or heat stroke.

- **Heat cramps** result from loss of electrolytes through sweating. Cramping of voluntary muscles, usually in association with vigorous exercise, is the hallmark sign. Heat-dissipating mechanisms are able to maintain normal core body temperature.

- **Heat exhaustion** is probably the most common hyperthermic syndrome. Its onset is sudden, with prostration and collapse, and it results from a failure of the cardiovascular system to compensate for hypovolemia, secondary to water depletion. After a period of collapse, which is usually brief, equilibrium is spontaneously reestablished if the victim is able to rehydrate.

- **Heat stroke** is associated with high ambient temperatures and high humidity. Thermoregulatory mechanisms fail, sweating ceases, and core body temperature rises. In the clinical setting, a rectal temperature of 106°F or higher is considered a grave prognostic sign, and the mortality rate for such patients exceeds 50%. The underlying mechanism is marked generalized peripheral vasodilation with peripheral pooling of blood and a decreased effective circulating blood volume. Necrosis of the muscles and myocardium may occur. Arrhythmias, disseminated intravascular coagulation, and other systemic effects are common. Elderly people, persons with cardiovascular disease, and otherwise healthy people undergoing physical stress (such as young athletes and military recruits) are prime candidates for heat stroke.

- **Malignant hyperthermia**, although similar sounding, is not caused by exposure to high temperatures. It is a genetic condition resulting from mutations in genes such as *RYR1* that control calcium levels in skeletal muscle cells. In affected individuals, exposure to certain anesthetics during surgery may trigger a rapid rise in calcium levels in skeletal muscle, which in turn leads to muscle rigidity and increased heat production. The resulting hyperthermia has a mortality rate of approximately 80% if untreated, but this falls to less than 5% if the condition is recognized and muscle relaxants are administered promptly.

### Hypothermia

Prolonged exposure to low ambient temperature leads to hypothermia. The condition is seen all too frequently in homeless alcoholics, in whom wet or inadequate clothing and dilation of superficial blood vessels, occurring as a result of the ingestion of alcohol, hasten the lowering of body temperature. At about 90°F, loss of consciousness occurs, followed by bradycardia and atrial fibrillation at lower core temperatures.

Chilling or freezing of cells and tissues causes injury by two mechanisms:

- **Direct effects** probably are mediated by physical disruptions within cells and high salt concentrations incident to the crystallization of the intra- and extracellular water.

- **Indirect effects** are the result of circulatory changes, which vary depending on the rate and the duration of the temperature drop. Slowly developing, prolonged chilling may induce vasoconstriction and increased permeability, leading to edema. Such changes are typical of “trench foot.” This condition developed in soldiers who spent long periods of time in waterlogged trenches during the First World War (1914–1918), frequently causing gangrene that necessitated amputation. Alternatively, with sudden sharp drops in temperature, the vasoconstriction and increased viscosity of the blood in the local area may cause ischemic injury and degenerative changes in peripheral nerves. In this situation, the vascular injury and increased permeability with exudation only become evident with rewarming. If the period of ischemia is prolonged, hypoxic changes and infarction of the affected tissues (e.g., gangrene of toes or feet) may result.

### Electrical Injury

Electrical injuries, which may be fatal, can arise from low-voltage currents (i.e., in the home and workplace) or from high-voltage currents carried in power lines or by lighting. Injuries are of two types: (1) burns and (2) ventricular fibrillation or cardiac and respiratory center failure.
resulting from disruption of normal electrical impulses. The type of injury and the severity and extent of burning depend on the amperage of the electric current and its path within the body.

Voltage in the household and the workplace (120 or 220 V) is high enough that with low resistance at the site of contact (as when the skin is wet), sufficient current can pass through the body to cause serious injury, including ventricular fibrillation. If current flow continues long enough, it generates enough heat to produce burns at the site of entry and exit as well as in internal organs. An important characteristic of alternating current, the type available in most homes, is that it induces tetanic muscle spasm, so that when a live wire or switch is grasped, irreversible clutching is likely to occur, prolonging the period of current flow. This results in a greater likelihood of extensive electrical burns and, in some cases, spasm of the chest wall muscles, producing death from asphyxia. Currents generated from high-voltage sources cause similar damage; however, because of the large current flows generated, these injuries are more likely to produce paralysis of medullary centers and extensive burns. Lightning is a classic cause of high-voltage electrical injury.

Injury Produced by Ionizing Radiation

Radiation is energy that travels in the form of waves or high-speed particles. It has a wide range of energies that span the electromagnetic spectrum; it can be divided into nonionizing and ionizing radiation. The energy of nonionizing radiation, such as ultraviolet (UV) and infrared light, microwaves, and sound waves, can move atoms in a molecule or cause them to vibrate but is not sufficient to displace electrons from atoms. By contrast, ionizing radiation has sufficient energy to remove tightly bound electrons. Collision of these free electrons with other atoms releases additional electrons, in a reaction cascade referred to as ionization. The main sources of ionizing radiation are (1) x-rays and gamma rays, which are electromagnetic waves of very high frequencies, and (2) high-energy neutrons, alpha particles (composed of two protons and two neutrons), and beta particles, which are essentially electrons. At equivalent amounts of energy, alpha particles induce heavy damage in a restricted area, whereas x-rays and gamma rays dissipate energy over a longer, deeper course, and produce considerably less damage per unit of tissue. Some of the total dose of ionizing radiation received by the U.S. population is human-made, mostly originating from medical devices and radioisotopes. In fact, the exposure of patients to ionizing radiation during radiologic imaging tests roughly doubled between the early 1980s and 2006, mainly because of much more widespread use of CT scans.

Ionizing radiation is indispensable in medical practice, but this application constitutes a two-edged sword. Radiation in this form is used in the treatment of cancer, in diagnostic imaging, and as therapeutic or diagnostic radioisotopes. However, it also is mutagenic, carcinogenic, and teratogenic.

The following terms are used to express exposure, absorption, and dose of ionizing radiation:
• Curie (Ci) represents the disintegrations per second of a spontaneously disintegrating radionuclide (radioisotope). One Ci is equal to \(3.7 \times 10^{10}\) disintegrations per second.
• Gray (Gy) is a unit that expresses the energy absorbed by a target tissue. It corresponds to the absorption of \(10^4\) ergs per gram of tissue. A centigray (cGy), which is the absorption of 100 ergs per gram of tissue, is equivalent to the exposure of tissue to 100 rads (R) (“radiation absorbed dose”). The cGy nomenclature has now replaced the rad in medical parlance.
• Sievert (Sv) is a unit of equivalent dose that depends on the biologic rather than the physical effects of radiation (it replaced a unit called the rem). For the same absorbed dose, various types of radiation differ in the extent of damage they produce. The equivalent dose controls for this variation and provides a uniform measuring unit. The equivalent dose (expressed in sieverts) corresponds to the absorbed dose (expressed in grays) multiplied by the relative biologic effectiveness of the radiation. The relative biologic effectiveness depends on the type of radiation, the type and volume of the exposed tissue, and the duration of the exposure, as well as other biologic factors (discussed next). The effective dose of x-rays, computed tomography (CT), and other imaging and nuclear medicine procedures are commonly expressed in millisieverts (mSv). For x-radiation, 1 mSv = 1 mGy.

Main Determinants of the Biologic Effects of Ionizing Radiation

In addition to the physical properties of the radiation, its biologic effects depend heavily on the following variables:
• Rate of delivery. The rate of delivery significantly modifies the biologic effect. Although the effect of radiant energy is cumulative, delivery in divided doses may allow cells to repair some of the damage in the intervals. Thus, fractional doses of radiant energy have a cumulative effect only to the extent that repair during the intervals is incomplete. Radiotherapy of tumors exploits the capability of normal cells to repair themselves and to recover more rapidly than tumor cells.
• Field size. The size of the field exposed to radiation has a great influence on its consequences. The body can sustain relatively high doses of radiation when they are delivered to small, carefully shielded fields, whereas smaller doses delivered to larger fields may be lethal.
• Cell proliferation. Because ionizing radiation damages DNA, rapidly dividing cells are more vulnerable to injury than are quiescent cells. Except at extremely high doses that impair DNA transcription, DNA damage is compatible with survival in nondividing cells, such as neurons and muscle cells. However, as discussed in Chapter 6, in dividing cells DNA damage is detected by sensors that produce signals leading to the upregulation of p53, the “guardian of the genome.” p53 in turn upregulates the expression of genes that initially lead to cell-cycle arrest and, if the DNA damage is too great to repair, genes that cause cell death through apoptosis. Understandably, therefore, tissues with a high rate of cell turnover, such as gonads, bone marrow, lymphoid tissue, and the mucosa of the GI tract, are extremely vulnerable to radiation, and the injury is manifested early after exposure.
DNA Damage and Carcinogenesis
The most important cellular target of ionizing radiation is DNA (Fig. 8.14). Damage to DNA caused by ionizing radiation that is not precisely repaired leads to mutations, which can manifest years or decades later as cancer. Ionizing radiation can cause many types of damage in DNA, including single-base damage, single- and double-strand breaks, and crosslinks between DNA and protein. In surviving cells, simple defects may be repairable by various enzyme repair systems contained in mammalian cells (see Chapter 6). These repair systems are linked to cell-cycle regulation through proteins such as ATM (ataxia-telangiectasia mutated) that initiate signal transduction after the damage, and p53, which can transiently arrest the cell cycle to allow for DNA repair or to trigger apoptosis of cells that are irreparable. However, double-strand breaks may persist without repair, or the repair of lesions may be imprecise (error prone), creating mutations. If cell-cycle checkpoints are not functioning (for instance, because of mutations in TP53), cells with abnormal and unstable genomes survive and may expand as abnormal clones to form tumors eventually.

