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23 Gases

23.1 INTRODUCTION

Pulmonary irritants, simple asphyxiants, toxic products of combustion, lacrimating agents, and chemical asphyxiants constitute a diverse group of toxic gases capable of causing a variety of local and pulmonary reactions. The sources of these compounds are as varied, encompassing both naturally occurring and synthetic chemicals developed over the last 50 years. In addition, exposures to the gases are encountered *accidentally*, at home or in the workplace with industrial products, as environmental hazards, or *intentionally*, as commercial sprays for individual protection, for law enforcement, or as potential bioterrorist weapons. The most common routes of exposure to these agents occurs through oral ingestion, local dermal or mucous membrane contact, or deep inhalation. Because of their seemingly unrelated chemical structures and properties, the gases are classified principally according to the clinical effects and metabolic consequences of exposure.

Physiologically, the respiratory system is composed of (1) the upper respiratory tract (URT), consisting of the nasal and oral cavities, pharynx, and larynx and (2) the lower respiratory tract (LRT), namely the trachea, bronchi, bronchioles, and lungs. Two main functions of the respiratory system are ventilation (inspiration and expiration of air down to the level of the alveoli) and gas exchange.* In support of these functions, the mucociliary system produces mucus. This tenacious fluid captures inhaled particles and transports them to the nasal and oral mucosa by ciliary action of epithelial cells of the URT and LRT. The cough reflex then acts to expectorate the sequestered mucus. Together, these innate reflex responses cooperate in the *clearance mechanism* of pulmonary function. For effective gas exchange, therefore, ventilation and perfusion must match closely (calculated as the *V/Q ratio*). Consequently, any alteration of the V/Q ratio, or interference with the *clearance mechanism* due to the presence of toxic gases, results in altered lung mechanics. This explains the ensuing clinical effects.

23.2 PULMONARY IRRITANTS

As the label implies, pulmonary irritants are chemicals that, when in contact with mucous membranes, produce an inflammatory response and cytotoxicity. The extent of trauma ranges from mild to severe irritation and depends on the nature of the chemical (solubility, concentration, pH). Table 23.1 lists commonly encountered

* Gas exchange involves the passage of gas molecules through the respiratory membranes. Oxygen diffuses from air in the alveoli, across the alveolar membranes, and into the capillary circulation. Carbon dioxide diffuses from the capillaries to the alveolar space. Gas exchange is driven by partial pressures of the gases in inspired air.

TABLE 23.1
Pulmonary Irritants: Sources, Chemical and Clinical Properties

Agent	Source	Industrial[a] or Household Uses	Chemical Properties	Acute Effects
Acrolein	Petroleum by-product, synthetic	Plastics, metals, aquatic herbicide	WS, F liquid	Local irritation, delayed pulmonary edema
Acrylonitrile	Synthetic	Acrylics, fumigant, chemical intermediate	WS, LS, F, explosive	Cyanide toxicity, skin vesiculation, dermatitis
Ammonia	Synthetic	Plastics, refrigerants, household cleaners, petroleum products	Alkaline, WS gas	Liquifaction necrosis, hemoptysis, ARDS, RADS[a]
Arsine (AsH_3)	Petroleum by-product	Glass, enamels, herbicides, textiles, preservative	Neutral gas, slightly WS (*garlic odor*)	Local irritation, hemolysis, renal failure, peripheral neuropathy
Carbon disulfide	Petroleum by-product, natural gas	Electroplating, degreaser, production of rayon	F liquid	Peripheral neuropathy, euphoria, restlessness, NV
Chlorine	Synthetic chemical intermediate	Bleach, chlorination of water, rubber, plastics, disinfectant	Greenish-yellow gas, oxidizing agent	Local, URT, LRT irritation
Formaldehyde	Environmental, synthetic, wood/coal smoke	Disinfectant, histological preservative (fixative)	Reducing agent, 37% gas in water	Local, URT, LRT irritation, convulsions, coma, respiratory failure
Hydrogen fluoride	Photographic film, solvents, plastics	Insecticide, bleach, metal and glass industry	Colorless gas, WS, LS	Local, URT, LRT irritation; cardiac arrhythmias

