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SECTION IX TOXICOLOGY

CHAPTER 56

Introduction to Toxicology: Occupational & Environmental

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Humans live in a chemical environment and inhale, ingest, or absorb from the skin many of these chemicals. Toxicology is concerned with the deleterious effects of these chemical agents on all living systems. In the biomedical area, however, the toxicologist is primarily concerned with adverse effects in humans resulting from exposure to drugs and other chemicals as well as the demonstration of safety or hazard associated with their use.

Occupational Toxicology

Occupational toxicology deals with the chemicals found in the workplace. The major emphasis of occupational toxicology is to identify the agents of concern, identify the acute and chronic diseases that they cause, define the conditions under which they may be used safely, and prevent absorption of harmful amounts of these chemicals. Occupational toxicologists may also define and carry out programs for the surveillance of exposed workers and the environment in which they work. Regulatory limits and voluntary guidelines have been elaborated to establish safe ambient air concentrations for many chemicals found in the workplace. Governmental and supragovernmental bodies throughout the world have generated workplace health and safety rules, including short-and long-term exposure limits for workers. These permissible exposure limits (PELS) have the power of law. Copies of the United States Occupational Safety and Health Administration (OSHA) standards may be found on OSHA's website at http://www.osha.gov. Copies of the United States Mine Safety and Health Administration (MSHA) standards may be found at http://www.msha.gov.

Voluntary organizations, such as the American Conference of Governmental Industrial Hygienists (ACGIH), periodically prepare lists of recommended **threshold limit values (TLVs)** for many chemicals. These guidelines are periodically updated, but regulatory imperatives in the United States are not updated except under certain extraordinary circumstances. These TLV guidelines are useful as reference points in the evaluation of potential workplace exposures. Copies of current TLV lists may be obtained from the ACGIH at http://www.acgih.org.

Environmental Toxicology

Environmental toxicology deals with the potentially deleterious impact of chemicals, present as pollutants of the environment, on

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living organisms. The term environment includes all the surroundings of an individual organism, but particularly the air, soil, and water. Although humans are considered a target species of particular interest, other species are of considerable importance as potential biologic targets.

Air pollution is a product of industrialization, technologic development, and increased urbanization. Humans may also be exposed to chemicals used in the agricultural environment as pesticides or in food processing that may persist as residues or ingredients in food products. Air contaminants are regulated in the United States by the Environmental Protection Agency (EPA) based on both health and esthetic considerations. Tables of regulated air contaminants and other regulatory issues that relate to air contaminants in the United States may be found at http://www.epa.gov. Many states also have individual air contaminant regulations that may be more rigorous than those of the EPA. Many other nations and some supragovernmental organizations regulate air contaminants.

The United Nations Food and Agriculture Organization and the World Health Organization (FAO/WHO) Joint Expert Commission on Food Additives adopted the term **acceptable daily intake (ADI)** to denote the daily intake of a chemical from food that, during an entire lifetime, appears to be without appreciable risk. These guidelines are reevaluated as new information becomes available. In the United States, the Food and Drug Administration (FDA) and the Department of Agriculture are responsible for the regulation of contaminants such as pesticides, drugs, and chemicals in foods. Major international problems have occurred because of traffic among nations in contaminated or adulterated foods from countries whose regulations and enforcement of pure food and drug laws are lax or nonexistent.

Ecotoxicology

Ecotoxicology is concerned with the toxic effects of chemical and physical agents on populations and communities of living organisms within defined ecosystems; it includes the transfer pathways of those agents and their interactions with the environment. Traditional toxicology is concerned with toxic effects on individual organisms; ecotoxicology is concerned with the impact on populations of living organisms or on ecosystems.

TOXICOLOGIC TERMS & DEFINITIONS

Hazard & Risk

Hazard is the ability of a chemical agent to cause injury in a given situation or setting; the conditions of use and exposure are primary considerations. To assess hazard, one needs to have knowledge about both the inherent toxicity of the substance and the amounts to which individuals are liable to be exposed. Humans may be able to use potentially toxic substances when the necessary conditions minimizing absorption are established and respected. However, hazard is often a description based on subjective estimates rather than objective evaluation.

Risk is defined as the expected frequency of the occurrence of an undesirable effect arising from exposure to a chemical or physical agent. Estimation of risk makes use of dose-response data and extrapolation from the observed relationships to the expected responses at doses occurring in actual exposure situations. The quality and suitability of the biologic data used in such estimates are major limiting factors.

Routes of Exposure

The route of entry for chemicals into the body differs in different exposure situations. In the industrial setting, inhalation is the major route of entry. The transdermal route is also quite important, but oral ingestion is a relatively minor route. Consequently, primary prevention should be designed to reduce or eliminate absorption by inhalation or by topical contact. Atmospheric pollutants gain entry by inhalation and by dermal contact. Water and soil pollutants are absorbed through inhalation, ingestion, and dermal contact.

Duration of Exposure

Toxic reactions may differ qualitatively depending on the duration of the exposure. A single exposure—or multiple exposures occurring over a brief period from seconds to 1 or 2 days—represents acute exposure. Multiple exposures continuing over a longer period of time represent chronic exposure. In the occupational setting, both acute (eg, accidental discharge) and chronic (eg, repetitive handling of a chemical) exposures occur. Exposures to chemicals found in the environment such as air and water pollutants often cause chronic exposure, but sudden large chemical releases may result in acute massive population exposure with serious or lethal consequences.

ENVIRONMENTAL CONSIDERATIONS

Certain chemical and physical characteristics are important for estimating the potential hazard involved for environmental toxicants. In addition to information regarding effects on different organisms, knowledge about the following properties is essential to predict the environmental impact: the degradability of the substance; its mobility through air, water, and soil; whether or not bioaccumulation occurs; and its transport and biomagnification through food chains. (See Box: Bioaccumulation & Biomagnification.) Chemicals that are poorly degraded (by abiotic or biotic pathways) exhibit environmental persistence and thus can accumulate. Typical examples of such chemicals include the persistent organic pollutants (POP) such as polychlorinated biphenyls and similar substances. Lipophilic substances such as the once-widespread organochlorine pesticides (eg, DDT) tend to bioaccumulate in body fat, resulting in tissue residues. Slowly released over time, these residues and their metabolites may have chronic adverse effects such as endocrine disruption. When the toxicant is incorporated into the food chain, biomagnification occurs as one species feeds on others and concentrates the chemical. Humans stand at the apex of the food chain. They may be

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Bioaccumulation & Biomagnification

If the intake of a long-lasting contaminant by an organism exceeds the latter's ability to metabolize or excrete the substance, the chemical accumulates within the tissues of the organism. This is called **bioaccumulation.**

Although the concentration of a contaminant may be virtually undetectable in water, it may be magnified hundreds or thousands of times as the contaminant passes up the food chain. This is called **biomagnification.**

The biomagnification of polychlorinated biphenyls (PCBs) in the Great Lakes of North America is illustrated by the following residue values available from *Environment Canada,* a report published by the Canadian government, and other sources.

Thus, the biomagnification for this substance in the food chain, beginning with phytoplankton and ending with the herring gull, is nearly 50,000-fold. Domestic animals and humans may eat fish from the Great Lakes, resulting in PCB residues in these species as well.

Source	PCB Concentration (ppm)[1]	Concentration Relative to Phytoplankton
Phytoplankton	0.0025	1
Zooplankton	0.123	49.2
Rainbow smelt	1.04	416
Lake trout	4.83	1,932
Herring gull	124	49,600

[1]Sources: *Environment Canada, The State of Canada's Environment,* 1991, Government of Canada, Ottawa; and other publications.

exposed to highly concentrated pollutant loads as bioaccumulation and biomagnification occur. The pollutants that have the widest environmental impact are poorly degradable; are relatively mobile in air, water, and soil; exhibit bioaccumulation; and also exhibit biomagnification.

SPECIFIC CHEMICALS

AIR POLLUTANTS

Five major substances account for about 98% of air pollution: carbon monoxide (CO, about 52%), sulfur oxides (about 14%), hydrocarbons (about 14%), nitrogen oxides (about 14%), and particulate matter (about 4%). The sources of these chemicals include transportation, industry, generation of electric power, space heating, and refuse disposal. Sulfur dioxide and smoke resulting from incomplete combustion of coal have been associated with acute adverse effects, particularly among the elderly and individuals with preexisting cardiac or respiratory disease. Ambient air pollution has been implicated as a contributing factor in bronchitis, obstructive ventilatory disease, pulmonary emphysema, bronchial asthma, and lung cancer. EPA standards for these substances apply to the general environment, and OSHA standards apply to workplace exposure.

Carbon Monoxide

Carbon monoxide (CO) is a colorless, tasteless, odorless, and nonirritating gas, a byproduct of incomplete combustion. The average concentration of CO in the atmosphere is about 0.1 ppm; in heavy traffic, the concentration may exceed 100 ppm. The recommended 2008 threshold limit values (TLV-TWA and TLV-STEL) are shown in Table 56–1.

A. Mechanism of Action

CO combines reversibly with the oxygen-binding sites of hemoglobin and has an affinity for hemoglobin that is about 220 times that of oxygen. The product formed—carboxyhemoglobin—cannot transport oxygen. Furthermore, the presence of carboxyhemoglobin interferes with the dissociation of oxygen from the remaining oxyhemoglobin, thus reducing the transfer of oxygen to tissues. The brain and the heart are the organs most affected. Normal nonsmoking adults have carboxyhemoglobin levels of less than 1% saturation (1% of total hemoglobin is in the form of carboxyhemoglobin); this level has been attributed to the endogenous formation of CO from heme catabolism. Smokers may exhibit 5–10% saturation, depending on their smoking habits. A person breathing air containing 0.1% CO (1000 ppm) would have a carboxyhemoglobin level of about 50%.

B. Clinical Effects

The principal signs of CO intoxication are those of hypoxia and progress in the following sequence: (1) psychomotor impairment; (2) headache and tightness in the temporal area; (3) confusion and loss of visual acuity; (4) tachycardia, tachypnea, syncope, and coma; and (5) deep coma, convulsions, shock, and respiratory failure. There is great variability in individual responses to a given carboxyhemoglobin concentration. Carboxyhemoglobin levels below 15% may produce headache and malaise; at 25% many workers complain of headache, fatigue, decreased attention span, and loss of fine motor coordination. Collapse and syncope may appear at around 40%; with levels above 60%, death may ensue as a result of irreversible damage to the brain and myocardium. The clinical effects may be aggravated by heavy labor, high altitudes, and high ambient temperatures. Although CO intoxication is usually thought of as a form of acute toxicity, there is some evidence that chronic exposure to low levels may lead to undesirable effects, including the development of atherosclerotic coronary disease in cigarette smokers. The fetus may be quite susceptible to the effects of CO exposure.

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C. Treatment

In cases of acute intoxication, removal of the individual from the exposure source and maintenance of respiration are essential, followed by administration of oxygen—the specific antagonist to CO—within the limits of oxygen toxicity. With room air at 1 atm, the elimination half-time of CO is about 320 minutes; with 100% oxygen, the half-time is about 80 minutes; and with hyperbaric oxygen (2–3 atm), the half-time can be reduced to about 20 minutes. If a hyperbaric oxygen chamber is readily available, it should be used in the treatment of CO poisoning for severely poisoned patients; however, there remain questions about its effectiveness. Progressive recovery from effectively treated CO poisoning, even of a severe degree, is often complete, although some patients demonstrate persistent impairment for a prolonged period of time.

Sulfur Dioxide

Sulfur dioxide (SO_2) is a colorless, irritant gas generated primarily by the combustion of sulfur-containing fossil fuels. The 2008 TLVs are given in Table 56–1.

A. Mechanism of Action

On contact with moist membranes, SO_2 forms sulfurous acid, which is responsible for its severe irritant effects on the eyes, mucous membranes, and skin. Approximately 90% of inhaled SO_2 is absorbed in the upper respiratory tract, the site of its principal effect. The inhalation of SO_2 causes bronchial constriction; parasympathetic reflexes and altered smooth muscle tone appear to be involved. Exposure to 5 ppm SO_2 for 10 minutes leads to increased resistance to airflow in most humans. Exposures of 5–10 ppm are reported to cause severe bronchospasm; 10–20% of the healthy young adult population is estimated to be reactive to even lower concentrations. The phenomenon of adaptation to irritating concentrations has been reported in workers. However, current studies have not confirmed this phenomenon. Asthmatic individuals are especially sensitive to SO_2.

TABLE 56–1 Threshold limit values (TLVs) of some common air pollutants and solvents.

Compound	TLV (ppm)	
	TWA[1]	STEL[2]
Benzene	0.5	2.5
Carbon monoxide	25	NA
Carbon tetrachloride	5	10
Chloroform	10	NA
Nitrogen dioxide	3	5
Ozone	0.05	NA
Sulfur dioxide	2	5
Tetrachloroethylene	25	100
Toluene	50	NA
1,1,1-Trichloroethane	350	450
Trichloroethylene	50	100

[1]TLV-TWA (time weighted average) is the concentration for a normal 8-hour workday or 40-hour workweek to which workers may be repeatedly exposed without adverse effects.

[2]TLV-STEL (short-term exposure limit) is the maximum concentration that should not be exceeded at any time during a 15-minute exposure period.

NA, none assigned.

B. Clinical Effects and Treatment

The signs and symptoms of intoxication include irritation of the eyes, nose, and throat and reflex bronchoconstriction. In asthmatic subjects, exposure to SO_2 may result in an acute asthmatic episode. If severe exposure has occurred, delayed-onset pulmonary edema may be observed. Cumulative effects from chronic low-level exposure to SO_2 are not striking, particularly in humans but these effects have been associated with aggravation of chronic cardiopulmonary disease. When combined exposure to high respirable particulate loads and SO_2 occurs, the mixed irritant load may increase the toxic respiratory response. Treatment is not specific for SO_2 but depends on therapeutic maneuvers used in the treatment of irritation of the respiratory tract and asthma.

Nitrogen Oxides

Nitrogen dioxide (NO_2) is a brownish irritant gas sometimes associated with fires. It is formed also from fresh silage; exposure of farmers to NO_2 in the confines of a silo can lead to silo-filler's disease. The 2008 TLVs are shown in Table 56–1.

A. Mechanism of Action

NO_2 is a relatively insoluble deep lung irritant capable of producing pulmonary edema. The type I cells of the alveoli appear to be the cells chiefly affected on acute exposure. At higher exposure, both type I and type II alveolar cells are damaged. Exposure to 25 ppm of NO_2 is irritating to some individuals; 50 ppm is moderately irritating to the eyes and nose. Exposure for 1 hour to 50 ppm can cause pulmonary edema and perhaps subacute or chronic pulmonary lesions; 100 ppm can cause pulmonary edema and death.

B. Clinical Effects and Treatment

The signs and symptoms of acute exposure to NO_2 include irritation of the eyes and nose, cough, mucoid or frothy sputum production, dyspnea, and chest pain. Pulmonary edema may appear within 1–2 hours. In some individuals, the clinical signs may subside in about 2 weeks; the patient may then pass into a second stage of abruptly increasing severity, including recurring pulmonary edema and fibrotic destruction of terminal bronchioles (bronchiolitis obliterans). Chronic exposure of laboratory animals to 10–25 ppm NO_2 has resulted in emphysematous changes; thus, chronic effects in humans are of concern. There is no specific treatment for acute intoxication by NO_2; therapeutic measures for the management of deep lung irritation and noncardiogenic pulmonary edema are used. These measures include maintenance of gas exchange with adequate oxygenation and alveolar ventilation. Drug therapy may include bronchodilators, sedatives, and antibiotics.