Fibrosis
A common consequence of cancer radiotherapy is the development of fibrosis in the irradiated field (Fig. 8.15). Fibrosis may occur weeks or months after irradiation,
leading to the replacement of dead parenchymal cells by connective tissue and the formation of scars and adhesions (see Chapter 3). As already mentioned, ionizing radiation causes vascular damage and consequent tissue ischemia. Vascular damage, the killing of tissue stem cells by ionizing radiation, and the release of cytokines and chemokines that promote an inflammatory reaction all contribute to fibroblast activation and the development of radiation-induced fibrosis.

**MORPHOLOGY**

Cells surviving radiant energy damage show a wide range of structural changes in chromosomes, including deletions, breaks, translocations, and fragmentation. The mitotic spindle often becomes disorderly, and polyplody and aneuploidy may be encountered. Nuclear swelling and condensation and clumping of chromatin may appear; breaks in the nuclear membrane also may be noted. Apoptosis may occur. Cells with abnormal nuclear morphology may be produced and persist for years, including giant cells with pleomorphic nuclei or more than one nucleus. At extremely high dose levels of radiant energy, features that foretell impending cell death, such as nuclear pyknosis, appear quickly.

In addition to affecting DNA and nuclei, radiant energy may induce a variety of cytoplasmic changes, including cytoplasmic swelling, mitochondrial distortion, and degeneration of the ER. Plasma membrane breaks and focal defects may appear. The histologic constellation of cellular pleomorphism, giant cell formation, changes in nuclei, and mitotic figures creates a more than passing similarity between radiation-injured cells and cancer cells, a problem that plagues the pathologist when evaluating postirradiation tissues for persistence or recurrence of cancer.

At the light microscopic level, vascular changes and interstitial fibrosis are prominent in irradiated tissues (Fig. 8.15). During the immediate postirradiation period, vessels may show only dilation. Later, or with higher doses, a variety of degenerative changes appear, including endothelial cell swelling and vacuolation, or even necrosis of the walls of small vessels such as capillaries and venules. Affected vessels may rupture or undergo thrombosis. Still later, endothelial cell proliferation and collagenous hylalnization with thickening of the media layer are seen in irradiated vessels, resulting in marked narrowing or obliteration of the vascular lumina. At this time, an increase in interstitial collagen in the irradiated field, leading to scarring and contractions, usually becomes evident.

**Effects on Organ Systems**

Fig. 8.16 depicts the main consequences of radiation injury. As already mentioned, the most sensitive organs and tissues are the gonads, the hematopoietic and lymphoid systems, and the lining of the GI tract. Estimated threshold doses for the effects of acute exposure to radiation in various organs are shown in Table 8.7. The changes in the hematopoietic and lymphoid systems, along with cancers induced by environmental or occupational exposure to ionizing radiation, are summarized as follows:

- **Hematopoietic and lymphoid systems.** The hematopoietic and lymphoid systems are extremely susceptible to radiation injury and deserve special mention. With high

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**Table 8.7 Estimated Threshold Doses for Acute Radiation Effects on Specific Organs**

<table>
<thead>
<tr>
<th>Health Effect</th>
<th>Organ/Structure</th>
<th>Dose (Sv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary sterility</td>
<td>Testes</td>
<td>0.15</td>
</tr>
<tr>
<td>Depression of hematopoiesis</td>
<td>Bone marrow</td>
<td>0.50</td>
</tr>
<tr>
<td>Reversible skin effects (e.g., erythema)</td>
<td>Skin</td>
<td>1.0–2.0</td>
</tr>
<tr>
<td>Permanent sterility</td>
<td>Ovaries</td>
<td>2.5–6.0</td>
</tr>
<tr>
<td>Temporary hair loss</td>
<td>Skin</td>
<td>3.0–5.0</td>
</tr>
<tr>
<td>Permanent sterility</td>
<td>Testis</td>
<td>3.5</td>
</tr>
<tr>
<td>Cataract</td>
<td>Lens of eye</td>
<td>5.0</td>
</tr>
</tbody>
</table>
dose levels and large exposure fields, severe lymphopenia may appear within hours of irradiation, along with shrinkage of the lymph nodes and spleen. Radiation directly destroys lymphocytes, both in the circulating blood and in tissues (nodes, spleen, thymus, gut). With sublethal doses of radiation, regeneration from viable progenitors is prompt, leading to restoration of a normal lymphocyte count. Hematopoietic precursors in the bone marrow are also quite sensitive to radiant energy, which produces a dose-dependent marrow aplasia. The acute effects of marrow irradiation on peripheral blood counts reflects the kinetics of turnover of the formed elements—the granulocytes, platelets, and red cells, which have half-lives of less than 1 day, 10 days, and 120 days, respectively. After a brief rise in the circulating neutrophil count, neutropenia appears within several days. Neutrophil counts reach their nadir, often at counts near zero, during the second week. If the patient survives, full recovery of granulocytes may require 2 to 3 months. Thrombocytopenia appears by the end of the first week, with the platelet count nadir occurring somewhat later than that of granulocytes; recovery is similarly delayed. Anemia appears after 2 to 3 weeks and may persist for months. Understandably, higher doses of radiation produce more severe cytopenias and more prolonged periods of recovery. Very high doses kill marrow stem cells and induce permanent aplasia (aplastic anemia) marked by a failure of blood count recovery, whereas with lower doses the aplasia is transient.

- Environmental exposure and cancer development. Any cell capable of division that has sustained mutations has the potential to become cancerous. Thus, an increased incidence of neoplasms may occur in any organ after exposure to ionizing radiation. The level of radiation required to increase the risk of cancer development is difficult to determine, but there is little doubt that acute or prolonged exposures that result in doses of 100 mSv cause serious consequences, including cancer. This is documented by the increased incidence of leukemias and tumors at various sites (such as thyroid, breast, and lung) in survivors of the atomic bombings of Hiroshima and Nagasaki, the increase in thyroid cancers in survivors of the Chernobyl accident, and the development of “second cancers,” such as acute myeloid leukemia, myelodysplastic syndrome, and solid tumors, in individuals who received radiation therapy for cancers such as Hodgkin lymphoma. It is believed that the risk of secondary cancers following irradiation is greatest in children. This is based in part on a large-scale epidemiologic study showing that children who receive at least two CT scans have very small but measurable increased risks for leukemia and malignant brain tumors, and on older studies showing that radiation therapy to the chest is particularly likely to produce breast cancers when administered to adolescent females.

- Occupational exposure and cancer development. Radon is a ubiquitous product of the spontaneous decay of uranium. The carcinogenic agents are two radon decay byproducts (polonium-214 and polonium-218, or “radon daughters”), which emit alpha particles and have a short half-life. These particulates are deposited in the lung, and chronic exposure in uranium miners may give rise to lung carcinomas. Risks also are present in those homes in which the levels of radon are very high, comparable to those found in mines. However, there is little or no evidence to suggest that radon contributes to the risk of lung cancer in the average household.

### Table 8.8 Effects of Whole-Body Ionizing Radiation

<table>
<thead>
<tr>
<th>Main site of injury</th>
<th>0–1 Sv</th>
<th>1–2 Sv</th>
<th>2–10 Sv</th>
<th>10–20 Sv</th>
<th>&gt;50 Sv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Leukopenia, hemorrhage, epilation, vomiting</td>
<td>Diarrhea, fever, electrolyte imbalance, vomiting</td>
<td>Ataxia, coma, convulsions, vomiting</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Small bowel</td>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing</td>
<td>1 day–1 week</td>
<td>4–6 weeks</td>
<td>5–14 days</td>
<td>1–4 hours</td>
<td></td>
</tr>
<tr>
<td>Lethality</td>
<td>None</td>
<td>Variable (0%–80%)</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

### SUMMARY

- Ionizing radiation may injure cells directly or indirectly by generating free radicals from water or molecular oxygen.
- Ionizing radiation damages DNA; therefore, rapidly dividing cells such as germ cells, and those in the bone marrow and GI tract are very sensitive to radiation injury.
- DNA damage that is not adequately repaired may result in mutations that predispose affected cells to neoplastic transformation.
- Ionizing radiation may cause vascular damage and sclerosis, resulting in ischemic necrosis of parenchymal cells and their replacement by fibrous tissue.

### NUTRITIONAL DISEASES

Millions of people in developing nations starve or live on the cruel edge of starvation, whereas those in the developed world, and more recently in the developing world, struggle to avoid calories and the attendant obesity or fear that what they eat may contribute to atherosclerosis and...
Alcoholic persons may sometimes suffer from an unreasonable fear of cardiovascular hypertension. So both the lack of nutrition and overnutrition are major health concerns.

Malnutrition

A healthy diet provides (1) sufficient energy, in the form of carbohydrates, fats, and proteins, for the body’s daily metabolic needs; (2) essential (as well as nonessential) amino acids and fatty acids, used as building blocks for synthesis of structural and functional proteins and lipids; and (3) vitamins and minerals, which function as co-enzymes or hormones in vital metabolic pathways or, as in the case of calcium and phosphate, as important structural components. In primary malnutrition, one or all of these components are missing from the diet. By contrast, in secondary, or conditional, malnutrition, the dietary intake of nutrients is adequate, and malnutrition results from nutrient malabsorption, impaired use or storage, excess losses, or increased requirements. The causes of secondary malnutrition can be grouped into three general but overlapping categories: GI diseases, chronic wasting diseases, and acute critical illness.