Hydrogen sulfide	Naturally occurring, organic decomposition	Petroleum, paper industries, metallurgy	F gas (*rotten egg odor*)	Irritant and asphyxiant, respiratory paralysis; mechanism similar to CN
Metal fumes (zinc chloride)	Welding	Undesirable product of welding and metal industries	Lustrous metal, WS	Local, URT, LRT irritation (*metal fume fever*)
Nitrogen dioxide	Synthetic, photochemical smog	Chemical intermediate, nitration	Reddish-brown gas, oxidizing agent	Local, URT, LRT irritation; pulmonary edema and arrest
Nitrogen oxide	Welding, farming, explosives	Undesirable product of welding and farming industries	Oxidizing agent	Pulmonary edema, methemoglobinemia
Ozone (O_3)	Welding, sewage treatment plants, air pollution	Disinfectant, bleaching, oxidizing agent	Bluish explosive gas or liquid, oxidizing agent	Irritation, pulmonary edema, chronic respiratory disease
Phosgene	Welding	Production of solvents, plastics, pesticides	Colorless gas, poor WS	Pulmonary edema, URT irritation
Sulfur dioxide	Synthetic	Preservative, disinfectant, bleaching	Colorless gas	Local, URT irritation
Sulfur oxide	Industrial, air pollution	Bleaching, paper industry	Oxidizing agent	Bronchoconstriction, cough, chest tightness

Note: F = flammable, WS = water soluble, N = nausea, V = vomiting, LS = lipid soluble, URT = upper respiratory tract, LRT = lower respiratory tract; ARDS = adult respiratory distress syndrome.

[a] Used in manufacturing, synthesis, or as part of industrial processes; RADS, reactive airway dysfunction, develops secondary to massive, acute, accidental, high-level irritant exposure. It is manifested by persistent, nonspecific hyperreactivity.

TABLE 23.2
Presentation of Signs and Symptoms of Pulmonary Irritants Depending on Site of Exposure

Pulmonary Target	Pathological Effects
Nasal, oral, ocular mucous membranes	Local irritation: rhinitis, conjunctivitis, sneezing, coughing, lacrimation
URT: nasal and oral cavities, pharynx, larynx	Burning throat, sinusitis, laryngitis, swelling, laryngoedema, dyspnea, epistaxis
LRT: trachea, bronchi, bronchioles, lungs	Nausea, vomiting, dyspnea, bronchospasm, chest pain, bronchitis, chemical pneumonitis, epithelial denudation, intravascular thrombosis, pulmonary edema, development of secondary infections

Note: LRT = lower respiratory tract, URT = upper respiratory tract.

pulmonary irritants, sources, and major pathophysiologic effects. Presentation of signs and symptoms of exposure to pulmonary irritants, summarized in Table 23.2, appears progressively. Toxicity depends on several factors: the extent of exposure (local contact or deep inhalation), duration of exposure, degree of remedial measures (physiologic clearance, availability of treatment), and development of secondary complications (such as infections).

23.3 SIMPLE ASPHYXIANTS

23.3.1 Introduction

Unlike the pulmonary irritants or the chemical asphyxiants (described below), simple asphyxiants are nonirritating, chemically inert gases. Simple asphyxiants interfere with pulmonary function by overwhelming the oxygen concentration in inspired air. The net result is a lowered oxygen content of inspired air and decreased oxygen availability for gas exchange. The toxicity of these agents depends on the available oxygen concentration remaining.

23.3.2 Gaseous Agents

The characteristics and properties of the simple asphyxiants are summarized in Table 23.3. The agents are naturally occurring atmospheric components, or are produced as products of industrial combustion. Toxic concentrations, however, are encountered in areas where the gases tend to accumulate. The acute effects and corresponding signs and symptoms of simple asphyxiants, therefore, result from replacing oxygen in inspired air with the gas, causing a decrease in oxygen concentration (Table 23.4).

Administration of therapeutic oxygen (O_2) is associated with toxicity, depending on the concentration, duration of inhalation, and the forced pressure. Respiratory asphyxiation or irritation occurs with prolonged inhalation (>24 h) of 100% O_2 at 1 atm of pressure. This concentration is capable of raising the partial pressure of

TABLE 23.3
Simple Asphyxiants, Sources, Chemical and Clinical Properties

Agent	Source	Industrial[a] or Household Uses	Chemical Properties
Carbon dioxide	Atmospheric, fermentation, mammalian metabolism, coal mines (*afterdamp*)	Carbonation, propellant, fumigation, aerosols, fire prevention	Colorless, odorless noncombustible gas heavier than air
Ethane	Petroleum by-product, constituent of natural gas	Fuel gas, refrigerant	Colorless, odorless flammable gas
Helium	Constituent of natural gas	Cryogen, lasers, welding, metal processing, carrier in GC, fill balloons and airships	Colorless, odorless nonflammable gas
Hydrogen	Electrolysis of water, action of HCl on Fe or Zn, hydrolysis of metal hydrides	Welding, chemical production, fill balloons and airships, coolant, thermonuclear reactors	Colorless, odorless flammable, explosive gas
Methane	Constituent of natural gas, action of aluminum carbide and water, coal mines (*firedamp*)	Illuminating and cooking gas, organic synthesis	Colorless, odorless flammable gas, lighter than air
Nitrogen	Atmospheric, mine gases, heating of Na azides	Inorganic synthesis, explosives, incandescent bulbs, cryogen, pharmaceutic aid	Odorless gas
Oxygen	Atmospheric, liquefaction of air	Welding, propellant, lighting, liquid fuels, therapeutic administration	Colorless, odorless gas, supports combustion
Radon (^{220}Rn)	Naturally occurring, decay product of ^{235}U	Study of chemical reactions, source of neutrons, study of radium	Radioactive isotope, α-emitter, colorless, odorless, tasteless gas
Xenon	Naturally occurring distillation/liquefaction of air	Gas lamps, leak detection systems for nuclear reactors	Colorless, odorless noncombustible tasteless gas

Note: GC = gas chromatography.

