chapter 8

Nutritional Disorders

I. MALNUTRITION

A. In affluent countries, malnutrition is found in children living below the poverty level; the elderly; alcoholics; persons on fad diets and with eating disorders, such as anorexia nervosa; and patients with severe wasting diseases.

B. In developing countries, protein-calorie malnutrition occurs in two forms—marasmus and kwashiorkor.

1. **Marasmus** is caused by widespread **deficiency of almost all nutrients,** notably protein and calories.
   - **a.** It often coexists with vitamin deficiencies.
   - **b.** It typically occurs in children younger than 1 year of age who are not breast-fed and do not have an adequate intake of substitute nutrients.
   - **c.** Clinical characteristics include retarded growth and loss of muscle and other protein-containing tissue, as well as loss of subcutaneous fat ("wasting away").
2. **Kwashiorkor** is caused by **protein deficiency** but with adequate caloric intake.
   - **a.** It usually affects children older than 1 year of age who are no longer breast-fed and receive a starch-rich, protein-poor diet.
   - **b.** Clinical characteristics include retarded growth and muscle wasting, caused by inadequate protein intake, but with preservation of subcutaneous fat.
   - **c.** Kwashiorkor is distinguished from marasmus by the presence of the following abnormalities:
     - **(1)** Fatty liver
     - **(2) Severe edema** due to protein deficiency and decreased oncotic pressure
     - **(3)** Anemia
     - **(4)** Malabsorption due to atrophy of the small intestinal villi
     - **(5) Depigmented bands** with pale streaking in the hair or skin

II. VITAMINS

A. Water-soluble vitamins (Table 8-1)

1. **General considerations.** Water-soluble vitamins include the **B complex vitamins,** B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_6 (pyridoxine), and B_{12} (cobalamin); folic acid; and vitamin C (ascorbic acid).
   - **a.** Because these vitamins are not stored in the body, regular intake is essential, except for vitamin B_{12}. Vitamin B_{12} is stored in the liver in quantities sufficiently large so that deprivation for months or years is necessary for deficiency to develop.
   - **b.** Toxicity from excessive intake is rare, because excess vitamin is excreted in the urine.

table 8-1 Water-Soluble Vitamins

	Metabolic Functions	Clinical Manifestations of Deficiency
Vitamin B_1 (thiamine)	Coenzyme thiamine pyrophosphate plays a key role in carbohydrate and amino acid intermediary metabolism	Wet beriberi; dry beriberi; Wernicke-Korsakoff syndrome
Vitamin B_2 (riboflavin)	Component of FAD and FMN and is essential in a variety of oxidation-reduction processes	Cheilosis; corneal vascularization; glossitis; dermatitis
Vitamin B_3 (niacin, nicotinic acid)	Component of NAD and NADP, essential to glycolysis, the citric acid cycle, and to a variety of oxidations (can be synthesized from tryptophan); deficiency requires diet lacking both niacin and tryptophan	Pellagra
Vitamin B_6 (pyridoxine)	Required for transamination, porphyrin synthesis, synthesis of niacin from tryptophan	Cheilosis; glossitis; anemia; convulsions in infants; neurologic dysfunction
Vitamin B_{12} (cobalamin)	1-Carbon transfers required for folate synthesis and activation of FH_4; $N^{5,10}$-methylene FH_4 is required for conversion of dUMP to dTMP in DNA synthesis	Megaloblastic anemia; neurologic dysfunction
Folic acid	1-Carbon transfers in a number of metabolic reactions; $N^{5,10}$-methylene FH_4 required for DNA synthesis	Megaloblastic anemia; neurologic dysfunction is not a feature (as it is in vitamin B_{12} deficiency)
Vitamin C (ascorbic acid)	Required for hydroxylation of proline and lysine, which are essential for collagen synthesis; hydroxylation of dopamine in synthesis of norepinephrine; enhances maintenance of reduced state of other metabolically active agents, such as iron and FH_4	Scurvy, defective formation of mesenchymal tissue and osteoid matrix; defective wound healing; hemorrhagic phenomena

FAD = flavin adenine dinucleotide; FMN = flavin mononucleotide; NAD = nicotinamide adenine dinucleotide; NADP = nicotinamide adenine dinucleotide phosphate; FH_4 = tetrahydrofolate; $N^{5,10}$-methylene; FH_4 = activated tetrahydrofolate.