Malnutrition is widespread and may be gross or subtle. Some common causes of dietary insufficiencies are listed here.

- **Poverty.** Homeless people, elderly persons, and children of the poor often suffer from severe malnutrition as well as trace nutrient deficiencies. In poor countries, poverty, together with droughts, crop failure, and livestock deaths, creates the setting for malnourishment of children and adults.
- **Ignorance.** Even the affluent may fail to recognize that infants, adolescents, and pregnant women have increased nutritional needs. Ignorance about the nutritional content of various foods also contributes to malnutrition, as follows: (1) iron deficiency often develops in infants exclusively fed artificial milk diets; (2) polished rice used as the mainstay of a diet may lack adequate amounts of thiamine; and (3) iodine often is lacking in food and water in regions removed from the oceans, unless supplementation is provided.
- **Chronic alcoholism.** Alcoholic persons may sometimes suffer from malnutrition but are more frequently lacking in several vitamins, especially thiamine, pyridoxine, folate, and vitamin A, as a result of dietary deficiency, defective GI absorption, abnormal nutrient utilization and storage, increased metabolic needs, and an increased rate of loss. A failure to recognize thiamine deficiency in patients with chronic alcoholism may result in irreversible brain damage (e.g., Korsakoff psychosis, discussed in Chapter 23).
- **Acute and chronic illnesses.** The basal metabolic rate becomes accelerated in many illnesses (in patients with extensive burns, it may double), resulting in increased daily requirements for all nutrients. Failure to recognize these nutritional needs may delay recovery. Malnutrition is often present in patients with advanced cancer and AIDS.
- **Self-imposed dietary restriction.** Anorexia nervosa, bulimia, and less overt eating disorders affect a large population of persons who are concerned about body image or suffer from an unreasonable fear of cardiovascular disease (anorexia and bulimia are discussed in a separate section in this chapter).
- **Other causes.** Additional causes of malnutrition include GI diseases, acquired and inherited malabsorption syndromes, specific drug therapies (which block uptake or use of particular nutrients), and total parenteral nutrition.

The remainder of this section presents a general overview of nutritional disorders. Particular attention is devoted to severe acute malnutrition, anorexia nervosa and bulimia, deficiencies of vitamins and trace minerals, and obesity, with a brief consideration of the relationships of diet to atherosclerosis and cancer. Other nutrients and nutritional issues are discussed in the context of specific diseases throughout the text.

Severe Acute Malnutrition

The World Health Organization defines severe acute malnutrition (SAM) as a state characterized by a greatly reduced weight for height ratio that is below 3 standard deviation of WHO standards. Worldwide about 16 million children under the age of 5 years are affected by it. It is common in poor countries, where as many as 25% of children may be affected and where it is a major contributor to the high death rates among the very young. In addition to loss of life, wars also exact a heavy toll on refugees who live in abject poverty. In camps set up for refugees from Syria, as many as 20% of the children are severely or moderately malnourished.

SAM previously called protein energy malnutrition (PEM) manifests as a range of clinical syndromes, all resulting from a dietary intake of protein and calories that is inadequate to meet the body’s needs. The two ends of the spectrum of SAM are known as marasmus and kwashiorkor.

It should be noted that from a functional standpoint, there are two protein compartments in the body: the somatic compartment, represented by proteins in skeletal muscles, and the visceral compartment, represented by protein stores in the visceral organs, primarily the liver. These two compartments are regulated differently, as detailed subsequently. The somatic compartment is affected more severely in marasmus and the visceral compartment is depleted more severely in kwashiorkor. Clinical assessment of undernutrition is discussed next, followed by descriptions of marasmus and kwashiorkor.

The diagnosis of SAM is obvious in its most severe forms. In mild to moderate forms, the usual approach is to compare the body weight for a given height against standard tables; other helpful parameters are fat stores, muscle mass, and levels of certain serum proteins. With a loss of fat, measured skinfold thickness (which includes skin and subcutaneous tissue) is reduced. If the somatic protein compartment is catabolized, the resultant reduction in muscle mass is reflected by reduced circumference of the midarm. Measurement of serum proteins (albumin, transferrin, and others) provides an estimate of the adequacy of the visceral protein compartment. Recent studies suggest a role for the gut microbiome in the pathogenesis of SAM. There is a substantial difference in the microbial flora of children with SAM when compared with the gut
The prevalence of kwashiorkor also is high in impoverished countries of Southeast Asia. Less severe forms may occur worldwide in persons with chronic diarrheal states, in which protein is not absorbed, or in those with chronic protein loss (e.g., protein-losing enteropathies, the nephrotic syndrome, or the aftermath of extensive burns). Rare cases of kwashiorkor resulting from fad diets or replacement of milk by rice-based beverages have been reported in the United States.

In kwashiorkor, unlike in marasmus, marked protein deprivation is associated with severe loss of the visceral protein compartment, and the resultant hypoalbuminemia gives rise to generalized or dependent edema (Fig. 8.17). The weight of children with severe kwashiorkor typically is 60% to 80% of normal. However, the true loss of weight is masked by the increased fluid retention (edema). In further contrast with marasmus, there is relative sparing of subcutaneous fat and muscle mass. The modest loss of these compartments may also be masked by edema.

Children with kwashiorkor have characteristic skin lesions with alternating zones of hyperpigmentation, desquamation, and hypopigmentation, giving a “flaky paint” appearance. Hair changes include loss of color or alternating bands of pale and darker color, straightening, fine texture, and loss of firm attachment to the scalp. Other features that distinguish kwashiorkor from marasmus include an enlarged, fatty liver (resulting from reduced synthesis of the carrier protein component of lipoproteins) and the development of apathy, listlessness, and loss of appetite. As in marasmus, vitamin deficiencies are likely to be present, as are defects in immunity and secondary infections. In kwashiorkor, the inflammation caused by infection produces a catabolic state that aggravates the malnutrition. As already mentioned, marasmus and kwashiorkor represent two ends of a spectrum, and considerable overlap exists.
Secondary Malnutrition

In the United States, secondary malnutrition often develops in chronically ill, older, and bedridden patients. It is estimated that more than 50% of older residents in nursing homes in the United States are malnourished. Weight loss of more than 5% resulting from malnutrition increases the risk of mortality in nursing home patients by almost 5-fold. A particularly severe form of secondary malnutrition, called cachexia, often develops in patients with advanced cancer (Chapter 6). The wasting is all too apparent and often presages death. Although loss of appetite may partly explain it, cachexia may appear before the appetite decreases. The underlying mechanisms are complex, but appear to involve cytokines secreted by tumor cells, particularly TNF, which are released as part of the host response to advanced tumors. These factors directly stimulate the degradation of skeletal muscle proteins, and also stimulate fat mobilization from lipid stores.

MORPHOLOGY

The hallmark anatomic changes in SAM are (1) growth failure, (2) peripheral edema in kwashiorkor, and (3) loss of body fat and atrophy of muscle, more marked in marasmus.

The liver in kwashiorkor, but not in marasmus, is enlarged and fatty; superimposed cirrhosis is rare.

In kwashiorkor (rarely in marasmus) the small bowel shows a decrease in the mitotic index in the crypts of the glands, associated with mucosal atrophy and loss of villi and microvilli. In such cases concurrent loss of small intestinal enzymes occurs, most often manifested as disaccharidase deficiency. Hence, infants with kwashiorkor are lactate intolerant initially and may not respond well to full-strength, milk-based diets. With treatment, the mucosal changes are reversible.

The bone marrow in both kwashiorkor and marasmus may be hypoplastic, mainly as a result of decreased numbers of red cell precursors. Thus, anemia is usually present, most often hypochromic, microcytic due to iron deficiency, but a concurrent deficiency of folate may lead to a mixed microcytic-macrocytic anemia.

The brain in infants who are born to malnourished mothers and who suffer from SAM during the first 1 or 2 years of life has been reported by some investigators to show cerebral atrophy, a reduced number of neurons, and impaired myelination of white matter.

Many other changes may be present, including (1) thymic and lymphoid atrophy (more marked in kwashiorkor than in marasmus), (2) anatomic alterations induced by intercurrent infections, particularly with endemic helminths and other parasites, and (3) deficiencies of other required nutrients such as iodine and vitamins.

Anorexia Nervosa and Bulimia

Anorexia nervosa is a state of self-induced starvation resulting in marked weight loss; bulimia is a condition in which the patient binges on food and then induces vomiting. Bulimia is more common than anorexia nervosa and carries a better prognosis. It is estimated to occur in 1% to 2% of women and 0.1% of men, with an average age at onset of 20 years. These disorders occur primarily in previously healthy young women who have acquired an obsession with attaining or maintaining thinness.

The clinical findings in anorexia nervosa generally are similar to those in SAM. In addition, effects on the endocrine system are prominent. Amenorrhea, resulting from decreased secretion of gonadotropin-releasing hormone (and consequent decreased secretion of luteinizing and follicle-stimulating hormones), is so common that its presence is almost a diagnostic feature. Other common findings, related to decreased thyroid hormone release, include cold intolerance, bradycardia, constipation, and changes in the skin and hair. In addition, dehydration and electrolyte abnormalities are frequent findings. Body hair may be increased but usually is fine and pale (lanugo). Bone density is decreased, most likely because of low estrogen levels, which mimics the postmenopausal acceleration of osteoporosis. As expected with severe malnutrition, anemia, lymphopenia, and hypoalbuminemia may be present. A major complication of anorexia nervosa is an increased susceptibility to cardiac arrhythmia and sudden death, both resulting from hypokalemia.