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Ozone

Ozone (O_3) is a bluish irritant gas that occurs normally in the earth's atmosphere, where it is an important absorbent of ultraviolet light. In the workplace, it can occur around high-voltage electrical equipment and around ozone-producing devices used for air and water purification. It is also an important oxidant found in polluted urban air. There is a near-linear gradient between exposure (1-hour level, 20–100 ppb) and response. See Table 56–1 for 2008 TLVs.

A. Clinical Effects and Treatment

O_3 is an irritant of mucous membranes. Mild exposure produces upper respiratory tract irritation. Severe exposure can cause deep lung irritation, with pulmonary edema when inhaled at sufficient concentrations. Ozone penetration in the lung depends on tidal volume; consequently, exercise can increase the amount of ozone reaching the distal lung. Some of the effects of O_3 resemble those seen with radiation, suggesting that O_3 toxicity may result from the formation of reactive free radicals. The gas causes shallow, rapid breathing and a decrease in pulmonary compliance. Enhanced sensitivity of the lung to bronchoconstrictors is also observed.

Exposure around 0.1 ppm O_3 for 10–30 minutes causes irritation and dryness of the throat; above 0.1 ppm, one finds changes in visual acuity, substernal pain, and dyspnea. Pulmonary function is impaired at concentrations exceeding 0.8 ppm. Airway hyperresponsiveness and airway inflammation have been observed in humans.

The response of the lung to O_3 is a dynamic one. The morphologic and biochemical changes are the result of both direct injury and secondary responses to the initial damage. Long-term exposure in animals results in morphologic and functional pulmonary changes. Chronic bronchitis, bronchiolitis, fibrosis, and emphysematous changes have been reported in a variety of species, including humans, exposed to concentrations above 1 ppm. There is no specific treatment for acute O_3 intoxication. Management depends on therapeutic measures used for deep lung irritation and noncardiogenic pulmonary edema (see Nitrogen Oxides, above).

SOLVENTS

Halogenated Aliphatic Hydrocarbons

These agents once found wide use as industrial solvents, degreasing agents, and cleaning agents. The substances include carbon tetrachloride, chloroform, trichloroethylene, tetrachloroethylene (perchloroethylene), and 1,1,1-trichloroethane (methyl chloroform). However, because of the likelihood that halogenated aliphatic hydrocarbons are carcinogenic to humans, carbon tetrachloride and trichloroethylene have largely been removed from the workplace. Perchloroethylene and trichloroethane are still in use for dry cleaning and solvent degreasing, but it is likely that their use will be very limited in the future. Dry cleaning as an occupation is listed as a class 2B carcinogenic activity by the International Agency for Research Against Cancer (IARC). Fluorinated aliphatics such as the freons and closely related compounds have also been used in the workplace and in consumer goods, but because of the severe environmental damage they cause, their use has been limited or eliminated by international treaty agreements. The common halogenated aliphatic solvents also create serious problems as persistent water pollutants. They are widely found in both groundwater and drinking water as a result of poor disposal practices.

See Table 56–1 for recommended TLVs.

A. Mechanism of Action and Clinical Effects

In laboratory animals, the halogenated hydrocarbons cause central nervous system depression, liver injury, kidney injury, and some degree of cardiotoxicity. Several are also carcinogenic in animals and are considered probable carcinogens in humans. Trichloroethylene and tetrachloroethylene are listed as "reasonably anticipated to be a human carcinogen" by the US National Toxicology Program, and as class 2A probable human carcinogens by IARC. These substances are depressants of the central nervous system in humans; chloroform is the most potent. Chronic exposure to tetrachloroethylene and possibly 1,1,1-trichloroethane can cause impaired memory and peripheral neuropathy. Hepatotoxicity is also a common toxic effect that can occur in humans after acute or chronic exposures; carbon tetrachloride is the most potent of the series. Nephrotoxicity can occur in humans exposed to carbon tetrachloride, chloroform, and trichloroethylene. With chloroform, carbon tetrachloride, trichloroethylene, and tetrachloroethylene, carcinogenicity has been observed in lifetime exposure studies performed in rats and mice and in some human epidemiologic studies. Reviews of the epidemiologic literature on the occupational exposure of workers to various halogenated aliphatic hydrocarbon solvents including trichloroethylene and tetrachloroethylene have found significant associations between exposure to the agent and renal, prostate, and testicular cancer. Other cancers have been found to be increased but their incidence has not reached statistical significance.

B. Treatment

There is no specific treatment for acute intoxication resulting from exposure to halogenated hydrocarbons. Management depends on the organ system involved.

Aromatic Hydrocarbons

Benzene is used for its solvent properties and as an intermediate in the synthesis of other chemicals. The 2008 recommended TLVs are given in Table 56–1. Benzene remains an important component of gasoline and may be found in premium gasolines at concentrations as high as 2%. In cold climates such as Alaska, benzene concentrations in gasoline may reach 5%. The PEL promulgated by OSHA is 1 ppm in the air and a 5 ppm limit for skin exposure. The National Institute for Occupational Safety and Health (NIOSH) and others have recommended that the exposure limits

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for benzene be further reduced to 0.1 ppm because excess blood cancers occur at the current PEL. The acute toxic effect of benzene is depression of the central nervous system. Exposure to 7500 ppm for 30 minutes can be fatal. Exposure to concentrations larger than 3000 ppm may cause euphoria, nausea, locomotor problems, and coma; vertigo, drowsiness, headache, and nausea may occur at concentrations ranging from 250 to 500 ppm. No specific treatment exists for the acute toxic effect of benzene.

Chronic exposure to benzene can result in very serious toxic effects, the most significant of which is bone marrow injury. Aplastic anemia, leukopenia, pancytopenia, and thrombocytopenia occur at higher levels of exposure, as does leukemia. Chronic exposure to much lower levels has been associated with leukemia of several types as well as lymphomas, myeloma, and myelodysplastic syndrome. Recent studies have shown the occurrence of leukemia following exposures as low as 2 ppm-years. The pluri-potent bone marrow stem cells appear to be a target of benzene or its metabolites and other stem cells may also be targets. Epidemiologic data confirm a causal association between benzene exposure and an increased incidence of leukemia in workers. Most organizations now classify benzene as a known human carcinogen.

Toluene (methylbenzene) does not possess the myelotoxic properties of benzene, nor has it been associated with leukemia. It is, however, a central nervous system depressant and a skin and eye irritant. It is also fetotoxic. See Table 56–1 for the TLVs. Exposure to 800 ppm can lead to severe fatigue and ataxia; 10,000 ppm can produce rapid loss of consciousness. Chronic effects of long-term toluene exposure are unclear because human studies indicating behavioral effects usually concern exposures to several solvents. In limited occupational studies, however, metabolic interactions and modification of toluene's effects have not been observed in workers also exposed to other solvents. Less refined grades of toluene contain benzene.

Xylene (dimethylbenzene) has been substituted for benzene in many solvent degreasing operations. Like toluene, the three xylenes do not possess the myelotoxic properties of benzene, nor have they been associated with leukemia. Xylene is a central nervous system depressant and a skin irritant. Less refined grades of xylene contain benzene. Estimated TLV-TWA and TLV-STEL are 100 and 150 ppm, respectively.

PESTICIDES

Organochlorine Pesticides

These agents are usually classified into four groups: DDT (chlorophenothane) and its analogs, benzene hexachlorides, cyclodienes, and toxaphenes (Table 56–2). They are aryl, carbocyclic, or heterocyclic compounds containing chlorine substituents. The individual compounds differ widely in their biotransformation and capacity for storage in tissues; toxicity and storage are not always correlated. They can be absorbed through the skin as well as by inhalation or oral ingestion. There are, however, important quantitative differences between the various derivatives; DDT in solution is poorly absorbed through the skin, whereas dieldrin absorption from the skin is very efficient. Organochlorine pesticides have largely been abandoned because they cause severe environmental damage. DDT continues to have very restricted use for domestic mosquito elimination in malaria-infested areas of Africa. This use is controversial, but it is very effective and is likely to remain in place for the foreseeable future. Organochlorine pesticide residues in humans, animals, and the environment present long-term problems that are not yet fully understood.

A. Human Toxicology

The acute toxic properties of all the organochlorine pesticides in humans are qualitatively similar. These agents interfere with inactivation of the sodium channel in excitable membranes and

TABLE 56–2 Organochlorine pesticides.

Chemical Class	Compounds	Toxicity Rating[1]	ADI
DDT and analogs	Dichlorodiphenyltrichloroethane (DDT)	4	0.005
	Methoxychlor	3	0.1
	Tetrachlorodiphenylethane (TDE)	3	…
Benzene hexachlorides	Benzene hexachloride (BHC; hexachlorocyclohexane)	4	0.008
	Lindane	4	0.008
Cyclodienes	Aldrin	5	0.0001
	Chlordane	4	0.0005
	Dieldrin	5	0.0001
	Heptachlor	4	0.0001
Toxaphenes	Toxaphene (camphechlor)	4	…

[1]Toxicity rating: Probable human oral lethal dosage for class 3 = 500–5000 mg/kg, class 4 = 50–500 mg/kg, and class 5 = 5–50 mg/kg. (See Gosselin et al, 1984.)

ADI, acceptable daily intake (mg/kg/d).

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cause rapid repetitive firing in most neurons. Calcium ion transport is inhibited. These events affect repolarization and enhance the excitability of neurons. The major effect is central nervous system stimulation. With DDT, tremor may be the first manifestation, possibly continuing to convulsions, whereas with the other compounds convulsions often appear as the first sign of intoxication. There is no specific treatment for the acute intoxicated state, and management is symptomatic.

The potential carcinogenic properties of organochlorine pesticides have been extensively studied, and results indicate that chronic administration to laboratory animals over long periods results in enhanced oncogenesis. Endocrine pathway disruption is the postulated mechanism. Extrapolation of the animal observations to humans is controversial. However, several large epidemiologic studies found no significant association between the risk of breast cancer and serum levels of DDE, the major metabolite of DDT. Similarly, the results of a case-control study conducted to investigate the relation between DDE and DDT breast adipose tissue levels and breast cancer risk did not support a positive association. In contrast, recent work supports an association between prepubertal exposure to DDT and brain cancer. In addition, recent studies suggest that the risk of testicular cancer is increased in persons with elevated DDE levels. The risk of non-Hodgkin's lymphoma (NHL) also seems to be increased in persons with elevated oxychlordane residues. Therefore, increased cancer risk in people exposed to the halogenated hydrocarbon pesticides is of concern.

B. Environmental Toxicology

The organochlorine pesticides are considered persistent chemicals. Degradation is quite slow when compared with other pesticides, and bioaccumulation, particularly in aquatic ecosystems, is well documented. Their mobility in soil depends on the composition of the soil; the presence of organic matter favors the adsorption of these chemicals onto the soil particles, whereas adsorption is poor in sandy soils. Once adsorbed, they do not readily desorb. These compounds induce significant abnormalities in the endocrine balance of sensitive animal and bird species, in addition to their adverse impact on humans. Their use is appropriately banned in most areas.

Organophosphorus Pesticides

These agents, some of which are listed in Table 56–3, are used to combat a large variety of pests. They are useful pesticides when in direct contact with insects or when used as **plant systemics,** where the agent is translocated within the plant and exerts its effects on insects that feed on the plant. These agents are based on compounds such as soman, sarin, and tabun, which were developed for use as war gases. Some of the less toxic organophosphorus compounds are used in human and veterinary medicine as local or systemic antiparasitics (see Chapters 7 and 53). The compounds are absorbed by the skin as well as by the respiratory and gastrointestinal tracts. Biotransformation is rapid, particularly when compared with the rates observed with the chlorinated hydrocarbon pesticides. Storm and collaborators reviewed current and suggested human inhalation occupational exposure limits for 30 organophosphate pesticides (see References).

TABLE 56–3 Organophosphorus pesticides.

Compound	Toxicity Rating[1]	ADI
Azinphos-methyl	5	0.005
Chlorfenvinphos	…	0.002
Diazinon	4	0.002
Dichlorvos	…	0.004
Dimethoate	4	0.01
Fenitrothion	…	0.005
Malathion	4	0.02
Parathion	6	0.005
Parathion-methyl	5	0.02
Trichlorfon	4	0.01

[1]Toxicity rating: Probable human oral lethal dosage for class 4 = 50-500 mg/kg, class 5 = 5-50 mg/kg, and class 6 = ≤ 5 mg/kg. (See Gosselin et al, 1984.)

ADI, acceptable daily intake (mg/kg/d).

A. Human Toxicology

In mammals as well as insects, the major effect of these agents is inhibition of acetylcholinesterase through phosphorylation of the esteratic site. The signs and symptoms that characterize acute intoxication are due to inhibition of this enzyme and accumulation of acetylcholine; some of the agents also possess direct cholinergic activity. These effects and their treatment are described in Chapters 7 and 8 of this book. Altered neurologic and cognitive functions, as well as psychological symptoms of variable duration, have been associated with exposure to these pesticides. Furthermore, there is some indication of an association of low arylesterase activity with neurologic symptom complexes in Gulf War veterans.

In addition to—and independently of—inhibition of acetylcholinesterase, some of these agents are capable of phosphorylating another enzyme present in neural tissue, the so-called **neuropathy target esterase.** This results in progressive demyelination of the longest nerves. Associated with paralysis and axonal degeneration, this lesion is sometimes called organophosphorus ester-induced delayed polyneuropathy (OPIDP). Delayed central and autonomic neuropathy may occur in some poisoned patients. Hens are particularly sensitive to these properties and have proved very useful for studying the pathogenesis of the lesion and for identifying potentially neurotoxic organophosphorus derivatives. In humans, neurotoxicity has been observed with **triorthocresyl phosphate (TOCP),** a noninsecticidal organophosphorus compound. It is also thought to occur with the pesticides dichlorvos, trichlorfon, leptophos, methamidophos, mipafox, trichloronat, and others. The polyneuropathy usually begins with burning and tingling sensations, particularly in the feet, with motor weakness a few days later. Sensory and motor difficulties may extend to the

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legs and hands. Gait is affected, and ataxia may be present. Central nervous system and autonomic changes may develop even later. There is no specific treatment for this form of delayed neurotoxicity. The long-term prognosis of neuropathy target esterase inhibition is highly variable. Reports of this type of neuropathy (and other toxicities) in pesticide manufacturing workers and in agricultural pesticide applicators have been published.

B. Environmental Toxicology

Organophosphorus pesticides are not considered to be persistent pesticides. They are relatively unstable and break down in the environment as a result of hydrolysis and photolysis. As a class they are considered to have a small impact on the environment in spite of their acute effects on organisms.

Carbamate Pesticides

These compounds (Table 56–4) inhibit acetylcholinesterase by carbamoylation of the esteratic site. Thus, they possess the toxic properties associated with inhibition of this enzyme as described for the organophosphorus pesticides. The effects and treatment are described in Chapters 7 and 8. The clinical effects due to carbamates are of shorter duration than those observed with organophosphorus compounds. The range between the doses that cause minor intoxication and those that result in lethality is larger with carbamates than with the organophosphorus agents. Spontaneous reactivation of cholinesterase is more rapid after inhibition by the carbamates. Although the clinical approach to carbamate poisoning is similar to that for organophosphates, the use of pralidoxime is not recommended.

The carbamates are considered to be nonpersistent pesticides. They exert only a small impact on the environment.

TABLE 56–4 Carbamate pesticides.

Compound	Toxicity Rating[1]	ADI
Aldicarb	6	0.005
Aminocarb	5	…
Carbaryl	4	0.01
Carbofuran	5	0.01
Dimetan	4	…
Dimetilan	4	…
Isolan	5	…
Methomyl	5	…
Propoxur	4	0.02
Pyramat	4	…
Pyrolan	5	…
Zectran	5	…

[1]Toxicity rating: Probable human oral lethal dosage for class 4 = 50–500 mg/kg, class 5 = 5–50 mg/kg, and class 6 = ≤ 5 mg/kg. (See Gosselin et al, 1984.)