2. **Dietary sources**
   a. **B complex vitamins** (except vitamin B_{12}): whole grain cereals, green leafy vegetables, fish, meat, and dairy foods
   b. **Vitamin B_{12}**: foods of animal origin only (vitamin B_{12} is synthesized by intestinal bacteria in animals)
   c. **Folic acid:** leafy vegetables, cereals, fruits, and a number of animal products
   d. **Vitamin C:** fruits (especially citrus fruits and tomatoes), vegetables, various meats, and milk
3. **Deficiencies.** Clinical manifestations are often shared. The most striking clinical manifestations are in tissues with active metabolism, because these vitamins are involved in the release and storage of energy. In B complex vitamins, deficiencies are often marked by glossitis, dermatitis, and diarrhea.
   a. **Vitamin B_1 (thiamine) deficiency** is most often associated with severe malnutrition. (In Western countries, it is usually associated with alcoholism and fad diets.) It results in three distinct syndromes:
   (1) **Dry beriberi** is characterized by **peripheral neuropathy** with resultant atrophy of the muscles of the extremities.
   (2) **Wet beriberi**
   (a) This condition is marked by **high-output cardiac failure,** often with dilated cardiomyopathy.
   (b) It results from peripheral dilation of arterioles and capillaries, leading to increased arteriovenous shunting, hypervolemia, and cardiac dilation.
   (3) **Wernicke-Korsakoff syndrome** most often occurs in a setting of thiamine deficiency and alcoholism.
   (a) This condition manifests by degenerative changes in the brain stem and diencephalon, with **hemorrhagic lesions** of cortical and bilateral paramedian masses of gray matter and the **mamillary bodies.**
   (b) It is characterized by **confusion, ataxia,** and **ophthalmoplegia** (Wernicke triad) and also by marked **memory loss and confabulation.**

b. **Vitamin B_2 (riboflavin) deficiency** is rare in the United States because riboflavin is almost always added to commercially prepared bread and cereals.
   (1) This condition occurs in chronic alcoholics, fad dieters, the elderly, and in persons with chronic debilitating diseases.
   (2) It manifests clinically by **cheilosis** (skin fissures at the angles of the mouth), **glossitis, corneal vascularization,** and **seborrheic dermatitis** of the face, scrotum, or vulva.

c. **Vitamin B_3 (niacin) deficiency**
   (1) This condition develops only when the diet lacks both niacin and tryptophan (niacin can be synthesized from the essential amino acid tryptophan). Niacin is a component of the nicotinamide adenine dinucleotides (NAD and NADP) and, as such, is essential to glycolysis, the citric acid cycle, and other metabolic processes.
   (2) It is manifest clinically as **pellagra,** which is characterized by the "three Ds": **dementia, dermatitis,** and **diarrhea.** Dermatitis affects exposed areas, such as the face and neck, and the dorsa of the hands and feet.

d. **Vitamin B_6 (pyridoxine) deficiency** may cause convulsions in infants, due to decreased activity of pyridoxal-dependent glutamate decarboxylase, which leads to deficient production of γ-aminobutyric acid (GABA), a neurotransmitter. It results in clinical manifestations similar to those of vitamin B_2 (riboflavin) deficiency. Although pyridoxine deficiency is uncommon, it occurs in the following conditions:
   (1) Chronic alcoholism
   (2) Association with therapeutic drugs, such as isonicotinic acid hydrazide (INH, an antituberculous agent), which react as competitive inhibitors for pyridoxine binding sites
   (3) A variety of syndromes characterized by an increased need for pyridoxine, including:
      (a) **Homocystinuria,** an inborn error of metabolism
      (b) **Pyridoxine-responsive anemia,** a microcytic anemia characterized by reduced heme synthesis

e. **Vitamin B_{12} (cobalamin) deficiency** results in a marked reduction in DNA replication and cell division.
   (1) This condition manifests clinically by **megaloblastic anemia** with **prominent neurologic dysfunction.**
   (2) The cause is almost always malabsorption but may occur in rare cases on a dietary basis in strict vegetarians. Cobalamin deficiency is not found in other settings of malnutrition, such as alcoholism.
      (a) The most common malabsorption disease is **pernicious anemia,** in which there is a lack of gastric intrinsic factor, a carrier protein essential to vitamin B_{12} absorption in the terminal small bowel.
      (b) Less commonly, malabsorption can result from a number of diverse causes, including Crohn disease (which often affects the terminal ileum), blind loop syndrome, and *Diphyllobothrium latum* (giant fish tapeworm) infestation.

f. **Folic acid deficiency**
   (1) This condition is most commonly of dietary origin and often occurs in alcoholics and fad dieters. It can be secondary to intestinal malabsorption or it can occur, without gross dietary deprivation, as a relative deficiency because of increased demand for folate (e.g., in pregnancy and in hemolytic anemia, which is due to shortening of the life span of the red blood cell). Sometimes it is secondary to cancer chemotherapy containing folic acid antagonists.
   (2) The result is **megaloblastic anemia.**
   (3) Folic acid deficiency **does not cause neurologic changes** (in contrast to vitamin B_{12} deficiency).