In bulimia, binge eating is the norm. Huge amounts of food, principally carbohydrates, are ingested, only to be followed by induced vomiting. Although menstrual irregularities are common, amenorrhea occurs in less than 50% of bulimic patients, probably because weight and gonadotropic levels are maintained near normal. The major medical complications are related to continual induced vomiting and chronic use of laxatives and diuretics. These include (1) electrolyte imbalances (hypokalemia), which predispose the patient to cardiac arrhythmias; (2) pulmonary aspiration of gastric contents; and (3) esophageal and stomach rupture. Nevertheless, there are no specific signs and symptoms for this syndrome, and the diagnosis must rely on a comprehensive psychologic assessment of the patient.

Vitamin Deficiencies

Before we summarize the functions of individual vitamins and the consequence of their deficiency, some general comments are in order.

- Thirteen vitamins are necessary for health; four—A, D, E, and K—are fat-soluble and the remainder are water-soluble. The distinction between fat- and water-soluble vitamins is important; although the former are more readily stored in the body, they may be poorly absorbed in fat malabsorption disorders, caused by disturbances of digestive functions (discussed in Chapter 15).
- Certain vitamins can be synthesized endogenously—vitamin D from precursor steroids, vitamin K and biotin by the intestinal microflora, and niacin from tryptophan, an essential amino acid. Notwithstanding this endogenous synthesis, a dietary supply of all vitamins is essential for health.
- Deficiency of a single vitamin is uncommon, and single- or multiple-vitamin deficiencies may accompany concurrent SAM.

In the following sections, vitamins A, D, and C are presented in some detail because of their wide-ranging
functions and the morphologic changes of deficient states. This is followed by a summary in tabular form of the main consequences of deficiencies of the remaining vitamins—E, K, and the B complex—and some essential minerals.

**Vitamin A**

The major functions of vitamin A are maintenance of normal vision, regulation of cell growth and differentiation, and regulation of lipid metabolism. Vitamin A is a generic name for a group of related fat-soluble compounds that include retinol, retinal, and retinoic acid, which have similar biologic activities. Retinol is the chemical name for vitamin A. It is the transport form and, as retinol ester, also the storage form. A widely used term, retinoids, refers to both natural and synthetic chemicals that are structurally related to vitamin A but may not necessarily have vitamin A activity. Animal-derived foods such as liver, fish, eggs, milk, and butter are important dietary sources of preformed vitamin A. Yellow and leafy green vegetables such as carrots, squash, and spinach supply large amounts of carotenoids, many of which are provitamins that are metabolized to active vitamin A in the body. Carotenoids contribute approximately 30% of the vitamin A in human diets; the most important of these is β-carotene, which is efficiently converted to vitamin A. The recommended dietary allowance for vitamin A is expressed in retinol equivalents, to take into account both preformed vitamin A and β-carotene.

Vitamin A is a fat-soluble vitamin, and its absorption requires bile, pancreatic enzymes, and some level of antioxidant activity in the food. Retinol (generally ingested as retinol ester) and β-carotene are absorbed through the intestinal wall, where β-carotene is converted to retinol (Fig. 8.18). Retinol is then transported in chylomicrons, where it is taken up into liver cells through the apolipoprotein E receptor. More than 90% of the body’s vitamin A reserves are stored in the liver, predominantly in the perisinusoidal stellate (Ito) cells. In healthy persons who consume an adequate diet, these reserves are sufficient to support the body’s needs for at least 6 months. Retinol esters stored in the liver can be mobilized; before release, retinol binds to a specific retinol-binding protein (RBP), synthesized in the liver. The uptake of retinol and RBP in peripheral tissues is dependent on cell surface RBP receptors. After uptake by cells, retinol is released, and the RBP is recycled back into the blood. Retinol may be stored in peripheral tissues as retinyl ester or may be oxidized to form retinoic acid.

**Function.** In humans, the best-defined functions of vitamin A are the following:

- *Maintaining normal vision in reduced light.* The visual process involves four forms of vitamin A-containing pigments: rhodopsin, located in rod cells, the most light-sensitive pigment and therefore important in reduced light; and three iodopsins, located in cone cells, each responsive to a specific color in bright light. The synthesis of rhodopsin from retinol involves (1) oxidation to all-trans-retinal, (2) isomerization to 11-cis-retinal, and (3) interaction with opsin to form rhodopsin. A photon of light causes the isomerization of 11-cis-retinal to all-trans-retinal, and a sequence of configuration changes in rhodopsin, which produce a visual signal. In the process, a nerve impulse is generated (by changes in membrane potential) and transmitted by means of neurons from the retina to the brain. During dark adaptation, some of the all-trans-retinal is reconverted to 11-cis-retinal, but most is reduced to retinol and lost to the retina, explaining the need for a continuous supply of retinol.

- *Potentiating the differentiation of specialized epithelial cells.* Vitamin A and retinoids play an important role in the orderly differentiation of mucus-secreting columnar epithelium; when a deficiency state exists, the epithelium undergoes squamous metaplasia, differentiating into a keratinizing epithelium. Activation of retinoic acid receptors (RARs) by their ligands causes the release of corepressors and the obligatory formation of heterodimers with another retinoid receptor, known as the retinoic X receptor (RXR). Both RAR and RXR have three
In addition, the retinoids, β-carotene, and some related carotenoids can function as photoprotective and antioxidant agents. Retinoids have broad biologic effects, including effects on embryonic development, cellular differentiation and proliferation, and lipid metabolism.

Retinoids are used clinically to treat skin disorders such as severe acne and certain forms of psoriasis, and also to treat acute promyelocytic leukemia. As discussed in Chapter 6, all-trans-retinoic acid induces the differentiation and subsequent apoptosis of acute promyelocytic leukemia cells through its ability to bind to a PML-RARα fusion protein that characterizes this form of cancer.

Deficiency States. Vitamin A deficiency occurs worldwide as a consequence of either poor nutrition or fat malabsorption. In children, stores of vitamin A are depleted by infections, and the absorption of the vitamin is poor in newborn infants. In adults, vitamin A deficiency, in conjunction with depletion of other fat-soluble vitamins, may develop in patients with malabsorption syndromes, such as celiac disease, Crohn disease, and colitis. Bariatric surgery and the continuous use of mineral oil laxatives also may lead to deficiency. The multiple effects of vitamin A deficiency are as follows:

• As was already discussed, vitamin A is a component of rhodopsin and other visual pigments. Not surprisingly, one of the earliest manifestations of vitamin A deficiency is impaired vision, particularly in reduced light (night blindness).

• Other effects of vitamin A deficiency are related to its role in maintaining the differentiation of epithelial cells (Fig. 8.19). Persistent deficiency gives rise to a series of changes involving epithelial metaplasia and keratization. The most devastating changes occur in the eyes and result in the clinical entity referred to as xerophthalmia (dry eye). First, there is dryness of the conjunctiva (xerosis conjunctivae) as the normal lachrymal and...
mucus-secreting epithelium are replaced by keratinized epithelium. This is followed by a buildup of keratin debris in small opaque plaques (Bilot spots) and, eventually, the erosion of the roughened corneal surface, leading to softening and destruction of the cornea (keratomalacia) and total blindness.

• Vitamin A deficiency also leads to replacement of the epithelium lining the upper respiratory passage and urinary tract by keratinizing squamous cells (squamous metaplasia). Loss of the mucociliary epithelium of the airways predisposes affected patients to pulmonary infections, and desquamation of keratin debris in the urinary tract predisposes to renal and bladder stones. Hyperplasia and hyperkeratinization of the epidermis with plugging of the ducts of the adnexal glands may produce follicular or papular dermatosis.

• Another serious consequence of the lack of vitamin A is immune deficiency. This impairment of immunity leads to higher mortality rates from common infections such as measles, pneumonia, and infectious diarrhea. In parts of the world with a high prevalence of vitamin A deficiency, dietary supplements reduce mortality rates for infectious disorders by 20% to 30%.

**Vitamin A Toxicity.** Both short- and long-term excesses of vitamin A may produce toxic manifestations—a point of concern because of the megadoses being touted by certain sellers of supplements. The consequences of acute hypervitaminosis A were first described in 1597 by Gerrit de Veer, a ship’s carpenter stranded in the Arctic, who recounted in his diary the serious symptoms that he and other crew members developed after eating polar bear liver. With this cautionary tale in mind, the adventurous eater should note that acute vitamin A toxicity also has been described in “hepatoaficionados” who feasted on the livers of whales, sharks, and even tuna!

The signs and symptoms of acute toxicity include headache, dizziness, vomiting, stupor, and blurred vision—all of which may be confused with those of a brain tumor. Chronic toxicity is associated with weight loss, anorexia, nausea, vomiting, and bone and joint pain. Retinoic acid stimulates the production and function of osteoclasts, leading to increased bone resorption and a consequent high risk of fractures. Although synthetic retinoids used for the treatment of acne are not associated with these complications, their use in pregnancy must be avoided because of the well-established teratogenic effect of retinoids.

**Vitamin D**

The major function of the fat-soluble vitamin D is the maintenance of adequate plasma levels of calcium and phosphorus to support metabolic functions, bone mineralization, and neuromuscular transmission. In this capacity, the vitamin is required for the prevention of bone diseases known as rickets (in children whose epiphyses have not already closed), osteomalacia (in adults), and hypocalcemic tetany. With respect to tetany, vitamin D maintains the correct concentration of ionized calcium in the extracellular fluid compartment. When deficiency develops, the drop in ionized calcium in the extracellular fluid results in continuous excitation of muscle (tetany). It should be noted, however, that any reduction in the level of serum calcium is rapidly corrected by excess secretion of parathyroid hormone. Hence tetany is quite uncommon. Our attention here is focused on the function of vitamin D in the regulation of serum calcium levels.