ADI, acceptable daily intake (mg/kg/d).

Botanical Pesticides

Pesticides derived from natural sources include **nicotine, rotenone,** and **pyrethrum.** Nicotine is obtained from the dried leaves of *Nicotiana tabacum* and *N rustica.* It is rapidly absorbed from mucosal surfaces; the free alkaloid, but not the salt, is readily absorbed from the skin. Nicotine reacts with the acetylcholine receptor of the postsynaptic membrane (sympathetic and parasympathetic ganglia, neuromuscular junction), resulting in depolarization of the membrane. Toxic doses cause stimulation rapidly followed by blockade of transmission. These actions are described in Chapter 7. Treatment is directed toward maintenance of vital signs and suppression of convulsions.

Rotenone (Figure 56–1) is obtained from *Derris elliptica*, *D mallaccensis*, *Lonchocarpus utilis,* and *L urucu.* The oral ingestion of rotenone produces gastrointestinal irritation. Conjunctivitis, dermatitis, pharyngitis, and rhinitis can also occur. Treatment is symptomatic.

Pyrethrum consists of six known insecticidal esters: pyrethrin I (Figure 56–1), pyrethrin II, cinerin I, cinerin II, jasmolin I, and jasmolin II. Synthetic pyrethroids account for an increasing percentage of worldwide pesticide usage. Pyrethrum may be absorbed after inhalation or ingestion; absorption from the skin is not significant. The esters are extensively biotransformed. Pyrethrum pesticides are not highly toxic to mammals. When absorbed in sufficient quantities, the major site of toxic action is the central nervous system; excitation, convulsions, and tetanic paralysis can occur. Voltage-gated sodium, calcium, and chloride channels are considered targets, as well as peripheral-type benzodiazepine receptors. Treatment of exposure is usually directed at management of symptoms. Anticonvulsants are not consistently effective. The chloride channel agonist, ivermectin, is of use, as are pentobarbital and mephenesin. The pyrethroids are highly irritating to the eyes, skin, and respiratory tree. They may cause irritant asthma and, potentially, reactive airways dysfunction syndrome (RADS) and even anaphylaxis. The most common injuries reported in humans result from their allergenic and irritant effects on the airways and skin. Cutaneous paresthesias have been observed in workers spraying synthetic pyrethroids. The use of persistent synthetic pyrethroids for aircraft disinfection to comply with international rules regarding prevention of transfer of insect vectors has resulted in respiratory and skin problems, as well as some neurologic complaints in flight attendants and other aircraft workers. Severe occupational exposures to synthetic pyrethroids in China resulted in marked effects on the central nervous system, including convulsions.

HERBICIDES

Chlorophenoxy Herbicides

2,4-Dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and their salts and esters are compounds of interest as herbicides used for the destruction of weeds (Figure 56–1). They have been assigned toxicity ratings of 4 or 3, respectively, which place the probable human lethal dosages at 50–500 or 500–5000 mg/kg, respectively.

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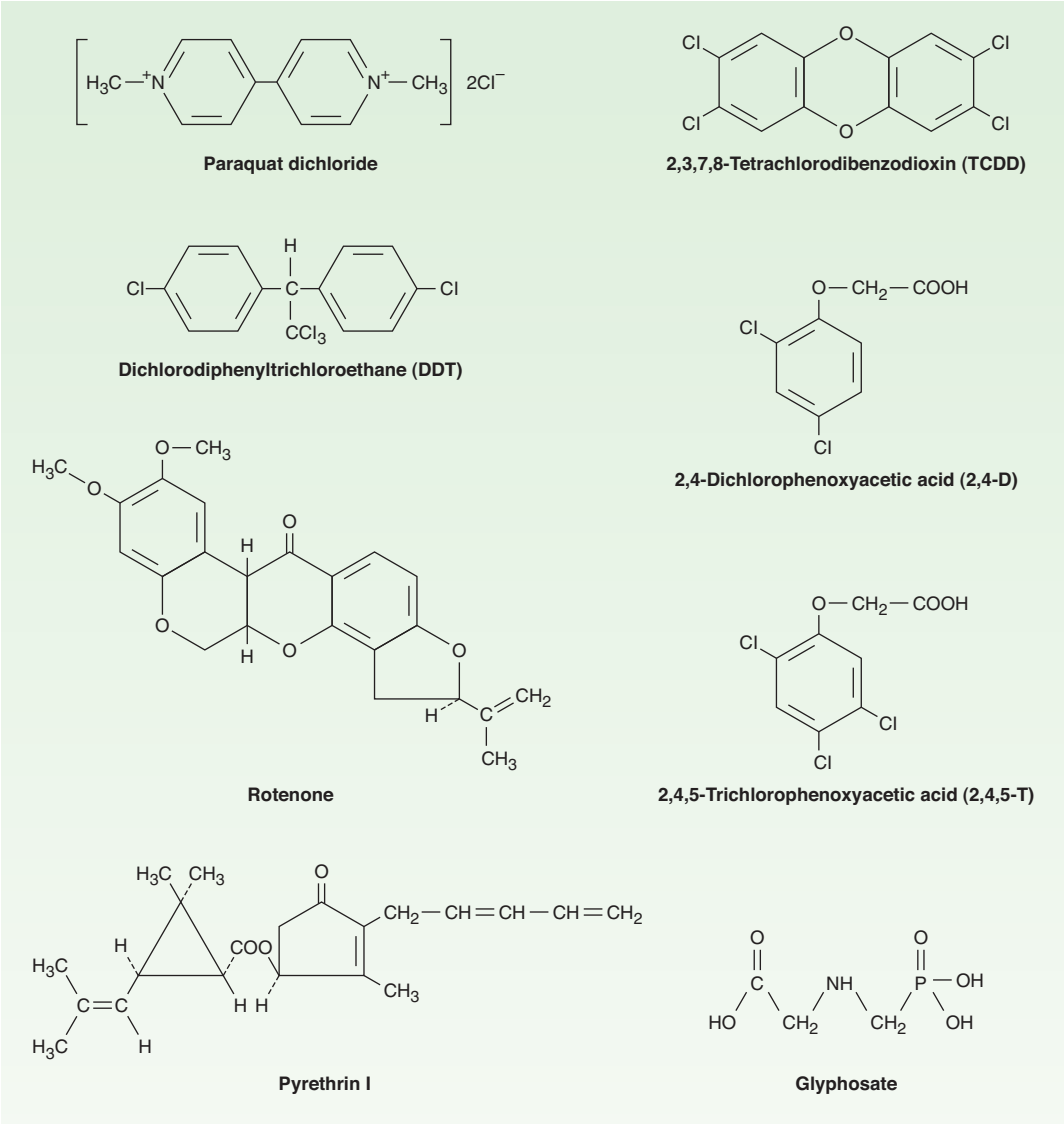

FIGURE 56–1 Chemical structures of selected herbicides and pesticides.

Because 2,4,5-T is often contaminated with dioxins and other polychlorinated compounds, it is no longer used. It was the compound used in "Agent Orange" and caused severe agricultural damage and social disruption.

In humans, 2,4-D in large doses can cause coma and generalized muscle hypotonia. Rarely, muscle weakness and marked hypotonia may persist for several weeks. In laboratory animals, signs of liver and kidney dysfunction have also been reported with chlorphenoxy herbicides. Several epidemiologic studies performed by the US National Cancer Institute confirmed the causal link between 2,4-D and non-Hodgkin's lymphoma. Evidence for a causal link to soft tissue sarcoma, however, is considered equivocal.

The toxicologic profile for these agents, particularly that of 2,4,5-T, is complicated by the presence of chemical contaminants (**dioxins**) produced during the manufacturing process (see below). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (dioxin, TCDD) is the most important of these contaminants. Dioxin is a potent animal carcinogen and a likely human carcinogen.

Glyphosate

Glyphosate (*N*-[phosphonomethyl] glycine, Figure 56–1) is now the most widely used herbicide in the world. It functions as a contact herbicide and is absorbed through the leaves and roots of plants. Because it is nonselective, it may damage important crops even when used as directed. Therefore, genetically modified plants such as soybean, corn, and cotton that are glyphosate-resistant have been developed and patented. They are widely grown throughout the world.

Glyphosate-related poisoning incidents are commonly reported. Most injuries are minor, although some lethal outcomes have been reported.

Glyphosate is a significant eye and skin irritant. It has caused lethal outcomes, although it is far less potent than the bipyridyl

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herbicides. Although the pure chemical seems to have little persistence and lower toxicity than other herbicides, the commercial formulations of glyphosate often contain surfactants and other active compounds that complicate the toxicity of the product. No specific treatment is available for glyphosate toxicity.

Bipyridyl Herbicides

Paraquat is the most important agent of this class (Figure 56–1). Its mechanism of action is said to be similar in plants and animals and involves single-electron reduction of the herbicide to free radical species. It has been given a toxicity rating of 4, which places the probable human lethal dosage at 50–500 mg/kg. Lethal human intoxications (accidental or suicidal) have been reported. Paraquat accumulates slowly in the lung by an active process and causes lung edema, alveolitis, and progressive fibrosis. It probably inhibits superoxide dismutase, resulting in intracellular free radical oxygen toxicity.

In humans, the first signs and symptoms after oral exposure are hematemesis and bloody stools. Within a few days, however, delayed toxicity occurs, with respiratory distress and the development of congestive hemorrhagic pulmonary edema accompanied by widespread cellular proliferation. Hepatic, renal, or myocardial involvement may also be evident. The interval between ingestion and death may be several weeks. Because of the delayed pulmonary toxicity, prompt removal of paraquat from the digestive tract is important. Gastric lavage, the use of cathartics, and the use of adsorbents to prevent further absorption have all been advocated; after absorption, treatment is successful in fewer than 50% of cases. Oxygen should be used cautiously to combat dyspnea or cyanosis, because it may aggravate the pulmonary lesions. Patients require prolonged observation, because the proliferative phase begins 1–2 weeks after ingestion. Management of severe paraquat poisoning is complex and largely symptomatic. Many approaches have been used, including immunosuppressive therapy to slow or stop the progressive pulmonary fibrosis. None of the currently proposed methods of treatment is universally successful.

ENVIRONMENTAL POLLUTANTS

Polychlorinated Biphenyls

The **polychlorinated biphenyls (PCBs, coplanar biphenyls)** have been used in a large variety of applications as dielectric and heat transfer fluids, lubricating oils, plasticizers, wax extenders, and flame retardants. Unfortunately, PCBs persist in the environment. Their industrial use and manufacture in the USA were terminated by 1977. The products used commercially were actually mixtures of PCB isomers and homologs containing 12–68% chlorine. These chemicals are highly stable and highly lipophilic, poorly metabolized, and very resistant to environmental degradation; they bioaccumulate in food chains. Food is the major source of PCB residues in humans.

A serious exposure to PCBs—lasting several months—occurred in Japan in 1968 as a result of cooking oil contamination with PCB-containing transfer medium (Yusho disease). Possible effects on the fetus and on the development of the offspring of poisoned women were reported. It is now known that the contaminated cooking oil contained not only PCBs but also polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Consequently, the effects that were initially attributed to the presence of PCBs are now thought to have been caused by a mixture of contaminants. Workers occupationally exposed to PCBs have exhibited the following clinical signs: dermatologic problems (chloracne, folliculitis, erythema, dryness, rash, hyperkeratosis, hyperpigmentation), some hepatic involvement, and elevated plasma triglycerides.

The effects of PCBs alone on reproduction and development, as well as their carcinogenic effects, have yet to be established in humans—whether workers or the general population—even though some subjects have been exposed to very high levels of PCBs. Repeated epidemiologic studies have found some increases in various cancers including melanoma, breast, pancreatic, and thyroid cancers, but the small number of cases and uncertain exposure status have left the carcinogenicity question unclear. In 1977, the IARC recommended that PCBs be regarded as likely carcinogenic to man, although the evidence for this classification was lacking. Some adverse behavioral effects in infants have been reported. An association between prenatal exposure to PCBs and deficits in childhood intellectual function was described for children born to mothers who had eaten large quantities of contaminated fish. The **polychlorinated dibenzo-*p*-dioxins (PCDDs),** or *dioxins*, have been mentioned as a group of congeners of which the most important is **2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).** In addition, there is a larger group of dioxin-like compounds, including certain **polychlorinated dibenzofurans (PCDFs)** and **coplanar biphenyls.** While PCBs were used commercially, PCDDs and PCDFs are unwanted byproducts that appear in the environment and in manufactured products as contaminants because of improperly controlled combustion processes. PCDD and PCDF contamination of the global environment is considered to represent a contemporary problem produced by human activities. Like PCBs, these chemicals are very stable and highly lipophilic. They are poorly metabolized and very resistant to environmental degradation.

In laboratory animals, TCDD administered in suitable doses has produced a wide variety of toxic effects, including a wasting syndrome (severe weight loss accompanied by reduction of muscle mass and adipose tissue), thymic atrophy, epidermal changes, hepatotoxicity, immunotoxicity, effects on reproduction and development, teratogenicity, and carcinogenicity. The effects observed in workers involved in the manufacture of 2,4,5-T (and therefore presumably exposed to TCDD) consisted of contact dermatitis and chloracne. In severely TCDD-intoxicated patients, discrete chloracne may be the only manifestation.

The presence of TCDD in 2,4,5-T is believed to be largely responsible for other human toxicities associated with the herbicide. There is epidemiologic evidence indicating an association between occupational exposure to the phenoxy herbicides and an excess incidence of non-Hodgkin's lymphoma. The TCDD contaminant in these herbicides seems to play a role in a number of cancers such as soft tissue sarcomas, lung cancer, Hodgkin's lymphomas, and others.

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Endocrine Disruptors

The potential hazardous effects of some chemicals in the environment are receiving considerable attention because of their estrogen-like or antiandrogenic properties. Compounds that affect thyroid function are also of concern. Since 1998, the process of prioritization, screening, and testing of chemicals for such actions has been undergoing worldwide development. These chemicals mimic, enhance, or inhibit a hormonal action. They include a number of plant constituents (phytoestrogens) and some mycoestrogens as well as industrial chemicals, particularly persistent organochlorine agents such as DDT and PCBs. Some brominated flame retardants are now being investigated as possible endocrine disrupters. Concerns exist because of their increasing contamination of the environment, the appearance of bioaccumulation, and their potential for toxicity. In vitro assays alone are unreliable for regulatory purposes, and animal studies are considered indispensable. Modified endocrine responses in some reptiles and marine invertebrates have been observed. In humans, however, a causal relation between exposure to a specific environmental agent and an adverse health effect due to endocrine modulation has not been established. Epidemiologic studies of populations exposed to higher concentrations of endocrine disrupting environmental chemicals are underway. There are indications that breast and other reproductive cancers are increased in these patients. Prudence dictates that exposure to environmental chemicals that disrupt endocrine function should be reduced.

Asbestos

Asbestos in many of its forms has been widely used in industry for over 100 years. All forms of asbestos that have been used in industry have been shown to cause progressive lung disease that is characterized by a fibrotic process. Higher levels of exposure produce the process called asbestosis. Lung damage develops even at low concentrations of shorter fibers, whereas higher concentrations of longer fibers are required to cause lung damage. Every form of asbestos, including chrysotile asbestos, causes an increase in lung cancer. Lung cancer occurs in people exposed at fiber concentrations well below concentrations that produce asbestosis. Cigarette smoking and exposure to radon daughters increase the incidence of asbestos-caused lung cancer in a synergistic fashion.