[a] Used in manufacturing, synthesis, or as part of industrial processes.

TABLE 23.4
Oxygen Concentration and Corresponding Signs and Symptoms Associated with Simple Asphyxiants

Oxygen Concentration in Inspired Air (%)	Acute Pathologic Effects
16–21 (normal)	No signs and symptoms
12–16	Tachypnea, tachycardia, muscular incoordination
10–12	Hypoxia; confusion, fatigue, dizziness
6–10	Hypoxia and decreased oxygen saturation; nausea, vomiting, lethargy, unconciousness
<6	Convulsions, apnea, cardiac arrest

oxygen (PO_2) in arterial blood to 600 mmHg.* Oxygen toxicity also occurs with administration of hyperbaric 100% O_2 (about 8 h at 2 atm of pressure or 1 h at 3 atm of pressure). With hyperbaric oxygen, arterial and venous plasma are at risk of complete saturation. For instance, at 2 to 3 atm of hyperbaric oxygen for 1 h, the volume percent O_2 dissolved in plasma is 6.1%; normal breathing at sea-level is 0.3 to 0.5%. For these high pressures, the PO_2 increases to 1500 to 2000. At this saturation level, patients experience signs and symptoms related to O_2 apnea, i.e., sore throat, coughing, retraction of eardrums, and obstruction of paranasal sinuses. Tracheobronchitis, pulmonary edema, and atalectasis (complete alveolar collapse) follow progressively. Other adverse reactions resulting from inhalation of high concentrations or hyperbaric oxygen include retrolental fibroplasia,** paresthesias, vertigo, loss of consciousness, nausea, and vomiting. The conditions are reversible upon discontinuation before onset of permanent damage.

Distinct among the simple asphyxiants is radon, a naturally occurring radioactive gas. Radon is a liquid below 211K but is found in the atmosphere at a concentration of 6×10^{-14} parts per million (ppm) in air. Although the isotopes (^{220}Rn and ^{222}Rn) are short-lived ($t_{1/2} = 3.825$ days for ^{222}Rn), these α-emitters release ionizing radiation and are strongly adsorbed onto various surfaces. These properties account for radon's ubiquitous and resilient presence in the earth's crust and atmosphere. Radon is a known carcinogen suspected to produce lung cancer in occupational exposures to hard rock mine workers. The EPA has established an action level of 4 pCi/l (0.02 working level) for home indoor radon, with a maximum permissible concentration of ^{222}Rn in air of 10^{-8} μCi/cc.

Normal atmospheric concentrations of carbon dioxide (CO_2) range between 0.027 and 0.036% v/v. Inhaling 2 to 5% carbon dioxide stimulates the medullary respiratory center in the brain stem, resulting in an increase in the respiratory minute volume (RMV). Initial local peripheral and skeletal muscle vasodilation and

*Normal PO_2 for arterial and venous blood, breathing air at sea level, is 100 and 40 mmHg, respectively.
** Characterized by retinal detachment in premature infants administered high oxygen at birth; a cause of blindness.

hypotension soon develop. In addition, since CO_2 freely diffuses between plasma and tissue, an increase in blood PCO_2 (hypercapnia) risks the development of respiratory acidosis. This development promotes medullary and peripheral chemoreceptors and sympathetic innervation. The net result is an increased tachycardia, arrythmias, and seizure activity* (5 to 10% CO_2 further stimulates RMV and produces a characteristic acidic oral taste).

Inhalation of 10% CO_2 for one minute causes *carbon dioxide narcosis*, a condition characterized by dizziness, dyspnea, sweating, malaise, restlessness, paresthesias, coma, convulsions, and death. Because it is heavier than air, CO_2 accumulates in low-lying, enclosed compartments, such as in mines, wells, and caverns.

23.4 TOXIC PRODUCTS OF COMBUSTION (TCP)

23.4.1 Introduction

TCPs are by-products of combustion, generated from a variety of mostly synthetic materials,** that are released with the smoke. TCPs include ammonia, acids, aldehydes, cyanide and isocyanates, carbon monoxide, halogenated hydrocarbons, oxides of nitrogen and sulfur, and styrene. Smoke inhalation of these substances produces toxicity from the heat in the gases, vapors, and fumes (thermal damage), or may act as simple asphyxiants or pulmonary irritants. As with the pulmonary irritants, URT and LRT injury depends on duration of exposure, respiratory minute volume (RMV***), and solubility.