**Metabolism.** The major source of vitamin D for humans is its endogenous synthesis in the skin by photochemical conversion of a precursor, 7-dehydrocholesterol, powered by the energy of solar or artificial UV light. Irradiation of this compound forms cholecalciferol, known as vitamin D₃; in the following discussion, for the sake of simplicity, the term vitamin D is used to refer to this compound. Under usual conditions of sun exposure, approximately 90% of the vitamin D needed is endogenously derived from 7-dehydrocholesterol present in the skin. However, blacks may have a lower level of vitamin D production in the skin because of melanin pigmentation (perhaps a small price to pay for protection against UV-induced cancers). The small remainder comes from dietary sources, such as deep-sea fish, plants, and grains. In plant sources, vitamin D is present in a precursor form, ergosterol, which is converted to vitamin D in the body.

The metabolism of vitamin D can be outlined as follows (Fig. 8.20):

1. Absorption of vitamin D along with other fats in the gut (or synthesis from precursors in the skin)
2. Binding to plasma α₂-globulin (vitamin D-binding protein) and transport to liver
3. Conversion to 25-hydroxyvitamin D (25-OH-D) by 25-hydroxylase in the liver
4. Conversion of 25-OH-D to 1,25-dihydroxyvitamin D [1,25-(OH)₂-D] (biologically the most active form of vitamin D) by α₁-hydroxylase in the kidney

Renal production of 1,25-(OH)₂-D is regulated by three mechanisms:

• Hypocalcemia stimulates secretion of parathyroid hormone (PTH), which in turn augments the conversion of 25-OH-D to 1,25-(OH)₂-D by activating α₁-hydroxylase.
• Hypophosphatemia directly activates α₁-hydroxylase, thereby increasing the formation of 1,25(OH)₂-D.
• In a feedback loop, increased levels of 1,25-(OH)₂-D downregulate the synthesis of this metabolite by inhibiting the action of α₁-hydroxylase (decreases in 1,25-(OH)₂-D have the opposite effect).

**Functions.** Like retinoids and steroid hormones, 1,25-(OH)₂-D acts by binding to a high-affinity nuclear receptor that in turn binds to regulatory DNA sequences, thereby inducing transcription of specific target genes. The receptors for 1,25-(OH)₂-D are present in most nucleated cells of the body, and they transduce signals that result in various biologic activities, beyond those involved in calcium and phosphorus homeostasis. Nevertheless, the best-understood functions of vitamin D relate to the maintenance of normal plasma levels of calcium and phosphorus, through action on the intestines, bones, and kidneys (Fig. 8.20).

The active form of vitamin D:

• Stimulates intestinal absorption of calcium through upregulation of calcium transport, in enterocytes
VITAMIN D DEFICIENCY

1. **α-1-hydroxylase**

2. 1,25-(OH)\(_2\)D

3. **Ca and P absorption**

4. PTH

5. Mobilization of Ca and P

6. **Serum Ca x P product**

7. Poor bone mineralization

**A**

NORMAL VITAMIN D METABOLISM

Ultraviolet irradiation of 7-dehydrocholesterol in skin

Vitamin D in blood

D-25-hydroxylase

25-OH-D

**B**

Fig. 8.20 (A) Normal vitamin D metabolism. (B) Vitamin D deficiency. There is inadequate substrate for the renal hydroxylase (1), yielding a deficiency of 1,25-(OH)\(_2\)D (2), and deficient absorption of calcium and phosphorus from the gut (3), with consequent depressed serum levels of both (4). The hypocalcemia activates the parathyroid glands (5), causing mobilization of calcium and phosphorus from bone (6a). Simultaneously, parathyroid hormone (PTH) induces wasting of phosphatase in the urine (6b) and calcium retention. Consequently, the serum levels of calcium are normal or nearly normal, but the phosphate is low; hence, mineralization is impaired (7).

- **Stimulates calcium resorption in renal distal tubules.**
- **Collaborates with PTH to regulate blood calcium.** This occurs in part through upregulation of RANK ligand on osteoblasts, which in turn activates RANK receptors on osteoclast precursors. RANK activation produces signals that increase osteoclast differentiation and bone resorptive activities (Chapter 21).
- **Promotes the mineralization of bone.** Vitamin D is needed for the mineralization of osteoid matrix and epiphyseal cartilage during the formation of flat and long bones. It stimulates osteoblasts to synthesize the calcium-binding protein osteocalcin, which promotes calcium deposition.

**Deficiency States**

**Vitamin D deficiency causes rickets in growing children and osteomalacia in adults;** these skeletal diseases have worldwide distribution. They may result from diets deficient in calcium and vitamin D, but probably more important is limited exposure to sunlight (for instance, in heavily veiled women; children born to mothers who have frequent pregnancies followed by lactation, which leads to vitamin D deficiency; and inhabitants of northern climates with scant sunlight). Other, less common causes of rickets and osteomalacia include renal disorders causing decreased synthesis of 1,25-(OH)\(_2\)-D or phosphate depletion, and malabsorption disorders. Although rickets and osteomalacia rarely occur outside high-risk groups, milder forms of vitamin D deficiency (also called vitamin D insufficiency) leading to bone loss and hip fractures are common among elderly persons. Studies also suggest that vitamin D may be important for preventing demineralization of bones. It appears that certain genetically determined variants of the vitamin D receptor are associated with an accelerated loss of bone minerals with aging and certain familial forms of osteoporosis (Chapter 21).

Whatever the basis, a deficiency of vitamin D tends to cause hypocalcemia. This in turn stimulates PTH production, which (1) activates renal α-1-hydroxylase, increasing the amount of active vitamin D and calcium absorption; (2) mobilizes calcium from bone; (3) decreases renal calcium excretion; and (4) increases renal excretion of phosphate. Thus, the serum level of calcium is restored to near normal, but hypophosphatemia persists, so mineralization of bone is impaired or there is high bone turnover.

An understanding of the morphologic changes in rickets and osteomalacia is facilitated by a brief summary of normal bone development and maintenance. The development of flat bones in the skeleton involves intramembranous ossification, whereas the formation of long tubular bones proceeds by endochondral ossification. With intramembranous bone formation, mesenchymal cells differentiate directly into osteoblasts, which synthesize the collagenous osteoid matrix on which calcium is deposited. By contrast, with endochondral ossification, growing cartilage at the epiphyseal plates is provisionally mineralized and then progressively resorbed and replaced by osteoid matrix, which undergoes mineralization to create bone (Fig. 8.21A).

**MORPHOLOGY**

The basic derangement in both rickets and osteomalacia is an excess of unmineralized bone matrix. The changes that occur in the growing bones of children with rickets, however, are complicated by inadequate provisional calcification.
of epiphyseal cartilage, deranging endochondral bone growth. The following sequence ensues in rickets:

- Overgrowth of epiphyseal cartilage caused by inadequate provisional calcification and failure of the cartilage cells to mature and disintegrate
- Persistence of distorted, irregular masses of cartilage, many of which project into the marrow cavity
- Deposition of osteoid matrix on inadequately mineralized cartilaginous remnants
- Disruption of the orderly replacement of cartilage by osteoid matrix, with enlargement and lateral expansion of the costochondral junction (Fig. 8.21B)
- Abnormal overgrowth of capillaries and fibroblasts in the disorganized zone resulting from microfractures and stresses on the inadequately mineralized, weak, poorly formed bone
- Deformation of the skeleton resulting from the loss of structural rigidity of the developing bones

The gross skeletal changes depend on the severity of the rachitic process: its duration; and, in particular, the stresses to which individual bones are subjected. During the nonambulatory stage of infancy, the head and chest sustain the greatest stresses. The softened occipital bones may become flattened, and the parietal bones can be buckled inward by pressure; with the release of the pressure, elastic recoil snaps the bones back into their original positions (craniotabes). An excess of osteoid produces frontal bossing and a squared appearance to the head. Deformation of the chest results from overgrowth of cartilage or osteoid tissue at the costochondral junction, producing the “rachitic rosary.” The weakened metaphyseal areas of the ribs are subject to the pull of the respiratory muscles, causing them to bend inward creating anterior protrusion of the sternum (pigeon breast deformity). The inward pull at the margin of the diaphragm creates the Harrison groove, girdling the thoracic cavity at the lower margin of the rib cage. The pelvis may become deformed. When an ambulating child develops rickets, deformities are likely to affect the spine, pelvis, and long bones (e.g., tibia), causing, most notably, lumbar lordosis and bowing of the legs (Fig. 8.21C).

In adults with osteomalacia, the lack of vitamin D deranges the normal bone remodeling that occurs throughout life. The newly formed osteoid matrix laid down by osteoblasts is inadequately mineralized, producing the excess of persistent osteoid that is characteristic of osteomalacia. Although the contours of the bone are not affected, the bone is weak and vulnerable to gross fractures or microfractures, which are most likely to affect vertebral bodies and femoral necks. On histologic examination, the unmineralized osteoid can be visualized as a thickened layer of matrix (which stains pink in hematoxylin and eosin preparations) arranged about the more basophilic, normally mineralized trabeculae.