All forms of asbestos also cause mesothelioma of the pleura or peritoneum at very low doses. Other cancers including colon cancer, laryngeal cancer, stomach cancer, and perhaps even lymphoma are increased in asbestos-exposed patients. The mechanism for asbestos-caused cancer is not yet delineated. Arguments that chrysotile asbestos does not cause mesothelioma are contradicted by many epidemiologic studies of worker populations. Recognition that all forms of asbestos are dangerous and carcinogenic has led many countries to ban all uses of asbestos. Countries such as Canada, Zimbabwe, and others that still produce asbestos argue that asbestos can be used safely with careful workplace environmental controls. However, studies of industrial practice make the "safe use" of asbestos highly improbable.

METALS

Occupational and environmental poisoning with metals, metalloids, and metal compounds is a major health problem. Exposure in the workplace is found in many industries, and exposure in the home and elsewhere in the nonoccupational environment is widespread. The classic metal poisons (arsenic, lead, and mercury) continue to be widely used. (Treatment of their toxicities is discussed in Chapter 57.) Occupational exposure and poisoning due to beryllium, cadmium, manganese, and uranium are relatively new occupational problems, which present new and previously unaddressed problems.

Beryllium

Beryllium (Be) is a light alkaline metal that confers special properties on the alloys and ceramics in which it is incorporated. One attractive property of beryllium is its nonsparking quality, which makes it useful in such diverse applications as the manufacture of dental appliances and of nuclear weapons. Beryllium-copper alloys find use as components of computers, in the encasement of the first stage of nuclear weapons, in devices that require hardening such as missile ceramic nose cones, and in the space shuttle heat shield tiles. Because of the use of beryllium in dental appliances, dentists and dental appliance makers are often exposed to beryllium dust in toxic concentrations.

Beryllium is highly toxic by inhalation and is classified by IARC as a class 1, known human carcinogen. Inhalation of beryllium particles produces progressive pulmonary fibrosis and may lead to cancer. Skin disease also develops in workers overexposed to beryllium. The pulmonary disease is called chronic beryllium disease (CBD) and is a chronic granulomatous pulmonary fibrosis. In the 5–15% of the population that is sensitive to beryllium, chronic beryllium disease is the result of activation of an autoimmune attack on the skin and lungs. The disease is progressive and may lead to severe disability and death. Although some treatment approaches to the management of chronic beryllium disease show promise, the prognosis is poor in most cases.

The current permissible exposure levels for beryllium of 0.01 mcg/m^3 averaged over a 30-day period or 2 mcg/m^3 over an 8-hour period are insufficiently protective to prevent chronic beryllium disease. Both NIOSH and the ACGIH have recommended that the PEL and TLV be reduced to 0.05 mcg/m^3. These recommendations have not yet been implemented.

Environmental beryllium exposure is not generally thought to be a hazard to human health except in the vicinity of industrial sites where air, water and soil pollution have occurred.

Cadmium

Cadmium (Cd) is a transition metal widely used in industry. Workers are exposed to cadmium in the manufacture of nickel cadmium batteries, pigments, low-melting-point eutectic materials; in solder; in television phosphors; and in plating operations. It is also used extensively in semiconductors and in plastics as a stabilizer. Cadmium smelting is often done from residual dust from

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lead smelting operations, and cadmium smelter workers often face both lead and cadmium toxicity.

Cadmium is toxic by inhalation and by ingestion. When metals that have been plated with cadmium or welded with cadmium-containing materials are vaporized by the heat of torches or cutting implements, the fine dust and fumes released produce an acute respiratory disorder called **cadmium fume fever.** This disorder, common in welders, is usually characterized by shaking chills, cough, fever, and malaise. Although it may produce pneumonia, it is usually transient. However, chronic exposure to cadmium dust produces a far more serious progressive pulmonary fibrosis. Cadmium also causes severe kidney damage, including renal failure if exposure continues. Cadmium is a human carcinogen and is listed as a group 1, known human carcinogen by the IARC.

The current OSHA PEL for cadmium is 5 mcg/m^3. This PEL, considered by OSHA to be the lowest feasible limit for the dust, is insufficiently protective of worker health.

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CHAPTER 57

Heavy Metal Intoxication & Chelators

Michael J. Kosnett, MD, MPH

CASE STUDY

A 48-year-old painter is referred for evaluation of recent onset of severe abdominal pains, headaches, and myalgias. For the last week, he has been removing old paint from an iron bridge using grinding tools and a blow torch. His employer states that all the bridge workers are provided with the equivalent of "haz-mat" (hazardous materials) suits. What tests should be carried out? Assuming positive test results, what therapy would be appropriate?

Some metals such as iron are essential for life, whereas others such as lead are present in all organisms but serve no useful biologic purpose. Some of the oldest diseases of humans can be traced to heavy metal poisoning associated with metal mining, refining, and use. Even with the present recognition of the hazards of heavy metals, the incidence of intoxication remains significant, and the need for preventive strategies and effective therapy remains high. Toxic heavy metals interfere with the function of essential cations, cause enzyme inhibition, generate oxidative stress, and alter gene expression. As a result, multisystem signs and symptoms are a hallmark of heavy metal intoxication.

When intoxication occurs, chelator molecules (from *chela* "claw"), or their in vivo biotransformation products, may be used to bind the metal and facilitate its excretion from the body. Chelator drugs are discussed in the second part of this chapter.

TOXICOLOGY OF HEAVY METALS

LEAD

Lead poisoning is one of the oldest occupational and environmental diseases in the world. Despite its recognized hazards, lead continues to have widespread commercial application, including production of storage batteries (nearly 90% of US consumption), ammunition, metal alloys, solder, glass, plastics, pigments, and ceramics. Corrosion of lead plumbing in older buildings or supply lines may increase the lead concentration of tap water. Environmental lead exposure, ubiquitous by virtue of the anthropogenic distribution of lead to air, water, and food, has declined considerably in the last three decades as a result of the elimination of lead as an additive in gasoline, as well as diminished contact with lead-based paint and other lead-containing consumer products, such as lead solder in canned food. Although these public health measures, together with improved workplace conditions, have decreased the incidence of serious overt lead poisoning, there remains considerable concern over the effects of low-level lead exposure. Extensive evidence indicates that lead may have subtle subclinical adverse effects on neurocognitive function and on blood pressure at low blood lead concentrations formerly not recognized as harmful. Lead serves no useful purpose in the human body. In key target organs such as the developing central nervous system, no level of lead exposure has been shown to be without deleterious effects.

Pharmacokinetics

Inorganic lead is slowly but consistently absorbed via the respiratory and gastrointestinal tracts. Inorganic lead is poorly absorbed through the skin. Absorption of lead dust via the respiratory tract is the most common cause of industrial poisoning. The intestinal tract is the primary route of entry in nonindustrial exposure (Table 57–1). Absorption via the gastrointestinal tract varies with the nature of the lead compound, but in general, adults absorb about 10–15% of the ingested amount, whereas young children absorb up to 50%. Low dietary calcium, iron deficiency, and ingestion on an empty stomach all have been associated with increased lead absorption.

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TABLE 57–1 Toxicology of selected arsenic, lead, and mercury compounds.

	Form Entering Body	Major Route of Absorption	Distribution	Major Clinical Effects	Key Aspects of Mechanism	Metabolism and Elimination
Arsenic	Inorganic arsenic salts	Gastrointestinal, respiratory (all mucosal surfaces)	Predominantly soft tissues (highest in liver, kidney). Avidly bound in skin, hair, nails	Cardiovascular: shock, arrhythmias. CNS: encephalopathy, peripheral neuropathy. Gastroenteritis; pancytopenia; cancer (many sites)	Inhibits enzymes; interferes with oxidative phosphorylation; alters cell signaling, gene expression	Methylation. Renal (major); sweat and feces (minor)
Lead	Inorganic lead oxides and salts	Gastrointestinal, respiratory	Soft tissues; redistributed to skeleton (> 90% of adult body burden)	CNS deficits; peripheral neuropathy; anemia; nephropathy; hypertension; reproductive toxicity	Inhibits enzymes; interferes with essential cations; alters membrane structure	Renal (major); feces and breast milk (minor)
	Organic (tetraethyl lead)	Skin, gastrointestinal, respiratory	Soft tissues, especially liver, CNS	Encephalopathy	Hepatic dealkylation (fast) → trialkymetabolites (slow) → dissociation to lead	Urine and feces (major); sweat (minor)
Mercury	Elemental mercury	Respiratory tract	Soft tissues, especially kidney, CNS	CNS: tremor, behavioral (erethism); gingivostomatitis; peripheral neuropathy; acrodynia; pneumonitis (high-dose)	Inhibits enzymes; alters membranes	Elemental Hg converted to Hg^{2+}. Urine (major); feces (minor)
	Inorganic: Hg^{+} (less toxic); Hg^{2+} (more toxic)	Gastrointestinal, skin (minor)	Soft tissues, especially kidney	Acute tubular necrosis; gastroenteritis; CNS effects (rare)	Inhibits enzymes; alters membranes	Urine
	Organic: alkyl, aryl	Gastrointestinal, skin, respiratory (minor)	Soft tissues	CNS effects, birth defects	Inhibits enzymes; alters microtubules, neuronal structure	Deacylation. Fecal (alkyl, major); urine (Hg^{2+} after deacylation, minor)

Once absorbed from the respiratory or gastrointestinal tract, lead enters the bloodstream, where approximately 99% is bound to erythrocytes and 1% is present in the plasma. Lead is subsequently distributed to soft tissues such as the bone marrow, brain, kidney, liver, muscle, and gonads; then to the subperiosteal surface of bone; and later to bone matrix. Lead also crosses the placenta and poses a potential hazard to the fetus. The kinetics of lead clearance from the body follows a multicompartment model, composed predominantly of the blood and soft tissues, with a half-life of 1–2 months; and the skeleton, with a half-life of years to decades. Approximately 70% of the lead that is eliminated appears in the urine, with lesser amounts excreted through the bile, skin, hair, nails, sweat, and breast milk. The fraction not undergoing prompt excretion, approximately half of the absorbed lead, may be incorporated into the skeleton, the repository of more than 90% of the body lead burden in most adults. In patients with high bone lead burdens, slow release from the skeleton may elevate blood lead concentrations for years after exposure ceases, and pathologic high bone turnover states such as hyperthyroidism or prolonged immobilization may result in frank lead intoxication. Migration of retained lead bullet fragments into a joint space or adjacent to bone has been associated with the development of lead poisoning signs and symptoms years or decades after an initial gunshot injury.

Pharmacodynamics

Lead exerts multisystemic toxic effects that are mediated by multiple modes of action, including inhibition of enzymatic function; interference with the action of essential cations, particularly calcium, iron, and zinc; generation of oxidative stress; changes in gene expression; alterations in cell signaling; and disruption of the integrity of membranes in cells and organelles.

A. Nervous System

The developing central nervous system of the fetus and young child is the most sensitive target organ for lead's toxic effect. Epidemiologic studies suggest that blood lead concentrations even less than 5 mcg/dL may result in subclinical deficits in neurocognitive function in lead-exposed young children, with no demonstrable threshold for a "no effect" level. The dose response between

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low blood lead concentrations and cognitive function in young children is nonlinear, such that the decrement in intelligence associated with an increase in blood lead from less than 1 to 10 mcg/dL (6.2 IQ points) exceeds that associated with a change from 10 to 30 mcg/dL (3.0 IQ points).

Adults are less sensitive to the central nervous system effects of lead, but long-term exposure to blood lead concentrations in the range of 10–30 mcg/dL may be associated with subtle, subclinical effects on neurocognitive function. At blood lead concentrations higher than 30 mcg/dL, behavioral and neurocognitive signs or symptoms may gradually emerge, including irritability, fatigue, decreased libido, anorexia, sleep disturbance, impaired visual-motor coordination, and slowed reaction time. Headache, arthralgias, and myalgias are also common complaints. Tremor occurs but is less common. Lead encephalopathy, usually occurring at blood lead concentrations higher than 100 mcg/dL, is typically accompanied by increased intracranial pressure and may cause ataxia, stupor, coma, convulsions, and death. Recent epidemiological studies suggest that lead may accentuate an age-related decline in cognitive function in older adults. In experimental animals, developmental lead exposure has been associated with increased expression of beta-amyloid, oxidative DNA damage, and Alzheimer's-type pathology in the aging brain. There is wide inter-individual variation in the magnitude of lead exposure required to cause overt lead-related signs and symptoms.

Overt peripheral neuropathy may appear after chronic high-dose lead exposure, usually following months to years of blood lead concentrations higher than 100 mcg/dL. Predominantly motor in character, the neuropathy may present clinically with painless weakness of the extensors, particularly in the upper extremity, resulting in classic wrist-drop. Preclinical signs of lead-induced peripheral nerve dysfunction may be detectable by electrodiagnostic testing.

B. Blood

Lead can induce an anemia that may be either normocytic or microcytic and hypochromic. Lead interferes with heme synthesis by blocking the incorporation of iron into protoporphyrin IX and by inhibiting the function of enzymes in the heme synthesis pathway, including aminolevulinic acid dehydratase and ferrochelatase. Within 2–8 weeks after an elevation in blood lead concentration (generally to 30–50 mcg/dL or greater), increases in heme precursors, notably free erythrocyte protoporphyrin or its zinc chelate, zinc protoporphyrin, may be detectable in whole blood. Lead also contributes to anemia by increasing erythrocyte membrane fragility and decreasing red cell survival time. Frank hemolysis may occur with high exposure. Basophilic stippling on the peripheral blood smear, thought to be a consequence of lead inhibition of the enzyme 3',5'-pyrimidine nucleotidase, is sometimes a suggestive—albeit insensitive and nonspecific—diagnostic clue to the presence of lead intoxication.

C. Kidneys

Chronic high-dose lead exposure, usually associated with months to years of blood lead concentrations greater than 80 mcg/dL, may result in renal interstitial fibrosis and nephrosclerosis. Lead nephropathy may have a latency period of years. Lead may alter uric acid excretion by the kidney, resulting in recurrent bouts of gouty arthritis ("saturnine gout"). Acute high-dose lead exposure sometimes produces transient azotemia, possibly as a consequence of intrarenal vasoconstriction. Studies conducted in general population samples have documented an association between blood lead concentration and measures of renal function, including serum creatinine and creatinine clearance. The presence of other risk factors for renal insufficiency, including hypertension and diabetes, may increase susceptibility to lead-induced renal dysfunction.

D. Reproductive Organs

High-dose lead exposure is a recognized risk factor for stillbirth or spontaneous abortion. Epidemiologic studies of the impact of low-level lead exposure on reproductive outcome such as low birth weight, preterm delivery, or spontaneous abortion have yielded mixed results. However, a well-designed nested case-control study detected an odds ratio for spontaneous abortion of 1.8 (95% CI 1.1–3.1) for every 5 mcg/dL increase in maternal blood lead across an approximate range of 5–20 mcg/dL. Recent studies have linked prenatal exposure to low levels of lead (eg, maternal blood lead concentrations of 5–15 mcg/dL) to decrements in physical and cognitive development assessed during the neonatal period and early childhood. In males, blood lead concentrations higher than 40 mcg/dL have been associated with diminished or aberrant sperm production.

E. Gastrointestinal Tract

Moderate lead poisoning may cause loss of appetite, constipation, and, less commonly, diarrhea. At high dosage, intermittent bouts of severe colicky abdominal pain ("lead colic") may occur. The mechanism of lead colic is unclear but is believed to involve spasmodic contraction of the smooth muscles of the intestinal wall, mediated by alteration in synaptic transmission at the smooth muscle-neuromuscular junction. In heavily exposed individuals with poor dental hygiene, the reaction of circulating lead with sulfur ions released by microbial action may produce dark deposits of lead sulfide at the gingival margin ("gingival lead lines"). Although frequently mentioned as a diagnostic clue in the past, in recent times this has been a relatively rare sign of lead exposure.