g. **Vitamin C (ascorbic acid) deficiency**
   (1) Characteristics include **defective formation of mesenchymal tissue and osteoid matrix** due to **impaired synthesis of hydroxyproline and hydroxylysine,** for which vitamin C is a cofactor. **Defective collagen fibrillogenesis** contributes to **impaired**

wound healing. Defective connective tissue also leads to fragile capillaries, resulting in **abnormal bleeding.**

(2) Ascorbic acid deficiency results in **scurvy,** which is characterized by muscle, joint, and bone pain; swollen, bleeding gums; subperiosteal hemorrhage; and perifollicular petechial hemorrhages. **Bone changes** in scurvy are secondary to **defective osteoid matrix formation.**

B. Fat-soluble vitamins (vitamins A, D, E, and K; Table 8-2)

1. General considerations

a. Deficiency may result from malnutrition and intestinal **malabsorption syndromes, pancreatic exocrine insufficiency,** or **biliary obstruction,** all of which are associated with poor absorption of fats.

b. Excess intake (i.e., **hypervitaminosis**) with resultant toxicity may occur, especially with vitamins A and D.

2. Vitamin A is a term for a group of compounds (retinoids) with similar activities that are provided by animal products, such as liver, egg yolk, and butter. Also, a variety of vegetables (e.g., carrots and green leafy vegetables) supply β-carotene, a vitamin A precursor. Vitamin A is essential for the maintenance of mucus-secreting epithelium. A derivative, retinol, is a component of the visual pigment rhodopsin.

a. Vitamin A deficiency can be caused by dietary deficiency or fat malabsorption. Clinical manifestations include:

(1) **Night blindness,** due to insufficient retinal rhodopsin

(2) **Squamous metaplasia** of the trachea, bronchi, renal pelvis (often associated with renal calculi), conjunctivae, and tear ducts. Ocular abnormalities can result in **xerophthalmia** (dry eyes) and **blindness** or in **keratomalacia** (corneal softening).

b. Hypervitaminosis A is most often caused by excessive intake of vitamin A preparations. It is manifest by **alopecia, hepatocellular damage,** and **bone changes.**

3. Vitamin D is synthesized in the skin by ultraviolet light from the precursor 7-dehydrocholesterol; exposure to sunlight is required for this biosynthesis. Other sources include foods, such as milk, butter, and eggs.

a. Vitamin D promotes intestinal calcium absorption mediated by a specific calcium-binding intestinal transport protein, as well as intestinal phosphorus absorption. In addition, vitamin D enhances bone calcification, apparently through its role in intestinal calcium absorption.

table 8-2 Fat-Soluble Vitamins

	Metabolic Functions	Clinical Manifestations of Deficiency
Vitamin A	Precursor in rhodopsin synthesis; important in glycoprotein synthesis; regulator of epithelial differentiation	Night blindness; squamous metaplasia in many tissues, most importantly in eyes, where blindness may result
Vitamin D (calciferol)	Active form 1α,25-dihydroxy-cholecalciferol (1,25-$(OH)_2D_3$, calcitriol) promotes intestinal calcium and phosphorus absorption and stimulates parathyroid hormone-mediated renal tubular reabsorption of calcium; thus maintains physiologic concentration of serum calcium; enhances calcification of bone	Rickets in children; osteomalacia in adults
Vitamin E (α-tocopherol)	Antioxidant; maintenance of cell membranes, probably by modulation of lipid peroxidation	Possible neurologic dysfunction
Vitamin K	Glutamyl carboxylation required for synthesis of γ-carboxyglutamyl residues of active serine proteases (e.g., clotting factors II, VII, IX, and X)	Hemorrhagic diatheses, such as hemorrhagic disease of the newborn

b. Vitamin D deficiency manifests clinically as **rickets in children** and as **osteomalacia in adults,** both due to **deficient calcification of osteoid matrix.** It can be caused by the following factors:

(1) Malnutrition

(2) Intestinal malabsorption

(3) Inadequate exposure to sunlight

(4) Liver disease, with impaired hepatic conversion of vitamin D to the 25-hydroxyl form, a precursor of active vitamin D, 1α,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$, calcitriol)

(5) Renal disease, with incomplete synthesis of active vitamin D

(6) Vitamin D–resistant rickets due to hereditary renal 1α-hydroxylase deficiency, which causes impaired synthesis of active vitamin D, impaired calcium absorption, and increased parathyroid hormone activity.

c. Hypervitaminosis D is manifest in children by **growth retardation** and is manifest in adults by **hypercalciuria, nephrocalcinosis,** and **renal calculi.**

4. **Vitamin E deficiency** is rare but is thought to result in neurologic dysfunction.