**Nonskeletal Effects of Vitamin D.** As mentioned earlier, the vitamin D receptor is present in various cells and tissues that do not participate in calcium and phosphorus homeostasis. In addition, macrophages, keratinocytes, and tissues such as breast, prostate, and colon can produce 1,25-dihydroxyvitamin D. It appears that pathogen-induced activation of Toll-like receptors in macrophages causes increased expression of vitamin D receptor as well as increased local synthesis of 1,25-dihydroxyvitamin D. This causes activation of vitamin-D-dependent gene expression in macrophages and other neighboring immune cells. The net effect of these changes on the immune response remains to be determined. It appears that in some patients with tuberculosis, vitamin D supplements increase lymphocyte counts and enhance the clearance of *Mycobacterium tuberculosis*. It has also been reported that low levels
of 1,25-dihydroxyvitamin D (<20 ng/mL) are associated with a 30% to 50% increase in the incidence of colon, prostate, and breast cancers, but whether or not vitamin D supplementation can reduce cancer risk has not been firmly established.

**Toxicity.** Prolonged exposure to sunlight may cause sunburns but it does not produce an excess of vitamin D, but megadoses of orally administered vitamin can lead to hypervitaminosis. In children, hypervitaminosis D may take the form of metastatic calcifications of soft tissues such as the kidney; in adults, it causes bone pain and hypercalcemia. As a point of some interest, the toxic potential of this vitamin is so great that in sufficiently large doses it is a potent rodenticide!

**Vitamin C (Ascorbic Acid)**

A deficiency of water-soluble vitamin C leads to the development of scurvy, characterized principally by bone disease in growing children and by hemorrhages and healing defects in both children and adults. Sailors of the British Royal Navy were nicknamed “limeys” because at the end of the 18th century the Navy began to provide lime and lemon juice to them to prevent scurvy during their long sojourns at sea. It was not until 1932 that ascorbic acid was identified and synthesized. Unlike vitamin D, ascorbic acid is not synthesized endogenously in humans, who therefore are entirely dependent on the diet for this nutrient. Vitamin C is present in milk and some animal products (liver, fish) and is abundant in a variety of fruits and vegetables. All but the most restricted diets provide adequate amounts of vitamin C.

**Function.** Ascorbic acid acts in a variety of biosynthetic pathways by accelerating hydroxylation and amidation reactions. The most clearly established function of vitamin C is the activation of prolyl and lysyl hydroxylases from inactive precursors, allowing for hydroxylation of procollagen. Inadequately hydroxylated procollagen cannot acquire a stable helical configuration or be adequately crosslinked, so it is poorly secreted from the fibroblasts. Those molecules that are secreted lack tensile strength, are more soluble, and are more vulnerable to enzymatic degradation. Collagen, which normally has the highest content of hydroxyproline, is most affected, particularly in blood vessels, accounting for the predisposition to hemorrhages in scurvy. In addition, a deficiency of vitamin C suppresses the synthesis of collagen polypeptides, independent of effects on proline hydroxylation. Vitamin C also has anti-oxidant properties. These include an ability to scavenge free radicals directly and the participation in metabolic reactions that regenerate the anti-oxidant form of vitamin E.

**Deficiency States.** Consequences of vitamin C deficiency are illustrated in Fig. 8.22. Fortunately, because of the abundance of ascorbic acid in foods, scurvy has ceased to be a global problem. It is sometimes encountered in affluent populations as a secondary deficiency, particularly among elderly persons, people who live alone, and chronic alcoholics — groups often characterized by erratic and inadequate eating patterns. Occasionally, scurvy appears in patients undergoing peritoneal dialysis and hemodialysis and among food faddists.

**Toxicity.** The popular notion that megadoses of vitamin C protect against the common cold or at least allay the symptoms has not been borne out by controlled clinical studies. Such slight relief as may be experienced probably is a result of the mild antihistamine action of ascorbic acid. The large excess of vitamin C is promptly excreted in the urine but may cause uricosuria and increased absorption of iron, with the potential for iron overload.

Other vitamins and some essential minerals are listed and briefly described in Tables 8.9 and 8.10. Folic acid and vitamin B₁₂ are discussed in Chapter 12.
Table 8.9 Vitamins: Major Functions and Deficiency Syndromes

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Functions</th>
<th>Deficiency Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fat-Soluble</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td>A component of visual pigment, Maintenance of specialized epithelia, Maintenance of resistance to infection</td>
<td>Night blindness, xerophthalmia, blindness Squamous metaplasia Vulnerability to infection, particularly measles</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Facilitates intestinal absorption of calcium and phosphorus and mineralization of bone</td>
<td>Rickets in children Osteomalacia in adults</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Major anti-oxidant; scavenges free radicals</td>
<td>Spinocerebellar degeneration</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Cofactor in hepatic carboxylation of procoagulants—factors II (prothrombin), VII, IX, X; and protein C and protein S</td>
<td>Bleeding diathesis</td>
</tr>
<tr>
<td><strong>Water-Soluble</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁ (thiamine)</td>
<td>As pyrophosphate, is coenzyme in decarboxylation reactions</td>
<td>Dry and wet beriberi, Wernicke syndrome, Korsakoff syndrome</td>
</tr>
<tr>
<td>Vitamin B₂ (riboflavin)</td>
<td>Converted to coenzymes flavin mononucleotide and flavin adenine dinucleotide, cofactors for many enzymes in intermediary metabolism</td>
<td>Cheliosis, stomatitis, glossitis, dermatitis, corneal vascularization</td>
</tr>
<tr>
<td>Niacin</td>
<td>Incorporated into nicotinamide adenine dinucleotide (NAD) and NAD phosphate; involved in a variety of oxidation-reduction (redox) reactions</td>
<td>Pellagra—“three Ds”: dementia, dermatitis, diarrhea</td>
</tr>
<tr>
<td>Vitamin B₆ (pyridoxine)</td>
<td>Derivatives serve as coenzymes in many intermediary reactions</td>
<td>Cheliosis, glossitis, dermatitis, peripheral neuropathy</td>
</tr>
<tr>
<td>Vitamin B₁₂ a</td>
<td>Required for normal folate metabolism and DNA synthesis</td>
<td>Combined system disease (megaloblastic anemia and degeneration of posteroselateral spinal cord tracts)</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Serves in many redox reactions and hydroxylations of collagen</td>
<td>Scurvy</td>
</tr>
<tr>
<td>Folate b</td>
<td>Essential for transfer and use of one-carbon units in DNA synthesis</td>
<td>Megaloblastic anemia, neural tube defects</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>Incorporated into coenzyme A</td>
<td>No nonexperimental anemia recognized</td>
</tr>
<tr>
<td>Biotin</td>
<td>Cofactor in carboxylation reactions</td>
<td>No clearly defined clinical syndrome</td>
</tr>
</tbody>
</table>

aSee also Chapter 12.

Table 8.10 Selected Trace Elements and Deficiency Syndromes

<table>
<thead>
<tr>
<th>Element</th>
<th>Function</th>
<th>Basis of Deficiency</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>Component of enzymes, principally oxidases</td>
<td>Inadequate supplementation in artificial diets Interference with absorption by other dietary constituents Inborn error of metabolism</td>
<td>Rash around eyes, mouth, nose, and anus called acrodermatitis enteropathica Anorexia and diarrhea Growth retardation in children Depressed mental function Depressed wound healing and immune response Impaired night vision Infertility</td>
</tr>
<tr>
<td>Iron</td>
<td>Essential component of hemoglobin as well as several iron-containing metalloenzymes</td>
<td>Inadequate diet Chronic diet loss</td>
<td>Hypochromic, microcytic anemia</td>
</tr>
<tr>
<td>Iodine</td>
<td>Component of thyroid hormone</td>
<td>Inadequate supply in food and water</td>
<td>Goiter and hypothyroidism</td>
</tr>
<tr>
<td>Copper</td>
<td>Component of cytochrome c oxidase, dopamine β-hydroxylase, tyrosinase, and lysyl oxidase (involved in crosslinking collagen)</td>
<td>Inadequate supplementation in artificial diet Interference with absorption</td>
<td>Muscle weakness Neurologic defects Abnormal collagen crosslinking</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Replaces calcium during remineralization of teeth, producing fluorapatite, which is more resistant to acids</td>
<td>Inadequate supply in soil and water</td>
<td>Dental caries</td>
</tr>
<tr>
<td>Selenium</td>
<td>Component of GSH peroxidase Anti-oxidant with vitamin E</td>
<td>Inadequate amounts in soil and water</td>
<td>Myopathy Cardiomyopathy (Keshan disease)</td>
</tr>
</tbody>
</table>
SUMMARY

NUTRITIONAL DISEASES

- Primary SAM is a common cause of childhood deaths in poor countries. The two main primary SAM syndromes are marasmus and kwashiorkor. Secondary SAM occurs in the chronically ill and in patients with advanced cancer (as a result of cachexia).
- Kwashiorkor is characterized by hypoaalbuminemia, generalized edema, fatty liver, skin changes, and defects in immunity. It is caused by diets low in protein but normal in calories.
- Marasmus is characterized by emaciation resulting from loss of muscle mass and fat with relative preservation of serum albumin. It is caused by diets severely lacking in calories—both protein and nonprotein.
- Anorexia nervosa is self-induced starvation; it is characterized by amenorrhea and multiple manifestations of low thyroid hormone levels. Bulimia is a condition in which food binges alternate with induced vomiting.
- Vitamins A and D are fat-soluble vitamins with a wide range of activities. Vitamin C and members of the vitamin B family are water-soluble (Table 8.9 lists vitamin functions and deficiency syndromes).