F. Cardiovascular System

Epidemiologic, experimental, and in vitro mechanistic data indicate that lead exposure elevates blood pressure in susceptible individuals. In populations with environmental or occupational lead exposure, blood lead concentration is linked with increases in systolic and diastolic blood pressure. Studies of middle-aged and elderly men and women have identified relatively low levels of lead exposure sustained by the general population to be an independent risk factor for hypertension. In addition, epidemiologic studies suggest that low to moderate levels of lead exposure are risk factors for increased cardiovascular mortality. Lead can also elevate blood pressure in experimental animals. The pressor effect of lead

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may be mediated by an interaction with calcium mediated contraction of vascular smooth muscle, as well as generation of oxidative stress and an associated interference in nitric oxide signaling pathways.

Major Forms of Lead Intoxication

A. Inorganic Lead Poisoning (Table 57–1)

1. Acute—Acute inorganic lead poisoning is uncommon today. It usually results from industrial inhalation of large quantities of lead oxide fumes or, in small children, from ingestion of a large oral dose of lead in the form of lead-based paint chips; small objects, eg, toys coated or fabricated from lead; or contaminated food or drink. The onset of severe symptoms usually requires several days or weeks of recurrent exposure and manifests as signs and symptoms of encephalopathy or colic. Evidence of hemolytic anemia (or anemia with basophilic stippling if exposure has been subacute) and elevated hepatic aminotransferases may be present.

The diagnosis of acute inorganic lead poisoning may be difficult, and depending on the presenting symptoms, the condition has sometimes been mistaken for appendicitis, peptic ulcer, biliary colic, pancreatitis, or infectious meningitis. Subacute presentation, featuring headache, fatigue, intermittent abdominal cramps, myalgias, and arthralgias, has often been mistaken for a flu-like viral illness. When there has been recent ingestion of lead-containing paint chips, glazes, or weights, radiopacities may be visible on abdominal radiographs.

2. Chronic—The patient with chronic lead intoxication usually presents with multisystemic findings, including complaints of anorexia, fatigue, and malaise; neurologic complaints, including headache, difficulty in concentrating, and irritability or depressed mood; weakness, arthralgias, or myalgias; and gastrointestinal symptoms. Lead poisoning should be strongly suspected in any patient presenting with headache, abdominal pain, and anemia; and less commonly with motor neuropathy, gout, and renal insufficiency. Chronic lead intoxication should be considered in any child with neurocognitive deficits, growth retardation, or developmental delay. It is important to recognize that adverse effects of lead that are of considerable public health significance, such as subclinical decrements in neurodevelopment in children and hypertension in adults, are usually nonspecific and may not come to medical attention.

The diagnosis of lead intoxication is best confirmed by measuring lead in whole blood. Although this test reflects lead currently circulating in blood and soft tissues and is not a reliable marker of either recent or cumulative lead exposure, most patients with lead-related disease have blood lead concentrations higher than the normal range. Average background blood lead concentrations in North America and Europe have declined by 90% in recent decades, and the geometric mean blood lead concentration in the United States in 2005–2006 was estimated to be 1.29 mcg/dL. Though predominantly a research tool, the concentration of lead in bone assessed by noninvasive K X-ray fluorescence measurement of lead has been correlated with long-term cumulative lead exposure, and its relationship to numerous lead-related disorders is a subject of ongoing investigation. Measurement of lead excretion in the urine after a single dose of a chelating agent (sometimes called a "chelation challenge test") primarily reflects the lead content of soft tissues and may not be a reliable marker of long-term lead exposure, remote past exposure, or skeletal lead burden. Because of the lag time associated with lead-induced elevations in circulating heme precursors, the finding of a blood lead concentration of 30 mcg/dL or more with no concurrent increase in zinc protoporphyrin suggests that the lead exposure was of recent onset.

B. Organolead Poisoning

Poisoning from organolead compounds is now very rare, in large part because of the worldwide phase-out of tetraethyl and tetramethyl lead as antiknock additives in gasoline. However, organolead compounds such as lead stearate or lead naphthenate are still used in certain commercial processes. Because of their volatility or lipid solubility, organolead compounds tend to be well absorbed through either the respiratory tract or the skin. Organolead compounds predominantly target the central nervous system, producing dose-dependent effects that may include neurocognitive deficits, insomnia, delirium, hallucinations, tremor, convulsions, and death.

Treatment

A. Inorganic Lead Poisoning

Treatment of inorganic lead poisoning involves immediate termination of exposure, supportive care, and the judicious use of chelation therapy. (Chelation is discussed later in this chapter.) Lead encephalopathy is a medical emergency that requires intensive supportive care. Cerebral edema may improve with corticosteroids and mannitol, and anticonvulsants may be required to treat seizures. Radiopacities on abdominal radiographs may suggest the presence of retained lead objects requiring gastrointestinal decontamination. Adequate urine flow should be maintained, but overhydration should be avoided. Intravenous **edetate calcium disodium ($CaNa_2EDTA$)** is administered at a dosage of 1000–1500 mg/m^2/d (approximately 30–50 mg/kg/d) by continuous infusion for up to 5 days. Some clinicians advocate that chelation treatment for lead encephalopathy be initiated with an intramuscular injection of **dimercaprol**, followed in 4 hours by concurrent administration of dimercaprol and EDTA. Parenteral chelation is limited to 5 or fewer days, at which time oral treatment with another chelator, **succimer**, may be instituted. In symptomatic lead intoxication without encephalopathy, treatment may sometimes be initiated with succimer. The end point for chelation is usually resolution of symptoms or return of the blood lead concentration to the premorbid range. In patients with chronic exposure, cessation of chelation may be followed by an upward rebound in blood lead concentration as the lead re-equilibrates from bone lead stores.

Although most clinicians support chelation for symptomatic patients with elevated blood lead concentrations, the decision to chelate asymptomatic subjects is more controversial. Since 1991, the Centers for Disease Control and Prevention (CDC) has recommended chelation for all children with blood lead concentrations of 45 mcg/dL or greater. However, a recent randomized,

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double-blind, placebo-controlled clinical trial of succimer in children with blood lead concentrations between 25 mcg/dL and 44 mcg/dL found no benefit on neurocognitive function or long-term blood lead reduction. Prophylactic use of chelating agents in the workplace should never be a substitute for reduction or prevention of excessive exposure.

Management of elevated blood lead levels in children and adults should include a conscientious effort to identify and reduce all potential sources of future lead exposure. Many local, state, or national governmental agencies maintain lead poisoning prevention programs that can assist in case management. Blood lead screening of family members or coworkers of a lead poisoning patient is often indicated to assess the scope of the exposure. Although the CDC blood lead level of concern for childhood lead poisoning of 10 mcg/dL has not been revised since 1991, the adverse impact of lower levels on children is widely acknowledged, and primary prevention of lead exposure is receiving increased emphasis. Although the US Occupational Safety and Health Administration (OSHA) lead regulations introduced in the late 1970s mandate that workers be removed from lead exposure for blood lead levels higher than 50–60 mcg/dL, an expert panel in 2007 recommended that removal be initiated for a single blood lead level greater than 30 mcg/dL, or when two successive blood lead levels measured over a 4-week interval are 20 mcg/dL or more. The longer-term goal should be for workers to maintain blood lead levels at lower than 10 mcg/dL, and for pregnant women to avoid occupational or avocational exposure that would result in blood lead levels higher than 5 mcg/dL. Environmental Protection Agency (EPA) regulations effective since 2010 require that contractors who perform renovation, repair, and painting projects that disturb lead-based paint in pre-1978 residences and child-occupied facilities must be certified and must follow specific work practices to prevent lead contamination.

B. Organic Lead Poisoning

Initial treatment consists of decontaminating the skin and preventing further exposure. Treatment of seizures requires appropriate use of anticonvulsants. Empiric chelation may be attempted if high blood lead concentrations are present.

Arsenic

Arsenic is a naturally occurring element in the earth's crust with a long history of use as a constituent of commercial and industrial products, as a component in pharmaceuticals, and as an agent of deliberate poisoning. Recent commercial applications of arsenic include its use in the manufacture of semiconductors, wood preservatives for industrial applications (eg, marine timbers or utility poles), nonferrous alloys, glass, gel-based insecticidal ant baits, and veterinary pharmaceuticals. In some regions of the world, groundwater may contain high levels of arsenic that has leached from natural mineral deposits. Arsenic in drinking water in the Ganges delta of India and Bangladesh is now recognized as one of the world's most pressing environmental health problems. Arsine, an arsenous hydride (AsH_3) gas with potent hemolytic effects, is manufactured predominantly for use in the semiconductor industry but may also be generated accidentally when arsenic-containing ores come in contact with acidic solutions.

It is of historical interest that Fowler's solution, which contains 1% potassium arsenite, was widely used as a medicine for many conditions from the eighteenth century through the mid-twentieth century. Organic arsenicals were the first pharmaceutical antimicrobials* and were widely used for the first half of the twentieth century until supplanted by sulfonamides and other more effective and less toxic agents.

Other organoarsenicals, most notably lewisite (dichloro-[2-chlorovinyl]arsine), were developed in the early twentieth century as chemical warfare agents. Arsenic trioxide was reintroduced into the United States Pharmacopeia in 2000 as an orphan drug for the treatment of relapsed acute promyelocytic leukemia and is finding expanded use in experimental cancer treatment protocols (see Chapter 54). Melarsoprol, another trivalent arsenical, is used in the treatment of advanced African trypanosomiasis (see Chapter 52).

Pharmacokinetics

Soluble arsenic compounds are well absorbed through the respiratory and gastrointestinal tracts (Table 57–1). Percutaneous absorption is limited but may be clinically significant after heavy exposure to concentrated arsenic reagents. Most of the absorbed inorganic arsenic undergoes methylation, mainly in the liver, to monomethylarsonic acid and dimethylarsinic acid, which are excreted, along with residual inorganic arsenic, in the urine. When chronic daily absorption is less than 1000 mcg of soluble inorganic arsenic, approximately two thirds of the absorbed dose is excreted in the urine within 2–3 days. After massive ingestions, the elimination half-life is prolonged. Inhalation of arsenic compounds of low solubility may result in prolonged retention in the lung and may not be reflected by urinary arsenic excretion. Arsenic binds to sulfhydryl groups present in keratinized tissue, and following cessation of exposure, hair, nails, and skin may contain elevated levels after urine values have returned to normal. However, arsenic in hair and nails as a result of external deposition may be indistinguishable from that incorporated after internal absorption.

Pharmacodynamics

Arsenic compounds are thought to exert their toxic effects by several modes of action. Interference with enzyme function may result from sulfhydryl group binding by trivalent arsenic or by substitution for phosphate. Inorganic arsenic or its metabolites may induce oxidative stress, alter gene expression, and interfere with cell signal transduction. Although on a molar basis, inorganic trivalent arsenic (As^{3+}, arsenite) is generally two to ten times more acutely toxic than inorganic pentavalent arsenic (As^{5+}, arsenate), in vivo interconversion is known to occur, and the full spectrum of arsenic toxicity has occurred after sufficient exposure to either form. Recent studies suggest that the trivalent form of the methylated metabolites (eg, monomethylarsonous acid [MMA^{III}])

*Paul Ehrlich's "magic bullet" for syphilis (arsphenamine, Salvarsan) was an arsenical.

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may be more toxic than the inorganic parent compounds. Reduced efficiency in the methylation of MMA to DMA, resulting in an elevated percentage of MMA in the urine, has been associated with an increased risk of chronic adverse effects. Arsenic methylation requires *S*-adenosylmethionine, a universal methyl donor in the body, and arsenic-associated perturbations in one-carbon metabolism may underlie some arsenic-induced epigenetic effects such as altered gene expression.

Arsine gas is oxidized in vivo and exerts a potent hemolytic effect associated with alteration of ion flux across the erythrocyte membrane; it also disrupts cellular respiration in other tissues. Arsenic is a recognized human carcinogen and has been associated with cancer of the lung, skin, and bladder. Marine organisms may contain large amounts of a well-absorbed trimethylated organoarsenic, arsenobetaine, as well as a variety of arsenosugars and arsenolipids. Arsenobetaine exerts no known toxic effects when ingested by mammals and is excreted in the urine unchanged; arsenosugars are partially metabolized to dimethylarsinic acid. Thio-dimethylarsinic acid has recently been identified as a common but minor human arsenic metabolite of uncertain toxicological significance.

Major Forms of Arsenic Intoxication

A. Acute Inorganic Arsenic Poisoning

Within minutes to hours after exposure to high doses (tens to hundreds of milligrams) of soluble inorganic arsenic compounds, many systems are affected. Initial gastrointestinal signs and symptoms include nausea, vomiting, diarrhea, and abdominal pain. Diffuse capillary leak, combined with gastrointestinal fluid loss, may result in hypotension, shock, and death. Cardiopulmonary toxicity, including congestive cardiomyopathy, cardiogenic or noncardiogenic pulmonary edema, and ventricular arrhythmias, may occur promptly or after a delay of several days. Pancytopenia usually develops within 1 week, and basophilic stippling of erythrocytes may be present soon after. Central nervous system effects, including delirium, encephalopathy, and coma, may occur within the first few days of intoxication. An ascending sensorimotor peripheral neuropathy may begin to develop after a delay of 2–6 weeks. This neuropathy may ultimately involve the proximal musculature and result in neuromuscular respiratory failure. Months after an acute poisoning, transverse white striae (Aldrich-Mees lines) may be visible in the nails.

Acute inorganic arsenic poisoning should be considered in an individual presenting with abrupt onset of gastroenteritis in combination with hypotension and metabolic acidosis. Suspicion should be further heightened when these initial findings are followed by cardiac dysfunction, pancytopenia, and peripheral neuropathy. The diagnosis may be confirmed by demonstration of elevated amounts of inorganic arsenic and its metabolites in the urine (typically in the range of several thousand micrograms in the first 2–3 days after acute symptomatic poisoning). Arsenic disappears rapidly from the blood, and except in anuric patients, blood arsenic levels should not be used for diagnostic purposes. Treatment is based on appropriate gut decontamination, intensive supportive care, and prompt chelation with **unithiol,** 3–5 mg/kg intravenously every 4–6 hours, or **dimercaprol,** 3–5 mg/kg intramuscularly every 4–6 hours. In animal studies, the efficacy of chelation has been highest when it is administered within minutes to hours after arsenic exposure; therefore, if diagnostic suspicion is high, treatment should not be withheld for the several days to weeks often required to obtain laboratory confirmation.

Succimer has also been effective in animal models and has a higher therapeutic index than dimercaprol. However, because it is available in the United States only for oral administration, its use may not be advisable in the initial treatment of acute arsenic poisoning, when severe gastroenteritis and splanchnic edema may limit absorption by this route.

B. Chronic Inorganic Arsenic Poisoning

Chronic inorganic arsenic poisoning also results in multisystemic signs and symptoms. Overt noncarcinogenic effects may be evident after chronic absorption of more than 0.01 mg/kg/d (~ 500–1000 mcg/d in adults). The time to appearance of symptoms varies with dose and interindividual tolerance. Constitutional symptoms of fatigue, weight loss, and weakness may be present, along with anemia, nonspecific gastrointestinal complaints, and a sensorimotor peripheral neuropathy, particularly featuring a stocking glove pattern of dysesthesia. Skin changes—among the most characteristic effects—typically develop after years of exposure and include a "raindrop" pattern of hyperpigmentation, and hyperkeratoses involving the hands and feet (Figure 57–1). Peripheral vascular disease and noncirrhotic portal hypertension may also occur. Epidemiologic studies suggest a possible link to hypertension, diabetes, chronic nonmalignant respiratory disease, and adverse reproductive outcomes. Cancer of the lung, skin, bladder, and possibly other sites, may appear years after exposure to doses of arsenic that are not high enough to elicit other acute or chronic effects.

Administration of arsenite in cancer chemotherapy regimens, often at a daily dose of 10–20 mg for weeks to a few months, has been associated with prolongation of the QT interval on the electrocardiogram and occasionally has resulted in malignant ventricular arrhythmias such as torsades de pointes.