5. **Vitamin K**

a. This vitamin is essential for carboxylation of glutamyl residues in the synthesis of the γ-carboxyglutamyl forms (active forms) of **clotting factors II, VII, IX,** and **X,** and of **protein C.**

b. It is provided by green and yellow vegetables and by dairy products.

c. It is synthesized by intestinal microorganisms.

d. Vitamin K deficiency results from fat malabsorption or alterations in the intestinal flora caused by antibiotics.

(1) This condition is characterized by a **hemorrhagic diathesis** (abnormal bleeding) marked by prolongation of the prothrombin and activated partial thromboplastin times.

(2) It is the cause of **hemorrhagic disease of the newborn,** which may result from a variety of causes, including deficient intake combined with inadequate intestinal bacterial colonization.

e. There are no known clinical manifestations of excess vitamin K.

III. OBESITY

A. Obesity is associated with increased risk of type 2 diabetes mellitus, hypertension, gallstones, and osteoarthritis.

B. When central in distribution (fat deposits principally surrounding abdominal viscera and subcutaneous areas of the trunk), it may be associated with an increased incidence of coronary artery disease.

C. It may, as is suggested by animal studies, be partly related to secretion of leptin, an anti-obesity hormone produced by adipocytes, and neuropeptide Y, a pro-obesity polypeptide secreted by the hypothalamus in response to leptin deficiency.

chapter 7

Environmental Pathology

I. PHYSICAL INJURY

A. Mechanical injury. Causes are various and include blunt force, sharp objects, or bullets. Mechanical injury can produce damage by cutting, tearing, or crushing tissues; by severe blood loss; or by interruption of blood or air supply.

1. **Terminology**
   a. An **abrasion or scrape** is a superficial tearing away of epidermal cells.
   b. A **laceration** is a jagged tear, often with stretching of the underlying tissue.
   c. An **incision** is a clean cut by a sharp object.
   d. A **puncture** is a deep tubular wound produced by a sharp, thin object.
   e. A **contusion** is a bruise caused by disruption of underlying small blood vessels; commonly the skin is affected, but internal organs may also be involved.
2. **Causes of death**
   a. **Hemorrhage** into body cavities
   b. **Fat embolism** from bone fractures
   c. **Ruptured viscera**
   d. **Secondary infection**
   e. **Renal shutdown** caused by acute tubular necrosis, especially when associated with myoglobin casts arising from crush injury of skeletal muscle
3. **Blunt force injuries**
   a. **Head injury**
      (1) **Brain damage,** with possible skull fracture, can be the direct result of cerebral trauma or caused by intracranial hemorrhage.
      (2) **Brain laceration** can be caused by a fracture with a penetrating injury by skull fragments.
      (3) **Brain contusion** may occur at the point of impact (**coup injury**) or on the opposite side of the brain (**contrecoup injury**).
   b. **Abdominal injury** may result in the following conditions:
      (1) **Contusion**
      (2) **Rupture of the spleen or liver,** sometimes with severe hemorrhage
      (3) **Rupture of the intestine,** which can result in **peritonitis**
   c. **Thoracic injury** may result in the following conditions:
      (1) **Rib fracture,** possibly with penetration into pulmonary parenchyma or thoracic wall vessels
      (2) **Hemothorax,** or hemorrhage in the pleural cavity
      (3) **Pneumothorax,** or air in the pleural cavity
4. **Knife and stab wounds** can be incisions or puncture wounds and result in highly variable consequences, depending on the site of the injury.
5. **Gunshot wounds**
   a. The entrance wound is usually smaller and rounder than the exit wound (and in some cases even smaller than the bullet because the skin is elastic) (Figure 7-1A).