Obesity

Excess adiposity (obesity) and excess body weight are associated with increased incidence of several of the most important diseases of humans, including type 2 diabetes, dyslipidemias, cardiovascular disease, hypertension, and cancer. It is a major public health problem in developed countries and an emerging health problem in developing nations, such as India. In the United States, obesity has reached epidemic proportions. The prevalence of obesity increased from 13% to 34% between 1960 and 2008, and as of 2015, 68.6% of Americans between 20 and 75 years of age were overweight as were 17% of the children. Globally, the World Health Organization (WHO) estimates that in 2015, 700 million adults were obese. The causes of this epidemic are complex but undoubtedly are related to societal changes in diet and levels of physical activity. Obesity is defined as a state of increased body weight, caused by adipose tissue accumulation, that is of sufficient magnitude to produce adverse health effects. How does one measure fat accumulation? Several high-tech methods have been devised, but for practical purposes the body mass index (BMI) is most commonly used. BMI is calculated as (weight in kilograms)/(height in meters)$^2$, or kg/m$^2$.

The BMI is closely correlated with body fat. BMIs in the range 18.5 to 25 kg/m$^2$ are considered normal, whereas BMIs between 25 and 30 kg/m$^2$ identify the overweight, and BMIs greater than 30 kg/m$^2$, the obese. It is generally agreed that a BMI greater than 30 kg/m$^2$ imparts a health risk. In the following discussion, for the sake of simplicity, the term obesity is applied to both the overweight and the truly obese.

The untoward effects of obesity are related not only to the total body weight but also to the distribution of the stored fat. Central, or visceral, obesity, in which fat accumulates in the trunk and in the abdominal cavity (in the mesentery and around visera), is associated with a much higher risk for several diseases than is a condition of excess accumulation of fat in a diffuse distribution in subcutaneous tissue.

The etiology of obesity is complex and incompletely understood. Involved are genetic, environmental, and psychologic factors. However, simply put, obesity is a disorder of energy balance. The two sides of the energy equation, intake and expenditure, are finely regulated by neural and hormonal mechanisms, so that body weight is maintained within a narrow range for many years. Apparently, this fine balance is controlled by an internal set point, or “lipostat,” that senses the quantity of energy stores (adipose tissue) and appropriately regulates food intake as well as energy expenditure. Several “obesity genes” have been identified. As might be expected, they encode the molecular components of the physiologic system that regulates energy balance. A key player in energy homeostasis is the LEP gene and its product, leptin. This unique member of the cytokine family, secreted by adipocytes, regulates both sides of the energy equation—intake of food and expenditure of energy. As discussed later, the net effect of leptin is to reduce food intake and to enhance the expenditure of energy.

In a simplified way, the neurohumoral mechanisms that regulate energy balance and body weight may be divided into three components (Fig. 8.23):

- The peripheral or afferent system generates signals from various sites. Its main components are leptin and adiponectin produced by fat cells, insulin from the pancreas, ghrelin from the stomach, and peptide YY from the ileum and colon. Leptin reduces food intake and is discussed in further detail later. Ghrelin secretion stimulates appetite, and it may function as a “meal-initiating” signal. Peptide YY, which is released postprandially by endocrine cells in the ileum and colon, is a satiety signal.
- The arcuate nucleus in the hypothalamus, processes and integrates the peripheral signals and generates new signals that are transmitted by (1) POMC (proopiomelanocortin) and CART (cocaine- and amphetamine-regulated transcript) neurons; and (2) NPY (neuropeptide Y) and AgRP (agouti-related peptide) neurons.
- The efferent system, which consists of hypothalamic neurons regulated by the arcuate nucleus, is organized along two pathways, anabolic and catabolic, which control food intake and energy expenditure, respectively.

POMC/CART neurons activate efferent neurons that enhance energy expenditure and weight loss through the production of molecules such as α-melanocyte stimulating hormone (MSH) that reduce food intake (anorexigenic effect). MSH signals through melanocortin receptor (MC4R). By contrast NPY/AgRP neurons activate efferent neurons that promote food intake (orexigenic effect) and weight gain. Signals transmitted by efferent neurons also communicate with forebrain and midbrain centers that control the autonomic nervous system.

Discussed next are two important components of the afferent system that regulate appetite and satiety: leptin and gut hormones, and adiponectin that regulates fat consumption.
**Leptin**

**Leptin is secreted by fat cells, and its output is regulated by the adequacy of fat stores.** BMI and body fat stores are directly related to leptin secretion. With abundant adipose tissue, leptin secretion is stimulated, and the hormone crosses the blood–brain barrier and travels to the hypothalamus, where it reduces food intake by stimulating POMC/CART neurons and inhibiting NPY/AgRP neurons. The opposite sequence of events occurs when there are inadequate stores of body fat: Leptin secretion is diminished and food intake is increased. In persons of stable weight, the activities of these pathways are balanced. Leptin also increases energy expenditure by stimulating physical activity, energy expenditure, and *thermogenesis*, and these may be the most important catabolic effects mediated by leptin through the hypothalamus. Although the effects of leptin on food intake and energy expenditure can be readily demonstrated in nonobese mice and humans, the anorexigenic response of leptin is blunted in states of obesity despite high levels of circulating leptin. Such leptin resistance in obese mice can be bypassed by intraventricular injection of leptin. In keeping with this observation,
injections of leptin in obese humans fail to affect food intake and energy expenditure, dashing initial enthusiasm of leptin therapy for obesity.

In rodents and humans, loss-of-function mutations affecting components of the leptin pathway give rise to massive obesity. Mice with mutations that disable the leptin gene or its receptor fail to sense the adequacy of fat stores, so they behave as if they are undernourished, eating ravenously. As in mice, mutations of the leptin gene or receptor in humans, although rare, may cause massive obesity. More common are mutations in the melanocortin receptor-4 gene (MC4R), found in 4% to 5% of patients with massive obesity. As mentioned earlier, MSH sends satiety signals by binding to this receptor. These monogenic traits underscore the importance of the leptin pathway in the control of body weight, and it is possible that more common types of defects in this pathway will be discovered in the obese. In closing it should be mentioned that, like leptin, insulin also exerts anorexigenic responses. However, the mechanism of this effect of insulin is less clear, and most of the evidence suggests the primacy of leptin in the regulation of adiposity.

**Adiponectin**

Adiponectin, produced in the adipose tissue, has been called a “fat-burning molecule” and the “guardian angel against obesity.” It directs fatty acids to muscle for their oxidation. It decreases the influx of fatty acids to the liver and the total hepatic triglyceride content. It also decreases glucose production in the liver, causing an increase in insulin sensitivity and protecting against the metabolic syndrome. In addition to its metabolic effects, adiponectin has anti-diabetic, anti-inflammatory, anti-atherogenic, anti-proliferative, and cardioprotective effects. Its serum levels are lower in obese than in lean individuals. These effects contribute to obesity-associated insulin resistance, type 2 diabetes, nonalcoholic fatty liver disease (Chapter 14), and possibly increased risk of certain cancers, discussed later.

**Adipose Tissue and Other Mediators**

In addition to leptin and adiponectin, adipose tissue produces other mediators, such as cytokines, chemokines, and steroid hormones, which allow adipose tissue to function as a link between lipid metabolism, nutrition, and inflammatory responses. The total number of adipocytes is established by the time of adolescence and is higher in people who were obese as children, providing another reason for concern about childhood obesity. Although in adults approximately 10% of adipocytes turn over annually, the number of adipocytes remains constant, regardless of individual body mass. Diets fail in part because the loss of fat from adipocytes causes leptin levels to fall, stimulating the appetite and diminishing energy expenditure.

**Gut Hormones**

Gut hormones are rapidly acting initiators and terminators of volitional eating. Prototypical examples are ghrelin and peptide YY (PYY). Ghrelin is produced in the stomach and the arcuate nucleus of the hypothalamus. It increases food intake, acting most likely by stimulating the NPY/AgRP neurons in the hypothalamus. Ghrelin levels normally rise before meals and fall 1 to 2 hours afterward, but this drop is attenuated in obese persons. Ghrelin levels are lower in obese individuals as compared to those with normal weight, and they increase with a reduction in obesity. Interestingly, the rise in ghrelin levels is much reduced in individuals in whom gastric bypass surgery is performed for the treatment of obesity, suggesting that the beneficial effects of such surgery may be in part due to a reduced surface of gastric mucosa that is exposed to food.

PYY is secreted from endocrine cells in the ileum and colon in response to the consumption of food. It decreases appetite and augments a sense of fullness (satiety). It acts, presumably, by stimulating POMC/CART neurons in the hypothalamus, thereby decreasing food intake.

PYY also reduces the rate of gastric emptying and intestinal motility (“ilea brake”), all of which contribute to satiety. PYY levels are reduced with obesity and may be of therapeutic value in the treatment of those who are overweight or obese.

**The Role of Gut Microbiome**

An interesting series of observations suggest that the gut microbiome may be involved in the development of obesity. In support of this notion is the finding that the profiles of gut microbiota differ between genetically obese mice and their lean littermates. The microbiome of genetically obese mice can harvest much more energy from food as compared to that of lean mice. Colonization of the gut of germfree mice by microbiota from obese mice (but not microbiota from lean mice) is associated with increased body weight. The relevance of these models to human obesity is tantalizing but remains to be proven.