The diagnosis of chronic arsenic poisoning involves integration of the clinical findings with confirmation of exposure. The urine concentration of the sum of inorganic arsenic and its primary metabolites MMA and DMA is less than 20 mcg/L in the general population. High urine levels associated with overt adverse effects may return to normal within days to weeks after exposure ceases. Because it may contain large amounts of nontoxic organoarsenic, all seafood should be avoided for at least 3 days before submission of a urine sample for diagnostic purposes. The arsenic content of hair and nails (normally less than 1 ppm) may sometimes reveal past elevated exposure, but results should be interpreted cautiously in view of the potential for external contamination.

Management of chronic arsenic poisoning consists primarily of termination of exposure and nonspecific supportive care. Although

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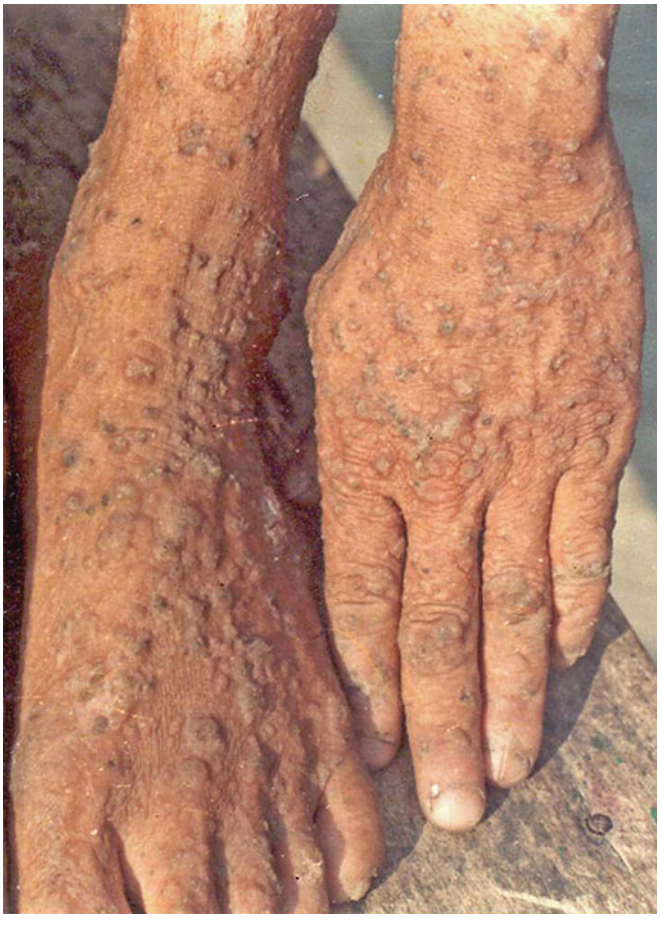

FIGURE 57–1 Dermatologic lesions associated with chronic ingestion of arsenic in drinking water. (Photo courtesy of Dipankar Chakraborti, PhD.)

empiric short-term oral chelation with **unithiol** or **succimer** for symptomatic individuals with elevated urine arsenic concentrations may be considered, it has no proven benefit beyond removal from exposure alone. Preliminary studies suggest that dietary supplementation of folate—thought to be a cofactor in arsenic methylation—might be of value in arsenic-exposed individuals, particularly men, who are also deficient in folate.

C. Arsine Gas Poisoning

Arsine gas poisoning produces a distinctive pattern of intoxication dominated by profound hemolytic effects. After a latent period that may range from 2 hours to 24 hours postinhalation (depending on the magnitude of exposure), massive intravascular hemolysis may occur. Initial symptoms may include malaise, headache, dyspnea, weakness, nausea, vomiting, abdominal pain, jaundice, and hemoglobinuria. Oliguric renal failure, a consequence of hemoglobin deposition in the renal tubules, often appears within 1–3 days. In massive exposures, lethal effects on cellular respiration may occur before renal failure develops. Urinary arsenic levels are elevated but are seldom available to confirm the diagnosis during the critical period of illness. Intensive supportive care—including exchange transfusion, vigorous hydration, and, in the case of acute renal failure, hemodialysis—is the mainstay of therapy. Currently available chelating agents have not been demonstrated to be of clinical value in arsine poisoning.

MERCURY

Metallic mercury as "quicksilver"—the only metal that is liquid under ordinary conditions—has attracted scholarly and scientific interest from antiquity. The mining of mercury was early recognized as being hazardous to health. As industrial use of mercury became common during the last 200 years, new forms of toxicity were recognized that were found to be associated with various transformations of the metal. In the early 1950s, a mysterious epidemic of birth defects and neurologic disease occurred in the Japanese fishing village of Minamata. The causative agent was determined to be methylmercury in contaminated seafood, traced to industrial discharges into the bay from a nearby factory. In addition to elemental mercury and alkylmercury (including methylmercury), other key mercurials include inorganic mercury salts and aryl mercury compounds, each of which exerts a relatively unique pattern of clinical toxicity.

Mercury is mined predominantly as HgS in cinnabar ore and is then converted commercially to a variety of chemical forms. Key industrial and commercial applications of mercury are found in the electrolytic production of chlorine and caustic soda; the manufacture of electrical equipment, thermometers, and other instruments; fluorescent lamps; and dental amalgam. The widespread use of elemental mercury in artisanal gold production is a growing problem in many developing countries. Mercury use in pharmaceuticals and in biocides has declined substantially in recent years, but occasional use in antiseptics and folk medicines is still encountered. Thimerosal, an organomercurial preservative that is metabolized in part to ethylmercury, has been removed from almost all the vaccines in which it was formerly present. Environmental exposure to mercury from the burning of fossil fuels, or the bioaccumulation of methylmercury in fish, remains a concern in some regions of the world. Low-level exposure to mercury released from dental amalgam fillings occurs, but systemic toxicity from this source has not been established.

Pharmacokinetics

The absorption of mercury varies considerably depending on the chemical form of the metal. Elemental mercury is quite volatile and can be absorbed from the lungs (Table 57–1). It is poorly absorbed from the intact gastrointestinal tract. Inhaled mercury is the primary source of occupational exposure. Organic short-chain alkylmercury compounds are volatile and potentially harmful by inhalation as well as by ingestion. Percutaneous absorption of metallic mercury and inorganic mercury can be of clinical concern following massive acute or long-term chronic exposure. Alkylmercury compounds appear to be well absorbed through the skin, and acute contact with a few drops of dimethylmercury has resulted in severe, delayed toxicity. After absorption, mercury is distributed to the tissues within a few hours, with the highest concentration occurring in the kidney. Inorganic mercury is

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excreted through the urine and feces. Excretion of inorganic mercury follows a multicompartment model: most is excreted within weeks to months, but a fraction may be retained in the kidneys and brain for years. After inhalation of elemental mercury vapor, urinary mercury levels decline with a half-life of approximately 1–3 months. Methylmercury, which has a blood and whole body half-life of approximately 50 days, undergoes biliary excretion and enterohepatic circulation, with more than two thirds eventually excreted in the feces. Mercury binds to sulfhydryl groups in keratinized tissue, and as with lead and arsenic, traces appear in the hair and nails.

Major Forms of Mercury Intoxication

Mercury interacts with sulfhydryl groups in vivo, inhibiting enzymes and altering cell membranes. The pattern of clinical intoxication from mercury depends to a great extent on the chemical form of the metal and the route and severity of exposure.

A. Acute

Acute inhalation of elemental mercury vapors may cause chemical pneumonitis and noncardiogenic pulmonary edema. Acute gingivostomatitis may occur, and neurologic sequelae (see following text) may also ensue. Acute ingestion of inorganic mercury salts, such as mercuric chloride, can result in a corrosive, potentially life-threatening hemorrhagic gastroenteritis followed within hours to days by acute tubular necrosis and oliguric renal failure.

B. Chronic

Chronic poisoning from inhalation of mercury vapor results in a classic triad of tremor, neuropsychiatric disturbance, and gingivostomatitis. The tremor usually begins as a fine intention tremor of the hands, but the face may also be involved, and progression to choreiform movements of the limbs may occur. Neuropsychiatric manifestations, including memory loss, fatigue, insomnia, and anorexia, are common. There may be an insidious change in mood to shyness, withdrawal, and depression along with explosive anger or blushing (a behavioral pattern referred to as **erethism**). Recent studies suggest that low-dose exposure may produce subclinical neurologic effects. Gingivostomatitis, sometimes accompanied by loosening of the teeth, may be reported after high-dose exposure. Evidence of peripheral nerve damage may be detected on electrodiagnostic testing, but overt peripheral neuropathy is rare. Acrodynia is an uncommon idiosyncratic reaction to subacute or chronic mercury exposure and occurs mainly in children. It is characterized by painful erythema of the extremities and may be associated with hypertension, diaphoresis, anorexia, insomnia, irritability or apathy, and a miliary rash. Chronic exposure to inorganic mercury salts, sometimes via topical application in cosmetic creams, has been associated with neurological symptoms and renal toxicity in case reports and case series.

Methylmercury intoxication affects mainly the central nervous system and results in paresthesias, ataxia, hearing impairment, dysarthria, and progressive constriction of the visual fields. Signs and symptoms of methylmercury intoxication may first appear several weeks or months after exposure begins. Methylmercury is a reproductive toxin. High-dose prenatal exposure to methylmercury may produce mental retardation and a cerebral palsy-like syndrome in the offspring. Low-level prenatal exposures to methylmercury have been associated with a risk of subclinical neurodevelopmental deficits.

A 2004 report by the Institute of Medicine's Immunization Safety Review Committee concluded that available evidence favored rejection of a causal relation between thimerosal-containing vaccines and autism. In like manner, a recent retrospective cohort study conducted by the CDC did not support a causal association between early prenatal or postnatal exposure to mercury from thimerosal-containing vaccines and neuropsychological functioning later in childhood.

Dimethylmercury is a rarely encountered but extremely neurotoxic form of organomercury that may be lethal in small quantities.

The diagnosis of mercury intoxication involves integration of the history and physical findings with confirmatory laboratory testing or other evidence of exposure. In the absence of occupational exposure, the urine mercury concentration is usually less than 5 mcg/L, and whole blood mercury is less than 5 mcg/L. In 1990, the Biological Exposure Index (BEI) Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) recommended that workplace exposures should result in urinary mercury concentrations less than 35 mcg per gram of creatinine and end-of-work-week whole blood mercury concentrations less than 15 mcg/L. To minimize the risk of developmental neurotoxicity from methylmercury, the US Environmental Protection Agency and the Food and Drug Administration (FDA) have advised pregnant women, women who might become pregnant, nursing mothers, and young children to avoid consumption of fish with high mercury levels (eg, swordfish) and to limit consumption of fish with lower levels of mercury to no more than 12 ounces (340 g, or two average meals) per week.

Treatment

A. Acute Exposure

In addition to intensive supportive care, prompt chelation with oral or intravenous **unithiol**, intramuscular **dimercaprol**, or oral **succimer** may be of value in diminishing nephrotoxicity after acute exposure to inorganic mercury salts. Vigorous hydration may help to maintain urine output, but if acute renal failure ensues, days to weeks of hemodialysis or hemodiafiltration in conjunction with chelation may be necessary. Because the efficacy of chelation declines with time since exposure, treatment should not be delayed until the onset of oliguria or other major systemic effects.

B. Chronic Exposure

Unithiol and **succimer** increase urine mercury excretion following acute or chronic elemental mercury inhalation, but the impact of such treatment on clinical outcome is unknown. Dimercaprol has been shown to redistribute mercury to the central nervous system

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from other tissue sites, and since the brain is a key target organ, dimercaprol should not be used in treatment of exposure to elemental or organic mercury. Limited data suggest that succimer, unithiol, and *N*-acetyl-L-cysteine (NAC) may enhance body clearance of methylmercury.

PHARMACOLOGY OF CHELATORS

Chelating agents are drugs used to prevent or reverse the toxic effects of a heavy metal on an enzyme or other cellular target, or to accelerate the elimination of the metal from the body. By forming a complex with the heavy metal, the chelating agent renders the metal unavailable for toxic interactions with functional groups of enzymes or other proteins, coenzymes, cellular nucleophiles, and membranes. Chelating agents contain one or more coordinating atoms, usually oxygen, sulfur, or nitrogen, which donate a pair of electrons to a cationic metal ion to form one or more coordinate-covalent bonds. Depending on the number of metal-ligand bonds, the complex may be referred to as mono-, bi-, or polydentate. Figure 57–2 depicts the hexadentate chelate formed by interaction of edetate (ethylenediaminetetraacetate) with a metal atom, such as lead.

In some cases, the metal-mobilizing effect of a therapeutic chelating agent may not only enhance that metal's excretion—a desired effect—but may also redistribute some of the metal to other vital organs. This has been demonstrated for dimercaprol, which redistributes mercury and arsenic to the brain while also enhancing urinary mercury and arsenic excretion. Although several chelating agents have the capacity to mobilize cadmium, their tendency to redistribute cadmium to the kidney and increase nephrotoxicity has negated their therapeutic value in cadmium intoxication.

In addition to removing the target metal that is exerting toxic effects on the body, some chelating agents may enhance excretion of essential cations, such as zinc in the case of calcium EDTA and diethylenetriaminepentaacetic acid (DTPA), and zinc and copper in the case of succimer. No clinical significance of this effect has been demonstrated, although some animal data suggest the possibility of adverse developmental impact. If prolonged chelation during the prenatal period or early childhood period is necessary, judicious supplementation of the diet with zinc might be considered.

The longer the half-life of a metal in a particular organ, the less effectively it will be removed by chelation. For example, in the case of lead chelation with calcium EDTA or succimer, or of plutonium chelation with DTPA, the metal is more effectively removed from soft tissues than from bone, where incorporation into bone matrix results in prolonged retention.

In most cases, the capacity of chelating agents to prevent or reduce the adverse effects of toxic metals appears to be greatest when such agents are administered very soon after an acute metal exposure. Use of chelating agents days to weeks after an acute metal exposure ends—or their use in the treatment of chronic metal intoxication—may still be associated with increased metal excretion. However, at that point, the capacity of such enhanced excretion to mitigate the pathologic effect of the metal exposure may be reduced.

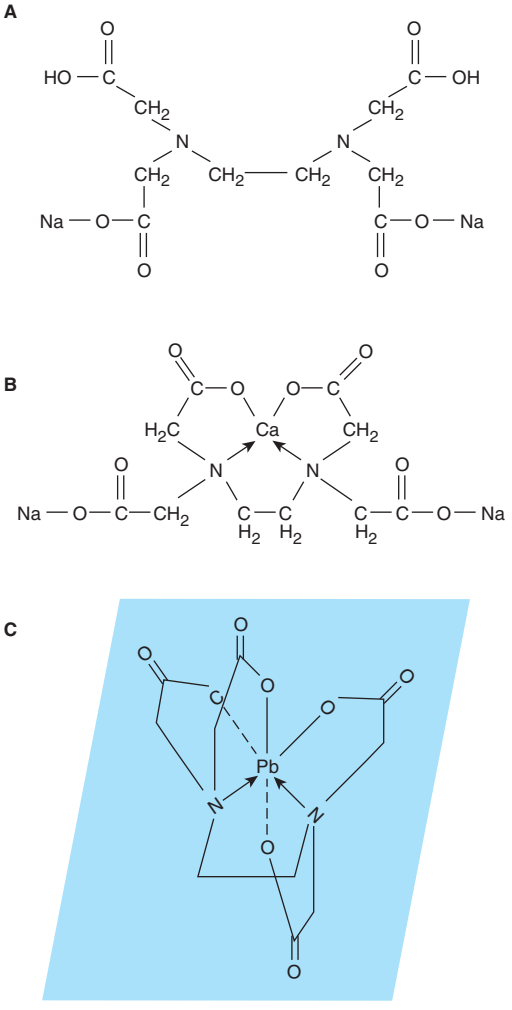

FIGURE 57–2 Salt and chelate formation with edetate (ethylenediaminetetraacetate, EDTA). **A:** In a solution of calcium disodium salt of EDTA, the sodium and hydrogen ions are chemically and biologically available. **B:** In solutions of calcium disodium edetate, calcium is bound by coordinate-covalent bonds with nitrogens as well as by the usual ionic bonds. **C:** In the lead–edetate chelate, lead is incorporated into five heterocyclic rings. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology,* 7th ed. Originally published by Lange Medical Publications. McGraw-Hill, 1980.)