23.4.2 Clinical Toxicity

URT and LRT toxicity are distinguished based on signs and symptoms. Upper airway injury is characterized primarily by local inflammation and irritation of ocular, oral, and nasal mucous membranes. Symptoms include conjunctivitis, lacrimation, rhinitis, pharyngitis, and stridor (an abnormal, high pitched musical sound caused by an obstruction in the larynx or trachea). Lower respiratory tract symptoms entail wheezing, deep chest pain, and carbonaceous sputum (material coughed up by the lungs, expectorated, and accompanied by the presence of particulate residues of combustion).

Treatment of smoke inhalation victims is primarily supportive, including decontamination (removal of clothes, washing or showering of patient) and removal of the individual from the source. This is followed by endotracheal intubation and administration of humidified oxygen, β-agonists and/or steroids for bronchospasm, and epinephrine for stridor. Carbon monoxide or cyanide poisoning, which often accompany smoke inhalation, may complicate the case (see below).

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* Interestingly, about 50% of patients receiving general anesthetics hypoventilate (decrease in normal respirations per minute, rpm), a state accompanied by depressed alveolar ventilation and retention of CO_2. Thus, hypoventilation increases blood PCO_2. Hyperventilation (increase in rpm) enhances elimination of blood CO_2 and causes respiratory alkalosis. The response here is peripheral vasodilation and a fall in blood pressure. Kidney, CNS, and intestinal arteries, however, constrict.

** Burning of cellulose acetate film, resins, paper, polystyrene, nylon, petroleum products, rubber, wool, polyurethane, acrylics, wood, and organic material generates TCPs.

*** RMV is a product of number of respirations per minute (rpm) by volume of air inspired per respiration (V_T, tidal volume).

23.5 LACRIMATING AGENTS (TEAR GAS)

23.5.1 Introduction

Before World War I, the mechanisms of biological and chemical alkylating agents were surfacing. The search for less toxic, yet severely irritating compounds was already progressing. Law enforcement and governing bodies were convinced that such chemicals could be used in domestic (personal protection, crowd control) or in military situations (war). This understanding prompted the effort to develop agents that could be effective tools for law enforcement while avoiding life-threatening force. Thus spawned the introduction of lacrimating agents, popularly referred to as tear gas or pepper spray. Unlike the pulmonary irritants or asphyxiants that have practical industrial and commercial applications, lacrimating agents were developed specifically to cause irritation.

23.5.2 Chemical Agents

The compounds consist mostly of chemically invariable groups of brominated or chlorinated, simple or aromatic hydrocarbons that cause severe local, upper respiratory, and lower respiratory illness. Most of the agents are highly lipid-soluble powders. They are dissolved in organic solvents to effect aerosol delivery, or burned and exploded for military use. Table 23.5 summarizes the properties, chemistry, and clinical effects of popular lacrimating agents currently used for domestic and military use. Today, the compounds are all organically synthesized and have otherwise limited commercial or industrial utility.

23.6 CHEMICAL ASPHYXIANTS

As noted above, chemical asphyxiants produce toxicity through induction of cellular hypoxia or anoxia. The agents alter the oxygen-carrying capacity of hemoglobin (such as with carbon monoxide) or inhibit cellular metabolic enzymes (cyanide, hydrogen sulfide), ultimately interfering with normal physiologic respiration. Among the chemical asphyxiants, carbon monoxide, cyanide, and hydrogen sulfide are the most frequently encountered chemical asphyxiants and are discussed below.

23.7 CARBON MONOXIDE (CO)

23.7.1 Incidence

Each year, nearly 500 unintentional deaths, and more than 1,700 suicides are related to carbon monoxide poisoning in the U.S. An estimated 3,000 to 5,000 people are treated annually for CO poisoning in emergency departments (EDs). Thousands more are either misdiagnosed or do not seek medical care. The statistics support the conclusion that CO poisoning is a serious public health issue.