**Clinical Consequences of Obesity**

Obesity, particularly central obesity, is a known risk factor for a number of conditions, including type 2 diabetes, cardiovascular disease, and cancer. Central obesity also stands at the center of a cluster of alterations known as the metabolic syndrome, characterized by abnormalities of glucose and lipid metabolism coupled with hypertension and evidence of a systemic proinflammatory state. This seems to be caused by the inflammasome response to free fatty acids and excess levels of lipids in cells and tissue. The inflammasome stimulates secretion of IL-1, which induces insulin resistance. The following associations are worthy of note:

- **Obesity is associated with insulin resistance and hyperinsulinemia**, important features of type 2 diabetes (Chapter 20). Excess insulin, in turn, may play a role in the retention of sodium, expansion of blood volume, production of excess norepinephrine, and smooth muscle proliferation that are the hallmarks of hypertension. Whatever the mechanism, the risk of developing hypertension among previously normotensive persons increases proportionately with weight.
- **Obese persons generally have hypertriglyceridemia and low HDL cholesterol levels**, factors that increase the risk of coronary artery disease. The association between obesity and heart disease is not straightforward, however, and such linkage as there is relates more to the associated diabetes and hypertension than to weight per se.
Insulin resistance leads to hyperglycemia six times more common in obese than in lean subjects. The mechanism is mainly an increase in total body cholesterol, increased cholesterol turnover, and augmented biliary excretion of cholesterol in the bile, which in turn predisposes affected persons to the formation of cholesterol-rich gallstones (Chapter 16).

Hyperventilation syndrome is a constellation of respiratory abnormalities in very obese persons. It has been called the pickwickian syndrome, after the fat lad who was constantly falling asleep in Charles Dickens’ *The Pickwick Papers*. Hypersomnia, both at night and during the day, is characteristic and is often associated with apneic pauses during sleep (sleep apnea), polycythemia, and eventual right-sided heart failure.

Marked adiposity is a predisposing factor for the development of degenerative joint disease (osteoarthritis). This form of arthritis, which typically appears in older persons, is attributed in large part to the cumulative effects of wear and tear on joints. The greater the body burden of fat, the greater the trauma to joints with the passage of time.

Markers of inflammation, such as C-reactive protein (CRP) and proinflammatory cytokines like TNF, are often elevated in obese persons. The basis for the inflammation is uncertain; both a direct proinflammatory effect of excess circulating lipids and increased release of cytokines from fat-laden adipocytes have been proposed. Whatever the cause, it is thought that chronic inflammation may contribute to many of the complications of obesity, including insulin resistance, metabolic abnormalities, thrombosis, cardiovascular disease, and cancer.

**Obesity and Cancer**

There is an increased incidence of certain cancers in the overweight, including cancers of the esophagus, thyroid, colon, and kidney in men and cancers of the esophagus, endometrium, gallbladder, and kidney in women. Overall, obesity is associated with approximately 20% of cancer deaths in women and 14% of deaths in men. The underlying mechanisms are unknown and are likely to be multiple.

- **Elevated insulin levels.** Insulin resistance leads to hyperinsulinemia, which includes multiple effects that may directly or indirectly contribute to cancer. For example, hyperinsulinemia causes a rise in levels of free insulin-like growth factor-1 (IGF-1). IGF-1 is a mitogen, and its receptor, IGFR-1, is highly expressed in many human cancers. IGFR-1 activates the RAS and PI3K/AKT pathways, which promote the growth of both normal and neoplastic cells (Chapter 6).
- **Obesity has effects on steroid hormones** that regulate cell growth and differentiation in the breast, uterus, and other tissues. Specifically, obesity increases the synthesis of estrogen from androgen precursors, increases androgen synthesis in ovaries and adrenals, and enhances estrogen availability in obese persons by inhibiting the production of sex-hormone-binding globulin (SHBG) in the liver.
- As discussed earlier, adiponectin secretion from adipose tissue is reduced in obese individuals. Adiponectin suppresses cell proliferation and promotes apoptosis. It also counteracts the actions of p53 and p21. In obese individuals these anti-neoplastic actions of adiponectin may be compromised.
- The proinflammatory state that is associated with obesity may itself be carcinogenic, through mechanisms discussed in Chapter 6.

### SUMMARY

#### OBESITY

- Obesity is a disorder of energy regulation. It increases the risk for a number of important conditions such as insulin resistance, type 2 diabetes, hypertension, and hypertriglyceridemia, which are associated with the development of coronary artery disease.
- The regulation of energy balance is very complex. It has three main components: (1) afferent signals, provided mostly by insulin, leptin, ghrelin, and peptide YY; (2) the central hypothalamic system, which integrates afferent signals and triggers the efferent signals; and (3) efferent signals, which control energy balance.
- Leptin plays a key role in energy balance. Its output from adipose tissues is regulated by the abundance of fat stores. Leptin binding to its receptors in the hypothalamus reduces food intake by stimulating POMC/CART neurons and inhibiting NPY/AgRP neurons.
- In addition to diabetes and cardiovascular disease, obesity also is associated with increased risk for certain cancers, nonalcoholic fatty liver disease, and gallstones.

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**Diet and Systemic Diseases**

The problems of under- and overnutrition, as well as specific nutrient deficiencies, have been discussed; however, the composition of the diet, even in the absence of any of these problems, may make a significant contribution to the causation and progression of a number of diseases. A few examples suffice here.

Currently, one of the most important and controversial issues is the contribution of diet to atherogenesis. The central question is whether dietary modification—specifically, reduction in the consumption of foods high in cholesterol and saturated animal fats (e.g., eggs, butter, beef)—can reduce serum cholesterol levels and prevent or retard the development of atherosclerosis (of most importance, coronary heart disease) in those with no previous disease. The central question is whether dietary modification—specifically, reduction in the consumption of foods high in cholesterol and saturated animal fats (e.g., eggs, butter, beef)—can reduce serum cholesterol levels and prevent or retard the development of atherosclerosis (of most importance, coronary heart disease) in those with no previous episode of cardiovascular disease. This is called “primary prevention”. We know some but not all the answers. The average adult in the United States consumes a large amount of fat and cholesterol daily, with a ratio of saturated fatty acids to polyunsaturated fatty acids of about 3:1. Lowering the level of saturates to the level of the polyunsaturates causes a 10% to 15% reduction in serum cholesterol within a few weeks. Vegetable oils (e.g., corn and safflower oils) and fish oils contain polyunsaturated fatty acids and are good sources of such cholesterol-lowering lipids. Fish oil fatty acids belonging to the omega-3, or n-3, family have more double bonds than do the omega-6, or n-6, fatty acids found in vegetable oils. A corollary of this idea is that supplementation of diet with fish oils might protect against atherosclerosis. One study of Dutch men whose usual
daily diet contained 30 g of fish showed a substantially lower frequency of death from coronary heart disease than that among comparable control subjects. However, other studies have shown that omega-3 fatty acid supplements do not reduce the risk of cardiovascular diseases, suggesting that yet unknown components of fish may be required for cardioprotection.

Other specific effects of diet on disease have been recognized:
- Restricting sodium intake reduces hypertension.
- Dietary fiber, or roughage, resulting in increased fecal bulk, is thought by some investigators to provide a preventive effect against diverticulosis of the colon.
- Caloric restriction has been convincingly demonstrated to increase life span in experimental animals, including monkeys. The basis for this striking observation is not clear (Chapter 2).
- Even lowly garlic has been touted to protect against heart disease (and also, alas, against kisses—and the devil), although research has yet to prove this effect unequivocally.

**Diet and Cancer**

With respect to carcinogenesis, three aspects of the diet are of concern: (1) the content of exogenous carcinogens, (2) the endogenous synthesis of carcinogens from dietary components, and (3) the lack of protective factors.

- An example of an exogenous carcinogen is aflatoxin, which is an important factor in the development of hepatocellular carcinomas in parts of Asia and Africa. Exposure to aflatoxin causes a specific mutation (codon 249) in the TP53 gene in tumor cells. The mutation can be used as a molecular signature for aflatoxin exposure in epidemiologic studies.
- The concern about endogenous synthesis of carcinogens or promoters from components of the diet relates principally to gastric carcinomas. Nitrosamines and nitrosamides are suspected to generate these tumors in humans, as they induce gastric cancer in animals. These compounds are formed in the body from nitrates and amines or amides derived from digested proteins. Sources of nitrates include sodium nitrate, added to foods as a preservative, and nitrates, present in common vegetables, which are reduced in the gut by bacterial flora. There is, then, the potential for endogenous production of carcinogenic agents from dietary components, which might well have an effect on the stomach.
- High animal fat intake combined with low fiber intake has been implicated in the causation of colon cancer. The most convincing explanation for this association is as follows: High fat intake increases the level of bile acids in the gut, which in turn modifies intestinal flora, favoring the growth of microaerophilic bacteria. The bile acids or bile acid metabolites produced by these bacteria might serve as carcinogens or promoters. The protective effect of a high-fiber diet might relate to (1) increased stool bulk and decreased transit time, which decreases the exposure of mucosa to putative offenders, and (2) the capacity of certain fibers to bind carcinogens and thereby protect the mucosa. Attempts to document these theories in clinical and experimental studies have, on the whole, led to contradictory results.
- Vitamins C and E, β-carotenes, and selenium have been assumed to have anti-carcinogenic effects because of their anti-oxidant properties. To date, however, no convincing evidence has emerged to show that these antioxidants act as chemopreventive agents. As already mentioned, retinoic acid promotes epithelial differentiation and is believed to reverse squamous metaplasia.

Thus, despite many tantalizing trends and proclamations by “diet gurus,” to date there is no definite proof that diet in general can cause or protect against cancer. Nonetheless, concern persists that carcinogens lurk in things as pleasurable as a juicy steak and rich ice cream.

**SUGGESTED READINGS**


Matthew JD, Forsythe AV, Brady Z, et al: Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians, *BMJ* 346:i2360, 2013. [A paper showing that children who have undergone CT scans have a 24% increased risk of cancer, adding to accruing evidence that CT scans increase the risk of secondary cancers in children and adolescents.]


A paper correlating increases in life expectancy in major U.S. cities with decreases in fine-particulate air pollution.