The most important chelating agents currently in use in the USA are described below.

DIMERCAPROL (2,3-DIMERCAPTOPROPANOL, BAL)

Dimercaprol (Figure 57–3), an oily, colorless liquid with a strong mercaptan-like odor, was developed in Great Britain during

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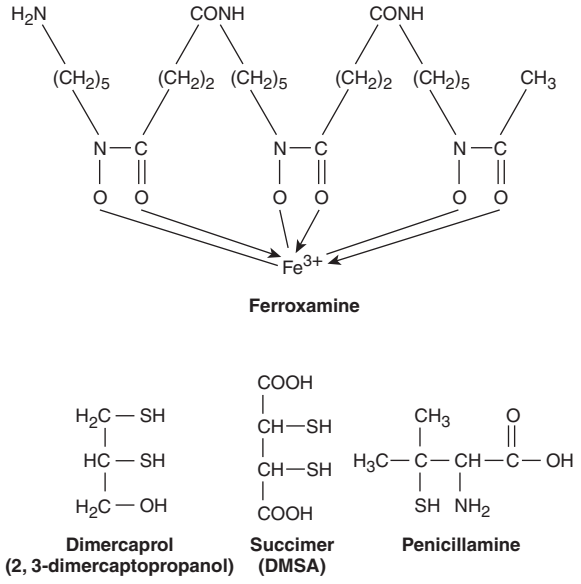

FIGURE 57–3 Chemical structures of several chelators. Ferroxamine (ferrioxamine) without the chelated iron is deferoxamine. It is represented here to show the functional groups; the iron is actually held in a caged system. The structures of the in vivo metal-chelator complexes for dimercaprol, succimer, penicillamine, and unithiol (see text) are not known and may involve the formation of mixed disulfides with amino acids. (Modified and reproduced, with permission from Meyers FH, Jawetz E, and Goldfien A: *Review of Medical Pharmacology,* 7th ed. Originally published by Lange Medical Publications. McGraw-Hill, 1980.)

World War II as a therapeutic antidote against poisoning by the arsenic-containing warfare agent lewisite. It thus became known as British anti-Lewisite, or BAL. Because aqueous solutions of dimercaprol are unstable and oxidize readily, it is dispensed in 10% solution in peanut oil and must be administered by intramuscular injection, which is often painful.

In animal models, dimercaprol prevents and reverses arsenic-induced inhibition of sulfhydryl-containing enzymes and, if given soon after exposure, may protect against the lethal effects of inorganic and organic arsenicals. Human data indicate that it can increase the rate of excretion of arsenic and lead and may offer therapeutic benefit in the treatment of acute intoxication by arsenic, lead, and mercury.

Indications & Toxicity

Dimercaprol is FDA-approved as single-agent treatment of acute poisoning by arsenic and inorganic mercury and for the treatment of severe lead poisoning when used in conjunction with edetate calcium disodium (EDTA; see below). Although studies of its metabolism in humans are limited, intramuscularly administered dimercaprol appears to be readily absorbed, metabolized, and excreted by the kidney within 4–8 hours. Animal models indicate that it may also undergo biliary excretion, but the role of this excretory route in humans and other details of its biotransformation are uncertain.

When used in therapeutic doses, dimercaprol is associated with a high incidence of adverse effects, including hypertension, tachycardia, nausea, vomiting, lacrimation, salivation, fever (particularly in children), and pain at the injection site. Its use has also been associated with thrombocytopenia and increased prothrombin time—factors that may limit intramuscular injection because of the risk of hematoma formation at the injection site. Despite its protective effects in acutely intoxicated animals, dimercaprol may redistribute arsenic and mercury to the central nervous system, and it is not advocated for treatment of chronic poisoning. Water-soluble analogs of dimercaprol—unithiol and succimer—have higher therapeutic indices and have replaced dimercaprol in many settings.

SUCCIMER (DIMERCAPTOSUCCINIC ACID, DMSA)

Succimer is a water-soluble analog of dimercaprol, and like that agent it has been shown in animal studies to prevent and reverse metal-induced inhibition of sulfhydryl-containing enzymes and to protect against the acute lethal effects of arsenic. In humans, treatment with succimer is associated with an increase in urinary lead excretion and a decrease in blood lead concentration. It may also decrease the mercury content of the kidney, a key target organ of inorganic mercury salts. In the USA, succimer is formulated exclusively for oral use, but intravenous formulations have been used successfully elsewhere. It is absorbed rapidly but somewhat variably after oral administration. Peak blood levels of succimer occur at approximately 3 hours. The drug binds in vivo to the amino acid cysteine to form 1:1 and 1:2 mixed disulfides, possibly in the kidney, and it may be these complexes that are the active chelating moieties. Experimental data suggest that multidrug-resistance protein 2 (Mrp2), one of a group of transporter proteins involved in the cellular excretion of xenobiotics, facilitates the renal excretion of mercury compounds that are bound to the transformed succimer and to unithiol. The elimination half-time of transformed succimer is approximately 2–4 hours.

Indications & Toxicity

Succimer is currently FDA-approved for the treatment of children with blood lead concentrations greater than 45 mcg/dL, but it is also commonly used in adults. The typical dosage is 10 mg/kg orally three times a day. Oral administration of succimer is comparable to parenteral EDTA in reducing blood lead concentration and has supplanted EDTA in outpatient treatment of patients who are capable of absorbing the oral drug. However, despite the demonstrated capacity of both succimer and EDTA to enhance lead elimination, their value in reversing established lead toxicity or in otherwise improving therapeutic outcome has yet to be established by a placebo-controlled clinical trial. In a recent study in lead-exposed juvenile rats, high-dose succimer did reduce lead-induced neurocognitive impairment when administered to animals with moderate- and high-dose lead exposure. Conversely, when administered to the control group that was not lead exposed, succimer

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was associated with a decrement in neurocognitive performance. Based on its protective effects against arsenic in animals and its ability to mobilize mercury from the kidney, succimer has also been used in the treatment of arsenic and mercury poisoning.

In limited clinical trials, succimer has been well tolerated. It has a negligible impact on body stores of calcium, iron, and magnesium. It induces a mild increase in urinary excretion of zinc and, less consistently, copper. This effect on trace metal balance has not been associated with overt adverse effects, but its long-term impact on neurodevelopment is uncertain. Gastrointestinal disturbances, including anorexia, nausea, vomiting, and diarrhea, are the most common side effects, occurring in less than 10% of patients. Rashes, sometimes requiring discontinuation of the medication, have been reported in less than 5% of patients. Mild, reversible increases in liver aminotransferases have been noted in 6–10% of patients, and isolated cases of mild to moderate neutropenia have been reported.

EDETATE CALCIUM DISODIUM (ETHYLENEDIAMINETETRAACETIC ACID, EDTA)

Ethylenediaminetetraacetic acid (Figure 57–2) is an efficient chelator of many divalent and trivalent metals in vitro. To prevent potentially life-threatening depletion of calcium, the drug should be administered only as the calcium disodium salt.

EDTA penetrates cell membranes relatively poorly and therefore chelates extracellular metal ions much more effectively than intracellular ions.

The highly polar ionic character of EDTA limits its oral absorption. Moreover, oral administration may increase lead absorption from the gut. Consequently, EDTA should be administered by intravenous infusion. In patients with normal renal function, EDTA is rapidly excreted by glomerular filtration, with 50% of an injected dose appearing in the urine within 1 hour. EDTA mobilizes lead from soft tissues, causing a marked increase in urinary lead excretion and a corresponding decline in blood lead concentration. In patients with renal insufficiency, excretion of the drug—and its metal-mobilizing effects—may be delayed.

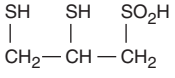
Indications & Toxicity

Edetate calcium disodium is indicated chiefly for the chelation of lead, but it may also have usefulness in poisoning by zinc, manganese, and certain heavy radionuclides. In spite of repeated claims in the alternative medicine literature, EDTA has no demonstrated usefulness in the treatment of atherosclerotic cardiovascular disease.

Because the drug and the mobilized metals are excreted via the urine, the drug is relatively contraindicated in anuric patients. In such instances, the use of low doses of EDTA in combination with high-flux hemodialysis or hemofiltration has been described. Nephrotoxicity from EDTA has been reported, but in most cases can be prevented by maintenance of adequate urine flow, avoidance of excessive doses, and limitation of a treatment course to 5 or fewer consecutive days. EDTA may result in temporary zinc depletion that is of uncertain clinical significance. Analogs of EDTA, the calcium and zinc disodium salts of DTPA, pentetate, have been used for removal ("decorporation") of certain transuranic, rare earth, and transition metal radioisotopes, and in 2004 were approved by the FDA for treatment of contamination with plutonium, americium, and curium.

UNITHIOL (DIMERCAPTOPROPANESULFONIC ACID, DMPS)

Unithiol, a dimercapto chelating agent that is a water-soluble analog of dimercaprol, has been available in the official formularies of Russia and other former Soviet countries since 1958 and in Germany since 1976. It has been legally available from compounding pharmacies in the USA since 1999. Unithiol can be administered orally and intravenously. Bioavailability by the oral route is approximately 50%, with peak blood levels occurring in approximately 3.7 hours. Over 80% of an intravenous dose is excreted in the urine, mainly as cyclic DMPS sulfides. The elimination half-time of total unithiol (parent drug and its transformation products) is approximately 20 hours. Unithiol exhibits protective effects against the toxic action of mercury and arsenic in animal models, and it increases the excretion of mercury, arsenic, and lead in humans. Animal studies and a few case reports suggest that unithiol may also have usefulness in the treatment of poisoning by bismuth compounds.



Unithiol

Indications & Toxicity

Unithiol has no FDA-approved indications, but experimental studies and its pharmacologic and pharmacodynamic profile suggest that intravenous unithiol offers advantages over intramuscular dimercaprol or oral succimer in the initial treatment of severe acute poisoning by inorganic mercury or arsenic. Aqueous preparations of unithiol (usually 50 mg/mL in sterile water) can be administered at a dosage of 3–5 mg/kg every 4 hours by slow intravenous infusion over 20 minutes. If a few days of treatment are accompanied by stabilization of the patient's cardiovascular and gastrointestinal status, it may be possible to change to oral administration of 4–8 mg/kg every 6–8 hours. Oral unithiol may also be considered as an alternative to oral succimer in the treatment of lead intoxication.

Unithiol has been reported to have a low overall incidence of adverse effects (< 4%). Self-limited dermatologic reactions (drug exanthems or urticaria) are the most commonly reported adverse effects, although isolated cases of major allergic reactions, including erythema multiforme and Stevens-Johnson syndrome, have

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been reported. Because rapid intravenous infusion may cause vasodilation and hypotension, unithiol should be infused slowly over an interval of 15–20 minutes.

PENICILLAMINE (D-DIMETHLCYSTEINE)

Penicillamine (Figure 57–3) is a white crystalline, water-soluble derivative of penicillin. D-Penicillamine is less toxic than the L isomer and consequently is the preferred therapeutic form. Penicillamine is readily absorbed from the gut and is resistant to metabolic degradation.

Indications & Toxicity

Penicillamine is used chiefly for treatment of poisoning with copper or to prevent copper accumulation, as in Wilson's disease (hepatolenticular degeneration). It is also used occasionally in the treatment of severe rheumatoid arthritis (see Chapter 36). Its ability to increase urinary excretion of lead and mercury had occasioned its use in outpatient treatment for intoxication with these metals, but succimer, with its stronger metal-mobilizing capacity and lower adverse-effect profile, has generally replaced penicillamine for these purposes.

Adverse effects have been seen in up to one third of patients receiving penicillamine. Hypersensitivity reactions include rash, pruritus, and drug fever, and the drug should be used with extreme caution, if at all, in patients with a history of penicillin allergy. Nephrotoxicity with proteinuria has also been reported, and protracted use of the drug may result in renal insufficiency. Pancytopenia has been associated with prolonged drug intake. Pyridoxine deficiency is a frequent toxic effect of other forms of the drug but is rarely seen with the D form. An acetylated derivative, *N*-acetylpenicillamine, has been used experimentally in mercury poisoning and may have superior metal-mobilizing capacity, but it is not commercially available.

DEFEROXAMINE

Deferoxamine is isolated from *Streptomyces pilosus.* It binds iron avidly (Figure 57–3) but binds essential trace metals poorly. Furthermore, though competing for loosely bound iron in iron-carrying proteins (hemosiderin and ferritin), it fails to compete for biologically chelated iron, as in microsomal and mitochondrial cytochromes and hemoproteins. Consequently, it is the parenteral chelator of choice for iron poisoning (see Chapters 33 and 58). Deferoxamine plus hemodialysis may also be useful in the treatment of aluminum toxicity in renal failure. Deferoxamine is poorly absorbed when administered orally and may increase iron absorption when given by this route. It should therefore be administered intramuscularly or, preferably, intravenously. It is believed to be metabolized, but the pathways are unknown. The iron-chelator complex is excreted in the urine, often turning the urine an orange-red color.

Rapid intravenous administration may result in hypotension. Adverse idiosyncratic responses such as flushing, abdominal discomfort, and rash have also been observed. Pulmonary complications (eg, acute respiratory distress syndrome) have been reported in some patients undergoing deferoxamine infusions lasting longer than 24 hours, and neurotoxicity and increased susceptibility to certain infections (eg, with *Yersinia enterocolitica*) have been described after long-term therapy of iron overload conditions (eg, thalassemia major).

DEFERASIROX

Deferasirox is a tridentate chelator with a high affinity for iron and low affinity for other metals, eg, zinc and copper. It is orally active and well absorbed. In the circulation, it binds iron, and the complex is excreted in the bile. Deferasirox was approved by the FDA in 2005 for the oral treatment of iron overload caused by blood transfusions, a problem in the treatment of thalassemia and myelodysplastic syndrome. More than five years of clinical experience suggest that daily long-term usage is generally well tolerated, with the most common adverse effects consisting of mild to moderate gastrointestinal disturbances (<15% of patients) and skin rash (≈ 5% of patients).

PRUSSIAN BLUE (FERRIC HEXACYANOFERRATE)

Ferric hexacyanoferrate (insoluble Prussian blue) is a hydrated crystalline compound in which Fe^{2+} and Fe^{3+}atoms are coordinated with cyanide groups in a cubic lattice structure. Although used as a dark blue commercial pigment for nearly 300 years, it was only three decades ago that its potential usefulness as a pharmaceutical chelator was recognized. Primarily by ion exchange, and secondarily by mechanical trapping or adsorption, the compound has high affinity for certain univalent cations, particularly cesium and thallium. Used as an oral drug, insoluble Prussian blue undergoes minimal gastrointestinal absorption (<1%). Because the complexes it forms with cesium or thallium are nonabsorbable, oral administration of the chelator diminishes intestinal absorption or interrupts enterohepatic and enteroenteric circulation of these cations, thereby accelerating their elimination in the feces. In clinical case series, the use of Prussian blue has been associated with a decline in the biologic half-life (ie, in vivo retention) of radioactive cesium and thallium.