TABLE 23.5
Lacrimating Agents: Chemical and Clinical Properties

Agent	Chemical (or *Common Name*)	Chemical Properties[a]	Uses	Acute Clinical Effects
Benzyl bromide	bromomethyl-benzene	Liquid, decomposed by water	Chemical war gas	Intense local irritation; large doses cause CNS depression
Bromoacetone	1-bromo-2-propanone	Liquid, turns violet in air	Chemical war gas	Intense local irritation
α-Bromobenzyl cyanide	α-bromobenzene acetonitrile; *camite*	Crystalline powder, odor of soured fruit	Chemical war gas	Intense local irritation
Chloroacetone	1-chloro-2-propanone	Liquid, pungent odor, turns dark with light	Tear gas component for police and military use; insecticide; lead, perfume and drug manufacturing	Intense local irritation
ω-Chloroaceto-phenone	2-chloro-1-phenylethanone; *chemical mace*	Crystalline powder	Riot control agent	Intense local irritation; URT and LRT irritation, pulmonary edema
o-Chlorobenzyl-idenemalononitrile	[(2-chloro-phenyl)methylene] propanedinitrile	Crystalline solid	Riot control agent, chemical warfare agent	Intense local irritation; URT and LRT irritation plus erythema, chest constriction, vesiculation
Chloropicrin	trichloronitro-methane; *acquinite*	Oily liquid	War gas, insecticide, disinfectant, fumigant	URT irritation and lacrimation, potent skin irritant, NVD (orally)

Note: NVD = nausea, vomiting, diarrhea, URT = upper respiratory tract, LRT = lower respiratory tract.

[a] At standard temperature and pressure (STP); All of the compounds are miscible or soluble in acetone, alcohol, chloroform or ether, and are poorly or slightly soluble in water; URT and LRT symptoms are as described in Table 23.2.

23.7.2 Chemical Characteristics and Sources of Exposure

CO is odorless, colorless, and nonirritating, and an abundant product of industrial combustion,* thus appropriately labeled as the *silent killer.*

Principal sources of the gas include commercial and passenger motor vehicle exhaust fumes (1% from new automobiles, above 10% in older models) as well as other gasoline, diesel, and propane-powered engines. Smoke from charcoal fires and organic materials, tobacco smoke (3 to 6% CO), and methylene chloride, account for the majority of sources. Methylene chloride is a useful industrial solvent in paint, cleaning, and food processing industries, as well as an aerosol propellant and insecticide. In fact, upon ingestion, methylene chloride is metabolized by hepatic mixed function oxidases (MFO) to carbon monoxide and carbon dioxide. Because of the wide distribution of the pollutant, it is not surprising to detect normal adult blood CO levels between 0.40% and 0.55%.

23.7.3 Toxicokinetics

Although CO has low aqueous (plasma) solubility, its binding affinity, particularly for hemoglobin (Hb), is high. Like other toxic gases, absorption and binding of CO to hemoglobin depends on the same factors that increase exposure to the substance — i.e., percent CO in ambient air, duration of exposure, and RMV. The degree of binding is estimated according to the following formula:

$$\% \text{ COHb} = \text{RMV} \times [\text{CO}] \times \text{time}$$

where % COHb is the percent carboxyhemoglobin formed, RMV is the respiratory minute volume (described above and equals about 6 l/min in average adults), [CO] is the CO concentration in ambient air, and time of exposure is in minutes. According to this formula, inhaling 500 ppm CO from exhaust fumes (0.05% in a typical open garage with a running motor vehicle engine) for 30 min yields a percent COHb concentration in blood equal to 15%. The compound is not metabolized, and its half-life is approximately 4 to 5 h.

23.7.4 Mechanism of Toxicity

The net effect of CO toxicity is tissue hypoxia. This is mediated through its reversible but high affinity for ferrous ion (Fe^{+2}) in hemoglobin in the red blood cell. The binding is estimated to range from 200 to 250 times that of molecular oxygen for Hb. The strength of the binding results in the formation of a stable carboxyhemoglobin (COHb) moiety. COHb then displaces the oxygen-carrying capacity of Hb, and shifts the *oxygen-Hb dissociation curve* leftward (Figure 23.1). The diagram illustrates the normal sigmoidal relationship between Hb saturation and the partial pressure of oxygen (PO_2, mmHg) dissolved in blood at normal body temperature.** At normal atmospheric pressure, the higher the PO_2, the more oxygen combines

* It is the most abundant pollutant, accounting for 0.001% atmospheric gases.

** The percent saturation expresses the average saturation of Hb with oxygen.

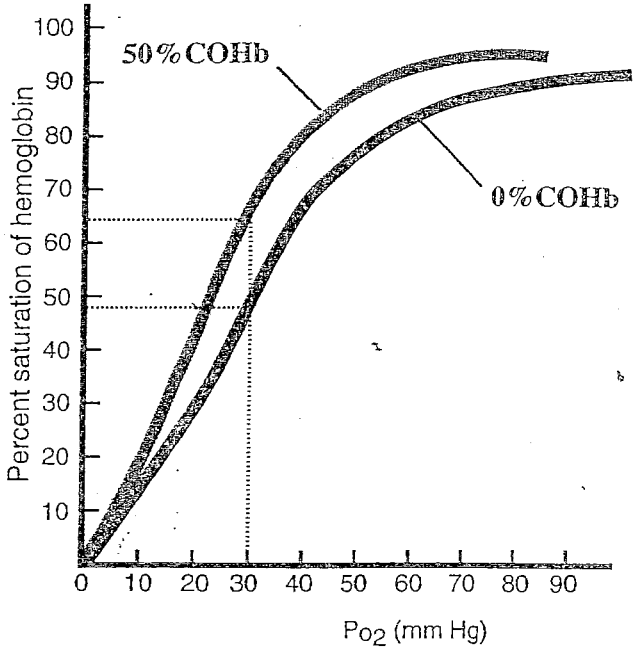

FIGURE 23.1 Oxygen-hemoglobin and carboxyhemoglobin dissociation curves.