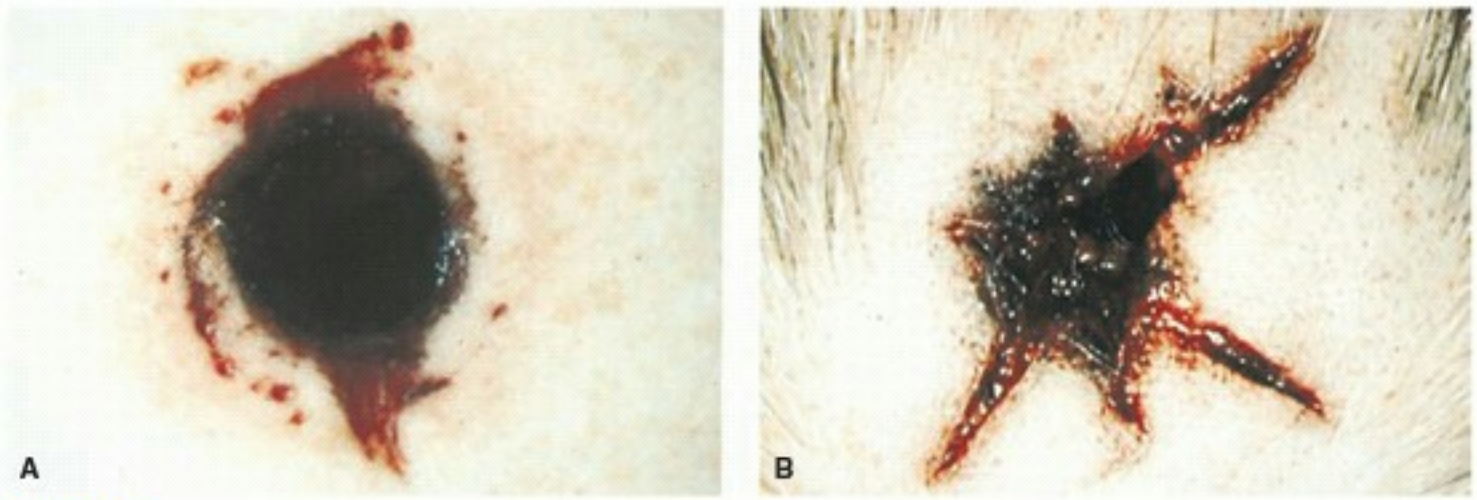

FIGURE 7-1 Bullet Wounds. The entrance wound is sharply punched out (A) while the exit wound is irregular with stellate lacerations (B). (Reprinted with permission from Rubin R, Strayer D, et al.: *Rubin's Clinicopathologic Foundations of Medicine*, 6th ed. Baltimore, Lippincott Williams & Wilkins, 2012, figure 8-18, p. 315.)

b. Exit wounds may be significantly larger than the bullet due to tumbling of the bullet (and tissue and bone fragments accompanying the bullet) and are usually irregular or stellate rather than round (Figure 7-1B).

c. In contact wounds, there may be burning around the margins of the wound (abrasion ring).

d. Contact wounds over the skull and other areas with skin closely overlying bone may demonstrate a stellate (star-shaped) appearance due to gases from the gun undermining the skin margins.

e. Close-range wounds (20 inches or less) demonstrate unburned powder particles in the skin (tattooing or stippling) and deposits of soot on the skin.

f. Long-range wounds are usually round or oval, demonstrating clean margins without evidence of stippling.

B. Thermal injury

1. Burns

a. Classification

(1) **First-degree burns (partial-thickness burns)** are characterized by hyperemia without significant epidermal damage; they generally heal without intervention.

(2) **Second-degree burns (partial-thickness burns)** are characterized by blistering and destruction of the epidermis with slight damage to the underlying dermis; they generally heal without intervention.

(3) **Third-degree burns (full-thickness burns)** are characterized by damage to the epidermis, dermis, and dermal appendages; skin and underlying tissue are often charred and blackened; these burns often require skin grafting.

b. Complications

(1) **Inhalation of smoke or toxic fumes** results in pulmonary or systemic damage.

(2) **Hypovolemia** results from fluid and electrolyte loss.

(3) **Curling ulcer** (acute gastric ulcer associated with severe burns)

(4) **Infection** is the most common cause of late fatalities. The most frequent organism is *Pseudomonas aeruginosa*.

(5) Ulcerating squamous cell carcinomas may arise in association with long-standing burn wounds (Marjolin ulcer).

2. Freezing

a. Tissue damage may be generalized, resulting in **death.**

b. Tissue damage may be localized, resulting in **frostbite;** exposed areas such as fingers, toes, earlobes, or nose are usually affected.

c. Severe, prolonged frostbite may result in **intracellular ice crystals, intravascular thrombosis,** and sometimes local **gangrene.**

table 7-1 Radiosensitivity of Specialized Cells

Degree of Sensitivity	Types	Characteristics
Radiosensitive	Lymphoid, hematopoietic, germ, gastrointestinal mucosal, rapidly dividing tumor cells	Regularly actively divide, especially those cells undergoing mitosis
Intermediate radiosensitivity	Fibroblasts; cells of endothelium, elastic tissue, salivary glands, eye	
Radioresistant	Cells of bone, cartilage, muscle, central nervous system, kidney, liver, and most endocrine glands	Cease division shortly after fetal development is complete

C. **Electrical injury.** When electric current passes through an individual, thus completing an electric circuit, electrical injury occurs.

1. Fatal electrical injury is usually caused by current passing through the brain or heart. It may cause **respiratory or cardiac arrest** or **cardiac arrhythmias.**
2. Electrical injury may result in small **cutaneous burns** with blister formation at the point of entry or exit of the electric current. At times, burns may be severe.