with Hb. The curve reaches a plateau at 100 mmHg PO_2, where Hb is almost completely saturated (98%). In the presence of CO, oxygen is displaced from Hb binding sites, rendering less oxygen available for delivery to tissues. The oxygen remaining within the Hb molecule combines more tightly with Hb. At any given PO_2, in the presence of CO, Hb is more saturated with oxygen. This phenomenon is known as the *Bohr effect* (the *Bohr effect* also occurs in metabolic alkalosis, and is stimulated by high blood pH or low blood PCO_2). In addition, CO also binds myoglobin and cytochrome oxidase enzymes with high intensity.

23.7.5 Signs and Symptoms of Acute Toxicity

Clinical presentation of CO poisoning depends on the time of exposure and the concentration of CO in the area, as noted above. Acute, high-concentration exposure, such as might occur in an enclosed space (automobile exhaust in a closed garage) will produce more severe signs and symptoms than chronic, low-concentration exposure (as with faulty heating systems). The latter scenario may be misdiagnosed as mimicking a bacterial or viral infection. Symptoms from acute, mild exposure range from asymptomatic to headache, dizziness, malaise, and fatigue. Moderate exposure may present with confusion, lethargy, ataxia, syncope, and nystagmus.* Severe intoxication manifests as seizures, pulmonary edema, myocardial infarction, and coma. The classic cherry-red discoloration of the face and extremities, due to uncompensated peripheral vasodilation, is evident only in severe poisoning. Blood samples for gas analysis must be obtained immediately after exposure (using blood gas CO-oximetry). Calculation of percentage of arterial

* Pendular or jerky rhythmical oscillation of the eyeballs.

blood oxyhemoglobin (SaO_2), based on blood gas analysis, is often falsely elevated because of COHb high affinity binding. Other routine clinical laboratory values may also lead to inaccurate conclusions.

Although recovery following nonfatal acute exposure is often complete within several days, subacute complications develop, depending on the severity of exposure. The complications include persistent neurologic and myocardial dysfunction, peripheral neuropathy, aspiration pneumonitis, and ischemic skin. Approximately 10 to 30% of victims of severe acute poisoning will display delayed-onset neurobehavioral dysfunction, also known as *CO-induced delayed neuropsychiatric syndrome* (CO-DNS). The condition is characterized by impaired cognitive function, personality changes, dementia, and symptoms resembling Parkinson's disease. Individuals at greater risk for development of complications are patients with a history of heart disease, anemia, and chronic obstructive pulmonary disease (COPD), and patients exposed in the presence of alcohol or respiratory depressants. Infants are also at greater risk for CO-DNS.

23.7.6 Treatment of Acute Poisoning

As with any agent suspected of causing CNS depression or disrupting cardiovascular function, clinical history and evaluation should determine other etiologies, such as intoxication with alcohol or other CNS depressants. Presence of concurrent cyanide poisoning (particularly in burn victims) may aggravate the complications. The goal of treatment of CO inhalation victims, then, is to reduce the development of cerebral and cardiovascular ischemia and to increase the dissociation of COHb. Initial management includes removal of the individual from the source (while minimizing muscle and spinal movement, if possible), followed by administration of supplemental humidified oxygen soon after. Maintenance of respiration, fluid and electrolyte replacement, and clinical chemistry determination are largely supportive. Administration of 100% normobaric* oxygen reduces the half-life of 50% COHb level from about 4 h in room air to approximately 50 to 60 min,** although longer periods may be required in high-risk patients. Treatment continues until COHb levels drop to within normal range.

23.8 CYANIDE

23.8.1 Chemical Characteristics, Occurrence, and Uses

Cyanic acid (hydrogen cyanate, HCNO) is the starting chemical principle for the various salt forms of cyanide, including the sodium (cyanogran, NaCN), potassium (KCN), and calcium (CaCN) salts. Hydrogen cyanide (HCN, hydrocyanic acid, prussic acid) is a gas and a catalyst and is prepared from the cyanate salts. In addition, the compounds occur naturally as cyanogenic glycosides. The compounds are found

* At 1 atm of pressure.

** Although some studies have demonstrated a further reduction of the half-life to less than 40 min with hyperbaric oxygen (i.e., 100% oxygen at 3 atm of pressure), the results from this mode of therapy are equivocal. As noted above, hyperbaric oxygen is associated with signs and symptoms of oxygen toxicity.

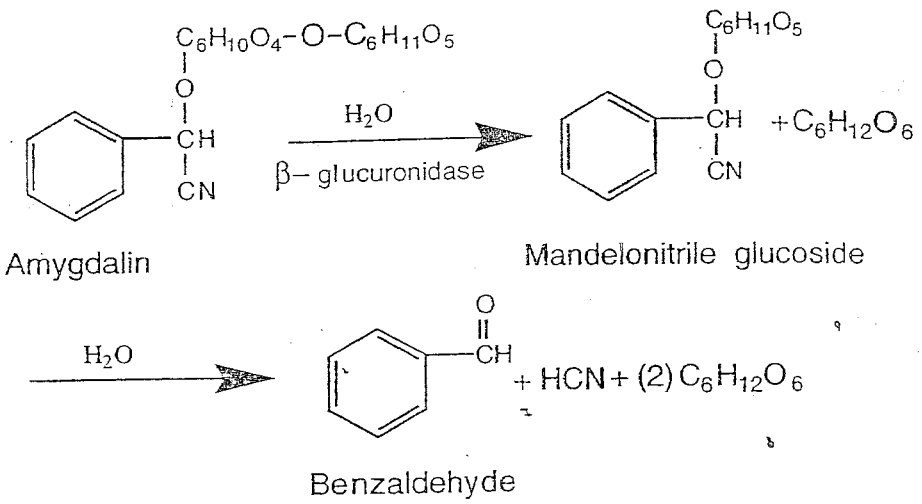

FIGURE 23.2 Cyanogenic glycosides and hydrolysis of amygdalin.

from 0.01 to 14% in the seeds of various nuts, including almonds (highest concentration, 2 to 14%), cherries, plums, apples, peaches, apricots, pears, plums, and rosaceous plants, as well as in bamboo sprouts and cassava. Figure 23.2 illustrates the hydrolysis of amygdalin, the most widely distributed cyanogenic glycoside. Most hydrolyzing agents, in the presence of the enzyme β-glucuronidase, are capable of producing the hydrolysis products of amygdalin, i.e., mandelonitrile glucoside (an intermediate) plus glucose, benzaldehyde, and hydrocyanic acid.

Cyanide compounds are also valuable industrial chemicals used in electroplating and electropolishing, manufacturing of plastics, extraction of gold and silver from ores, as fumigants, in fertilizer, and in artificial nail glue removers. Therapeutically, sodium nitroprusside, a direct arterial vasodilator used in the treatment of emergency hypertension, releases five molecules of CN when metabolized, which also accumulates with fast infusion rates (see Chapter 18, "Cardiovascular Drugs"). As with CO poisoning, fire victims are also prone to CN intoxication.

23.8.2 Mechanism of Toxicity

Cyanide produces histotoxic anoxia by inhibiting oxidative phosphorylation, resulting in arrest of cellular respiration (see Figure 16.3, Chapter 16). By binding to cytochrome a/a3, CN forms a CN–cytochrome oxidase–Fe^{+3} complex. The complex interferes with the transfer of electrons to O_2, the final electron acceptor. Ultimately, CN blocks the electron transport chain and inhibits metabolic respiration. It provokes a decrease in cellular oxygen utilization, prevents oxidative phosphorylation of ADP to ATP, and prompts an increase in venous PO_2 (arterialization of venous blood).* The decrease in aerobic respiration forces the cell to revert to anaerobic metabolism, which generates excess lactic acid, triggering metabolic acidosis.

* Interestingly, the patient is not **cyanotic**, and availability and binding of oxygen are not compromised. In fact, arterial PO_2 appears normal (100 mmHg).

23.8.3 Toxicokinetics

Acute lethal toxicity results within 1 h from an oral dose of 100 to 200 mg, while inhalation of 150 to 200 ppm of HCN gas is fatal (approximately only 60% of the population can smell 0.2 to 5.0 ppm). Trace amounts of CN are generally detoxified slowly by binding to circulating methemoglobin (methHb). The resulting cyanomethemoglobin complex prevents access to the cytochrome enzymes. Normally circulating rhodanese enzyme (thiosulfate cyanide sulfur transferase) transfers a sulfur group to the cyanomethemoglobin complex, forming a relatively nontoxic thiocyanate ion that is eventually eliminated by renal excretion. Chronic, low dose intoxication is more insidious.

23.8.4 Signs and Symptoms of Acute Toxicity

Signs and symptoms precipitate rapidly with exposure to HCN vapors. Initially symptoms of neurological toxicity appear, including headache, nausea, vomiting, weakness, and dizziness. The chemical stimulates chemoreceptors in the carotid artery, triggering reflex hyperpnea (increase in respirations), tachypnea (gasping for air), and pulmonary edema. Hypotension with reflex tachycardia completes the cardiovascular presentation. With high doses, the victim is stuporous yet responsive, where the condition may deteriorate to hypoxic convulsions, hypotension, coma, and death.