D. **Radiation injury**

1. **Ultraviolet light (sunlight)**
   a. Ultraviolet radiation causes **sunburn,** which is characterized by erythema, often with superficial desquamation and, in severe cases, blister formation.
   b. It is associated with premalignant cutaneous lesions **(actinic keratosis)** and malignant cutaneous lesions, such as **squamous and basal cell carcinomas and melanoma.**
2. **Ionizing radiation**
   a. Ionizing radiation is from x-ray, radioactive waste, nuclear disasters, and other exposures.
   b. Cell damage results from the formation of toxic free radicals, which affect vital cell components, such as DNA and intracellular membranes.
   c. **Localized radiation** results in the following conditions:
      (1) **Skin changes** include dermatitis, ulceration, and skin malignancies.
      (2) **Pulmonary changes** include acute changes similar to those of adult respiratory distress syndrome, and chronic changes, such as septal fibrosis, bronchiolar metaplasia, and hyaline thickening of blood vessel walls.
      (3) **Gastrointestinal inflammation and ulceration**
      (4) **Hematopoietic alterations,** including bone marrow depression or leukemia
      (5) **Neoplasia includes** myeloid (but not lymphoid) leukemias and cancers of bone, skin, thyroid, lung, or breast.
   d. **Severe and generalized radiation** occurs in whole body irradiation, such as that seen in nuclear disasters.
      (1) **Severe central nervous system (CNS) injury** is primarily caused by capillary damage.
      (2) **Gastrointestinal mucosal denudation**
      (3) **Acute bone marrow failure**
3. **Radiosensitivity of specialized cells (Table 7-1)**
   a. Lymphocytes are the earliest blood cells to be affected.
   b. The most sensitive cells are lymphoid, hematopoietic, germ, gastrointestinal mucosal, and those from rapidly dividing tumors.

II. CHEMICAL ABUSE

A. **Alcohol abuse.** This is an important cause of death and disability from several causes ranging from automobile accidents to homicides. A constellation of changes that are collectively grouped as **chronic alcoholism** is characteristic, and common pathologic findings include:

1. **Alcoholic hepatitis and cirrhosis**
2. **Acute and chronic pancreatitis**
3. **Gastritis**
4. **Oral, pharyngeal, laryngeal, esophageal, and gastric carcinoma** (especially in association with combined abuse of alcohol and tobacco)
5. **Alcoholic (dilated) cardiomyopathy**
6. **Aspiration pneumonia**
7. **Myopathy**
8. **Peripheral neuropathy**
9. **Cerebral dysfunction,** such as thiamine deficiency-mediated **Wernicke-Korsakoff syndrome,** sometimes referred to as alcoholic encephalopathy
   - **a.** The cause is a combination of alcoholism and thiamine deficiency.
   - **b.** The syndrome is often associated with hemorrhagic necrosis of mamillary bodies.
   - **c.** Wernicke syndrome is a combination of ataxia, confusion, ophthalmoplegia, and often nystagmus.
   - **d.** Korsakoff syndrome is manifest by memory loss and confabulation.
10. Fetal alcohol syndrome, which involves microcephaly, mental retardation, and facial and cardiac defects

B. Tobacco abuse (Figure 7-2). Associated conditions include:

1. Squamous cell carcinoma of the larynx, squamous cell and small cell bronchogenic carcinoma, and transitional cell carcinoma of the urinary bladder
2. Chronic obstructive pulmonary disease
3. Atherosclerosis and other vascular occlusive diseases, such as Buerger disease

C. Drug abuse

1. **Cocaine** can result in the following effects and complications:
   - **a. Mood elevation,** sometimes followed by irritability, anxiety, and depression, which may lead to suicide
   - **b. Increased myocardial irritability,** which can lead to fatal arrhythmias
   - **c. Hypertension,** which can predispose to cerebral hemorrhage
   - **d. Nasal congestion, ulceration, or septal perforation,** from intranasal use
   - **e. Burn injury,** due to volatile inflammable substances used in cocaine free-base preparation
   - **f. Viral** (human immunodeficiency virus [HIV] or hepatitis B) or **bacterial** (infective endocarditis) **infection** (from intravenous use). Infective endocarditis due to intravenous drug abuse often involves the valves of the right side of the heart.

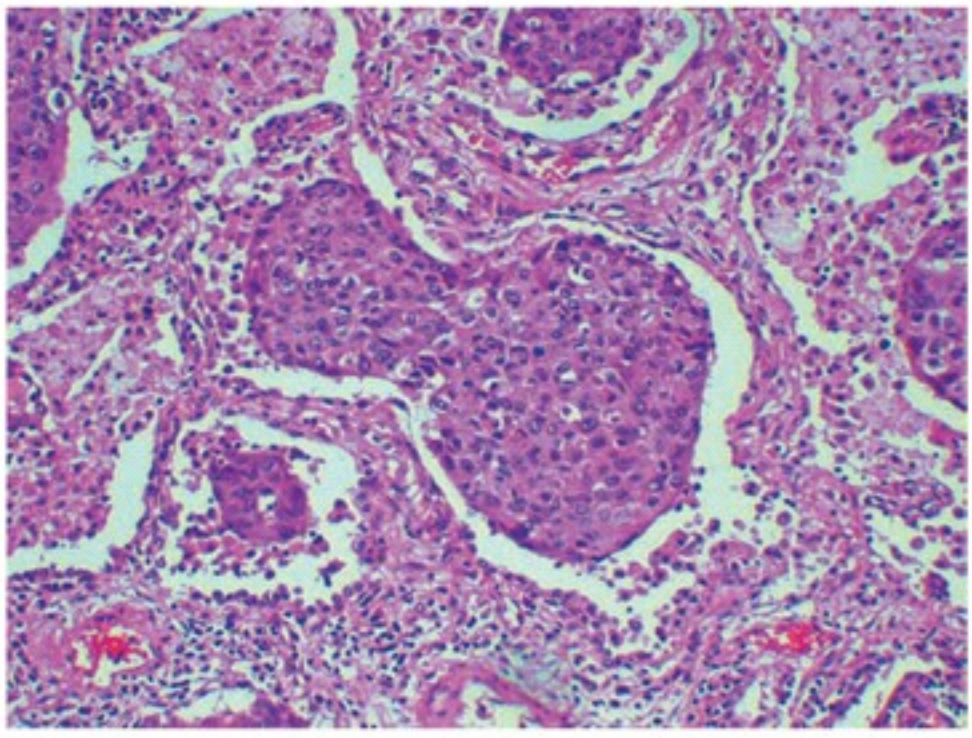

FIGURE 7-2 Squamous cell carcinoma of the lung. Lung cancer is one of the most common consequences of cigarette smoking. It can also be a consequence of asbestos exposure. (Reprinted with permission from Rubin R, Strayer D, et al., eds.: *Rubin's Pathology. Clinicopathologic Foundations of Medicine,* 6th ed. Baltimore, Lippincott Williams & Wilkins, 2012, figure 5-19A, p. 168.)

g. Epileptic seizures, respiratory arrest, myocardial infarction, and, in newborns of addicted mothers, multiple small cerebral infarcts

2. **Heroin** is usually administered intravenously and can result in the following effects and complications:
   a. **Physical dependence,** with severe withdrawal symptoms
   b. **Infections,** such as HIV, hepatitis B, and infective endocarditis
   c. **Adult respiratory distress syndrome**
   d. **Death** from respiratory or cardiac arrest or from pulmonary edema

III. ENVIRONMENTAL CHEMICAL INJURIES (TABLE 7-2)

A. Methyl alcohol (methanol)

1. This chemical is converted to the cellular toxins formaldehyde and formic acid, resulting in transient metabolic acidosis.
2. It damages the cells of the retina, optic nerve, and CNS, resulting in **blindness.**

B. Carbon monoxide (CO)

1. This gas inhibits the capacity of hemoglobin to function as an oxygen carrier because hemoglobin has an affinity for CO that is 200 times greater than its affinity for oxygen.
2. It can result in irreversible **hypoxic injury,** often leading to death; neurons of the brain are most vulnerable. Foci of neuronal necrosis in the basal ganglia, lenticular nuclei, and cortical gray areas are characteristic. When fatal, it causes a **cherry-red color of the skin, blood, viscera, and muscles.**

C. Carbon tetrachloride (CCl_4). This chemical induces **centrilobular necrosis and fatty change** in the liver.

D. Cyanide

1. This chemical **inhibits intracellular cytochrome oxidase** by binding with ferric iron, thus preventing cellular oxidation. **Death** occurs within minutes.
2. Generalized petechial hemorrhages and a scent of bitter almonds are noted at autopsy.