23.8.5 Treatment of Acute Poisoning

As with CO poisoning, initial management of patients with CN intoxication includes removal of the individual from the source, decontamination (removal of clothes, flushing with water, if necessary), and administration of activated charcoal or gastric lavage if the victim is encountered soon after ingestion. The goal of treatment is to immediately decrease CN binding to cytochrome enzymes with the specific antidote available. The Cyanide Antidote Package (various manufacturers) consists of three major components:

1. Amyl nitrite inhalant, 0.3 ml (12 aspirols)
2. Sodium nitrite, 300 mg in 10 ml (2 ampoules)
3. Sodium thiosulfate, 12.5 g in 50 ml (25% solution, 2 ampoules)

plus disposable syringes, stomach tube, tourniquet, and instructions. The primary mechanism of detoxification involves conversion of CN to the nontoxic thiocyanate ion, in preparation for renal elimination. Initially, either i.v. sodium nitrite (300 mg over 3 to 5 min)* or amyl nitrite inhalant (1 or 2 crushed aspirols every 2 to 3 min, if i.v. route is not accessible) are administered. Thus, the nitrites induce formation of cyanomethemoglobin-Fe^{+3} (CN–Hb–Fe^{+3}) complex in preference to CN–cytochrome oxidase–Fe^{+3}. Nitrites convert reduced Hb–Fe^{+2} ([H]) to oxidized methHb

* In children, initial dose of sodium nitrite (mg/kg) is calculated according to the patient's Hb level (g/dl).

([O]), freeing cytochrome oxidase enzyme to resume oxidative phosphorylation. The sequence is outlined in Reaction 1:

$$Hb\text{-}Fe^{+2} + NO_2 \rightarrow Hb\text{-}Fe^{+3} + NO \qquad (23.1)$$

Since methHb has a greater affinity for CN than cytochrome oxidase, it induces the transfer of CN from the cytochrome enzyme complex to methHb, forming cyanomethemoglobin (CN–Hb–Fe^{+3}) according to Reaction 2:

$$Hb\text{-}Fe^{+3} + CN\text{–cytochrome–}Fe^{+3} \rightarrow CN\text{–}Hb\text{–}Fe^{+3} + \text{cytochrome–}Fe^{+3} \qquad (23.2)$$

Peak methHb levels are reached within 30 min of i.v. administration in adults. Since cyanomethemoglobin is relatively unstable and reversible, the subsequent step is to force renal excretion of the CN moiety by administration of sodium thiosulfate. As mentioned above, this requires the rhodanase enzyme reaction that naturally detoxifies trace amounts of circulating CN ions. This reaction (3, below) is accelerated by supplying exogenous sulfur from the administration of sodium thiosulfate ($Na_2S_2O_3$). $Na_2S_2O_3$ (12.5 g i.v. over 10 min) is administered immediately after sodium nitrite (400 mg/kg, up to 12.5 g total in children). The treatment results in the formation of thiocyanate, sodium sulfite, and regenerated methemoglobin, respectively.

$$CN\text{-}Hb\text{-}Fe^{+3} + Na_2S_2O_3 \rightarrow CN\text{-}S + Na_2SO_3 + Hb\text{–}Fe^{+3} \qquad (23.3)$$

Adverse reactions associated with nitrites involve hypotension and the risk of production of excess, life-threatening amounts of methemoglobin. In excess, methemoglobin decreases availability of oxyhemoglobin (reduced form) necessary for oxygen transport. Other antidotes for CN poisoning, such as 4-methylaminophenol (4-DMAP), hydroxycobalamin, dicobalt-EDTA, and hyperbaric oxygen, are not FDA approved or recommended.

Permanent neurological damage (Parkinson-like syndrome) is a complication of severe CN toxicity. Higher levels of thiocyanate are also implicated in the development of tobacco amblyopia (in chronic smokers) and tropical ataxic neuropathy (in diets rich in cassava).

23.9 METHODS OF DETECTION

Clinical chemistry analysis, hematology assays (including hemoglobin and hematocrit tests) and arterial blood gas determinations are not clinically useful indicators for CO poisoning. Routine blood gas analysis (pulse oximetry), used to measure changes in oxyhemoglobin content, may not be sensitive enough, due to the high affinity COHb complex. Carboxyhemoglobin blood levels are useful if performed soon after acute exposure. Automated spectrophotometric devices (CO-oximeters) provide valuable measures of carboxyhemoglobin, oxyhemoglobin, and methemoglobin, the levels of which are correlated with severity of CO exposure. The tech-