E. Lead. This chemical may be **ingested,** particularly from lead in paint, or may be **inspired,** particularly from automotive emissions. When ingested or inhaled in toxic amounts, it is manifested clinically by:

1. **Red blood cell changes**
   a. **Basophilic stippling**
   b. **Hypochromic microcytic anemia**
      (1) The cause is deficient heme synthesis mediated by the inhibition of **δ-aminolevulinic acid (ALA) dehydratase** and by decreased incorporation of iron into heme.
      (2) Defects result in accumulation of both ALA and erythrocyte protoporphyrin, leading to protoporphyrinemia, porphyrinuria, and aminolevulinic aciduria.

table 7-2 Some Environmental Toxins and Their Effects

Toxin	Predominant Adverse Effects
Methyl alcohol	Blindness
Carbon monoxide	Severe hypoxic injury caused by displacement of oxyhemoglobin by carboxyhemoglobin
Carbon tetrachloride	Hepatic centrilobular necrosis and fatty change
Cyanide	Cessation of intracellular oxidation because of cytochrome oxidase inhibition
Lead	Anemia; basophilic stippling of erythrocytes; encephalopathy; neuropathy; lead line; Fanconi syndrome
Mercuric chloride	Gastrointestinal ulcerations; calcification and necrosis of renal convoluted tubules

2. **Encephalopathy,** characterized by irritability and sometimes by seizures and coma
3. **Neuropathy,** characterized by wristdrop and footdrop
4. **Fanconi syndrome,** characterized by impaired proximal renal tubular reabsorption of phosphate, glucose, and amino acids
5. **Lead line,** characterized by mucosal deposits of lead sulfide at the junction of the teeth and gums
6. **Increased radiodensity of the epiphyses of the long bones**

F. **Mercuric chloride.** Ingestion results in **focal gastrointestinal ulceration and severe renal damage** with widespread necrosis and calcification of the proximal convoluted tubules. Proximal convoluted tubular necrosis is characteristic of injury from a number of nephrotoxins.

G. **Vinyl chloride.** This chemical can lead to hemangiosarcoma (angiosarcoma) of the liver.

H. **β-Naphthylamine and aniline dyes.** These chemicals can lead to transitional cell carcinoma of the urinary bladder.

I. **Ethylene glycol.** This chemical can cause acute tubular necrosis, as well as tubular precipitation of calcium oxalate crystals, which can be seen with polarized light.

J. **Polychlorinated biphenyls (PCBs)**

1. These nonbiodegradable **environmental pollutants** were used to manufacture a variety of products, such as adhesives and plasticizers. Because of their toxicity, their production is now outlawed.
2. Exposure produces a syndrome of chloracne, impotence, and visual changes.

IV. ADVERSE EFFECTS OF THERAPEUTIC DRUGS

These effects can manifest with a wide variety of clinically significant abnormalities. For example:

A. Antibiotics

1. **Development of drug-resistant organisms** is often mediated by plasmids carrying specific drug-resistant genes.
   a. Methicillin-resistant *Staphylococcus aureus* (MRSA)
      (1) Was once limited to hospital-acquired infections but now arises in the community as well
      (2) Antibiotic resistance is conferred by the *mecA* gene, which encodes penicillin-binding protein 2a.
   b. Vancomyocin-resistant enterococcus (VRE)
      (1) Common in hospital patients
      (2) Vancomyocin resistance can be conferred by the *vanA*, *vanB*, or *vanC* gene.
2. ***Clostridium difficile* colitis** often affects patients whose normal gut flora has been obliterated by antibiotic treatment.
3. **Acute hemolytic anemia** is associated with a variety of antibiotics including penicillin and cephalosporins.
4. **Fatal aplastic anemia** can occur as a result of an idiosyncratic reaction to chloramphenicol.

B. Sulfonamides

1. **Immune complex disease,** such as polyarteritis nodosa, can develop when sulfonamides, acting as haptens, stimulate antibody production.
2. **Crystallization of sulfonamides within the renal collecting system** causes calculi with obstruction, infection, or both.

3. **Bone marrow failure**
4. **Acute, self-limited hemolytic anemia** may be induced in individuals with erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency.

C. Analgesics

1. **Aspirin**
   a. **Gastroduodenal bleeding** may be caused by aspirin-induced gastritis or peptic ulcer or by inhibition of platelet cyclooxygenase with resultant thromboxane A_2 deficiency and impaired platelet plug formation.
   b. **Reye syndrome** occurs in children following an acute febrile viral illness, almost always in association with aspirin intake. It is characterized by microvesicular fatty change in the liver and encephalopathy.
   c. **Allergic reactions** include urticaria, asthma, nasal polyps, and angioneurotic edema.
2. **Phenacetin**
   a. **Chronic analgesic nephritis and renal papillary necrosis** (the drug has been withdrawn from the US market)
   b. **Urothelial neoplasms,** especially transitional cell carcinoma of the renal pelvis
   c. **Acute hemolysis** in G6PD-deficient individuals

D. Cancer chemotherapeutic drugs

1. **Toxic effects,** including hair loss, gastrointestinal erosions and ulcerations, and, most significantly, bone marrow failure
2. **Acute leukemia or other malignancies**