Indications & Toxicity

In 2003, the FDA approved Prussian blue for the treatment of contamination with radioactive cesium (^{137}Cs) and intoxication with thallium salts. Approval was prompted by concern over potential widespread human contamination with radioactive cesium caused by terrorist use of a radioactive dispersal device ("dirty bomb"). The drug is part of the Strategic National Stockpile of pharmaceuticals and medical material maintained by the CDC (http://www.bt.cdc.gov/stockpile/#material). (***Note:*** Although soluble forms of Prussian blue, such as potassium

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ferric hexacyanoferrate, may have better utility in thallium poisoning, only the insoluble form is currently available as a pharmaceutical.)

After exposure to ^{137}Cs or thallium salts, the approved adult dosage is 3 g orally three times a day; the corresponding pediatric dosage (2–12 years of age) is 1 g orally three times a day. Serial monitoring of urine and fecal radioactivity (^{137}Cs) and urinary thallium concentrations can guide the recommended duration of therapy. Adjunctive supportive care for possible acute radiation illness (^{137}Cs) or systemic thallium toxicity should be instituted as needed.

Prussian blue has not been associated with significant adverse effects. Constipation, which may occur in some cases, should be treated with laxatives or increased dietary fiber.

PREPARATIONS AVAILABLE

Deferasirox (Exjade)
Oral: 125, 250, 500 mg tablets

Deferoxamine (Desferal)
Parenteral: Powder to reconstitute, 500, 2000 mg/vial

Dimercaprol (BAL in Oil)
Parenteral: 100 mg/mL for IM injection

Edetate calcium [calcium EDTA] (Calcium Disodium Versenate)
Parenteral: 200 mg/mL for injection

Penicillamine (Cuprimine, Depen)
Oral: 125, 250 mg capsules; 250 mg tablets

Pentetate Calcium Trisodium ([calcium DTPA] and Pentetate Zinc Trisodium [zinc DTPA])
Parenteral: 200 mg/mL for injection

Prussian Blue (Radiogardase)
Oral: 500 mg capsules

Succimer (Chemet)
Oral: 100 mg capsules

Unithiol (Dimaval)
Bulk powder available for compounding as oral capsules, or for infusion (50 mg/mL)

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CASE STUDY ANSWER

This scenario is highly suspicious for acute lead intoxication. Lead-based paints have been commonly used as anticorrosion coatings on iron and steel structures, and grinding and torch cutting can result in high-dose exposure to inhaled lead dust and fumes. Measurement of a whole blood lead concentration would be a key diagnostic test. If an elevated blood lead concentration is confirmed, the primary therapeutic intervention will be removal of the individual from further work exposure until blood lead concentration has declined and symptoms resolved. If the blood lead concentration is in excess of 80 mcg/dL (~ 4 μmol/L), treatment with a chelating agent, such as oral succimer or parenteral edetate calcium disodium, should be strongly considered. Upon return to work, use of proper respiratory protection and adherence to protective work practices are essential.

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CHAPTER

58

Management of the Poisoned Patient

Kent R. Olson, MD

CASE STUDY

A 62-year-old woman with a history of depression is found in her apartment in a lethargic state. An empty bottle of bupropion is on the bedside table. In the emergency department, she is unresponsive to verbal and painful stimuli. She has a brief generalized seizure, followed by a respiratory arrest. The emergency physician performs endotracheal intubation and administers a drug intravenously, followed by another substance via a nasogastric tube. The patient is admitted to the intensive care unit for continued supportive care and recovers the next morning. What drug might be used intravenously to prevent further seizures? What substance is commonly used to adsorb drugs still present in the gastrointestinal tract?

Over 1 million cases of acute poisoning occur in the USA each year, although only a small number are fatal. Most deaths are due to intentional suicidal overdose by an adolescent or adult. Childhood deaths due to accidental ingestion of a drug or toxic household product have been markedly reduced in the last 40 years as a result of safety packaging and effective poisoning prevention education.

Even with a serious exposure, poisoning is rarely fatal if the victim receives prompt medical attention and good supportive care. Careful management of respiratory failure, hypotension, seizures, and thermoregulatory disturbances has resulted in improved survival of patients who reach the hospital alive.

This chapter reviews the basic principles of poisoning, initial management, and specialized treatment of poisoning, including methods of increasing the elimination of drugs and toxins.

TOXICOKINETICS & TOXICODYNAMICS

The term **toxicokinetics** denotes the absorption, distribution, excretion, and metabolism of toxins, toxic doses of therapeutic agents, and their metabolites. The term **toxicodynamics** is used to denote the injurious effects of these substances on body functions. Although many similarities exist between the pharmacokinetics and toxicokinetics of most substances, there are also important differences. The same caution applies to pharmacodynamics and toxicodynamics.

SPECIAL ASPECTS OF TOXICOKINETICS

Volume of Distribution

The volume of distribution (V_d) is defined as the apparent volume into which a substance is distributed in the body (see Chapter 3). A large V_d implies that the drug is not readily accessible to measures aimed at purifying the blood, such as hemodialysis. Examples of drugs with large volumes of distribution (> 5 L/kg) include antidepressants, antipsychotics, antimalarials, opioids, propranolol, and verapamil. Drugs with a relatively small V_d (< 1 L/kg) include salicylate, ethanol, phenobarbital, lithium, valproic acid, and phenytoin (see Table 3–1).

Clearance

Clearance is a measure of the volume of plasma that is cleared of drug per unit time (see Chapter 3). The total clearance for most drugs is the sum of clearances via excretion by the kidneys and metabolism by the liver. In planning a detoxification strategy, it is important to know the contribution of each organ to total clearance. For example, if a drug is 95% cleared by liver metabolism and only 5% cleared by renal excretion, even a dramatic increase in urinary concentration of the drug will have little effect on overall elimination.

Overdosage of a drug can alter the usual pharmacokinetic processes, and this must be considered when applying kinetics to

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poisoned patients. For example, dissolution of tablets or gastric emptying time may be slowed so that absorption and peak toxic effects are delayed. Drugs may injure the epithelial barrier of the gastrointestinal tract and thereby increase absorption. If the capacity of the liver to metabolize a drug is exceeded, the first-pass effect will be reduced and more drug will be delivered to the circulation. With a dramatic increase in the concentration of drug in the blood, protein-binding capacity may be exceeded, resulting in an increased fraction of free drug and greater toxic effect. At normal dosage, most drugs are eliminated at a rate proportional to the plasma concentration (first-order kinetics). If the plasma concentration is very high and normal metabolism is saturated, the rate of elimination may become fixed (zero-order kinetics). This change in kinetics may markedly prolong the apparent serum half-life and increase toxicity.

SPECIAL ASPECTS OF TOXICODYNAMICS

The general dose-response principles described in Chapter 2 are relevant when estimating the potential severity of an intoxication. When considering quantal dose-response data, both the therapeutic index and the overlap of therapeutic and toxic response curves must be considered. For instance, two drugs may have the same therapeutic index but unequal safe dosing ranges if the slopes of their dose-response curves are not the same. For some drugs, eg, sedative-hypnotics, the major toxic effect is a direct extension of the therapeutic action, as shown by their graded dose-response curve (see Figure 22–1). In the case of a drug with a linear dose-response curve (drug A), lethal effects may occur at 10 times the normal therapeutic dose. In contrast, a drug with a curve that reaches a plateau (drug B) may not be lethal at 100 times the normal dose.

For many drugs, at least part of the toxic effect may be different from the therapeutic action. For example, intoxication with drugs that have atropine-like effects (eg, tricyclic antidepressants) reduces sweating, making it more difficult to dissipate heat. In tricyclic antidepressant intoxication, there may also be increased muscular activity or seizures; the body's production of heat is thus enhanced, and lethal hyperpyrexia may result. Overdoses of drugs that depress the cardiovascular system, eg, β blockers or calcium channel blockers, can profoundly alter not only cardiac function but all functions that are dependent on blood flow. These include renal and hepatic elimination of the toxin and that of any other drugs that may be given.

APPROACH TO THE POISONED PATIENT

HOW DOES THE POISONED PATIENT DIE?

An understanding of common mechanisms of death due to poisoning can help prepare the caregiver to treat patients effectively. Many toxins depress the central nervous system (CNS), resulting in obtundation or coma. Comatose patients frequently lose their airway protective reflexes and their respiratory drive. Thus, they may die as a result of airway obstruction by the flaccid tongue, aspiration of gastric contents into the tracheobronchial tree, or respiratory arrest. These are the most common causes of death due to overdoses of narcotics and sedative-hypnotic drugs (eg, barbiturates and alcohol).

Cardiovascular toxicity is also frequently encountered in poisoning. Hypotension may be due to depression of cardiac contractility; hypovolemia resulting from vomiting, diarrhea, or fluid sequestration; peripheral vascular collapse due to blockade of α-adrenoceptor-mediated vascular tone; or cardiac arrhythmias. Hypothermia or hyperthermia due to exposure as well as the temperature-dysregulating effects of many drugs can also produce hypotension. Lethal arrhythmias such as ventricular tachycardia and fibrillation can occur with overdoses of many cardioactive drugs such as ephedrine, amphetamines, cocaine, digitalis, and theophylline; and drugs not usually considered cardioactive, such as tricyclic antidepressants, antihistamines, and some opioid analogs.

Cellular hypoxia may occur in spite of adequate ventilation and oxygen administration when poisoning is due to cyanide, hydrogen sulfide, carbon monoxide, and other poisons that interfere with transport or utilization of oxygen. Such patients may not be cyanotic, but cellular hypoxia is evident by the development of tachycardia, hypotension, severe lactic acidosis, and signs of ischemia on the electrocardiogram.

Seizures, muscular hyperactivity, and rigidity may result in death. Seizures may cause pulmonary aspiration, hypoxia, and brain damage. Hyperthermia may result from sustained muscular hyperactivity and can lead to muscle breakdown and myoglobinuria, renal failure, lactic acidosis, and hyperkalemia. Drugs and poisons that often cause seizures include antidepressants, isoniazid (INH), diphenhydramine, cocaine, and amphetamines.

Other organ system damage may occur after poisoning and is sometimes delayed in onset. Paraquat attacks lung tissue, resulting in pulmonary fibrosis, beginning several days after ingestion. Massive hepatic necrosis due to poisoning by acetaminophen or certain mushrooms results in hepatic encephalopathy and death 48–72 hours or longer after ingestion.

Finally, some patients may die before hospitalization because the behavioral effects of the ingested drug may result in traumatic injury. Intoxication with alcohol and other sedative-hypnotic drugs is a common contributing factor to motor vehicle accidents. Patients under the influence of hallucinogens such as phencyclidine (PCP) or lysergic acid diethylamide (LSD) may suffer trauma when they become combative or fall from a height.

INITIAL MANAGEMENT OF THE POISONED PATIENT

The initial management of a patient with coma, seizures, or otherwise altered mental status should follow the same approach regardless of the poison involved: supportive measures are the basics (**"ABCDs"**) of poisoning treatment.

First, the **airway** should be cleared of vomitus or any other obstruction and an oral airway or endotracheal tube inserted if

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needed. For many patients, simple positioning in the lateral, left-side-down position is sufficient to move the flaccid tongue out of the airway. **Breathing** should be assessed by observation and pulse oximetry and, if in doubt, by measuring arterial blood gases. Patients with respiratory insufficiency should be intubated and mechanically ventilated. The **circulation** should be assessed by continuous monitoring of pulse rate, blood pressure, urinary output, and evaluation of peripheral perfusion. An intravenous line should be placed and blood drawn for serum glucose and other routine determinations.

At this point, every patient with altered mental status should receive a challenge with concentrated **dextrose,** unless a rapid bedside blood glucose test demonstrates that the patient is not hypoglycemic. Adults are given 25 g (50 mL of 50% dextrose solution) intravenously, children 0.5 g/kg (2 mL/kg of 25% dextrose). Hypoglycemic patients may appear to be intoxicated, and there is no rapid and reliable way to distinguish them from poisoned patients. Alcoholic or malnourished patients should also receive 100 mg of thiamine intramuscularly or in the intravenous infusion solution at this time to prevent Wernicke's syndrome.

The opioid antagonist **naloxone** may be given in a dose of 0.4–2 mg intravenously. Naloxone reverses respiratory and CNS depression due to all varieties of opioid drugs (see Chapter 31). It is useful to remember that these drugs cause death primarily by respiratory depression; therefore, if airway and breathing assistance have already been instituted, naloxone may not be necessary. Larger doses of naloxone may be needed for patients with overdose involving propoxyphene, codeine, and some other opioids. The benzodiazepine antagonist **flumazenil** (see Chapter 22) may be of value in patients with suspected benzodiazepine overdose, but it should not be used if there is a history of tricyclic antidepressant overdose or a seizure disorder, as it can induce convulsions in such patients.

History & Physical Examination

Once the essential initial ABCD interventions have been instituted, one can begin a more detailed evaluation to make a specific diagnosis. This includes gathering any available history and performing a toxicologically oriented physical examination. Other causes of coma or seizures such as head trauma, meningitis, or metabolic abnormalities should be sought and treated. Some common intoxications are described under Common Toxic Syndromes.

A. History

Oral statements about the amount and even the type of drug ingested in toxic emergencies may be unreliable. Even so, family members, police, and fire department or paramedical personnel should be asked to describe the environment in which the toxic emergency occurred and should bring to the emergency department any syringes, empty bottles, household products, or over-the-counter medications in the immediate vicinity of the possibly poisoned patient.

B. Physical Examination

A brief examination should be performed, emphasizing those areas most likely to give clues to the toxicologic diagnosis. These include vital signs, eyes and mouth, skin, abdomen, and nervous system.

1. Vital signs—Careful evaluation of vital signs (blood pressure, pulse, respirations, and temperature) is essential in all toxicologic emergencies. Hypertension and tachycardia are typical with amphetamines, cocaine, and antimuscarinic (anticholinergic) drugs. Hypotension and bradycardia are characteristic features of overdose with calcium channel blockers, β blockers, clonidine, and sedative hypnotics. Hypotension with tachycardia is common with tricyclic antidepressants, trazodone, quetiapine, vasodilators, and β agonists. Rapid respirations are typical of salicylates, carbon monoxide, and other toxins that produce metabolic acidosis or cellular asphyxia. Hyperthermia may be associated with sympathomimetics, anticholinergics, salicylates, and drugs producing seizures or muscular rigidity. Hypothermia can be caused by any CNS-depressant drug, especially when accompanied by exposure to a cold environment.

2. Eyes—The eyes are a valuable source of toxicologic information. Constriction of the pupils (miosis) is typical of opioids, clonidine, phenothiazines, and cholinesterase inhibitors (eg, organophosphate insecticides), and deep coma due to sedative drugs. Dilation of the pupils (mydriasis) is common with amphetamines, cocaine, LSD, and atropine and other anticholinergic drugs. Horizontal nystagmus is characteristic of intoxication with phenytoin, alcohol, barbiturates, and other sedative drugs. The presence of both vertical and horizontal nystagmus is strongly suggestive of phencyclidine poisoning. Ptosis and ophthalmoplegia are characteristic features of botulism.

3. Mouth—The mouth may show signs of burns due to corrosive substances, or soot from smoke inhalation. Typical odors of alcohol, hydrocarbon solvents, or ammonia may be noted. Poisoning due to cyanide can be recognized by some examiners as an odor like bitter almonds.

4. Skin—The skin often appears flushed, hot, and dry in poisoning with atropine and other antimuscarinics. Excessive sweating occurs with organophosphates, nicotine, and sympathomimetic drugs. Cyanosis may be caused by hypoxemia or by methemoglobinemia. Icterus may suggest hepatic necrosis due to acetaminophen or *Amanita phalloides* mushroom poisoning.

5. Abdomen—Abdominal examination may reveal ileus, which is typical of poisoning with antimuscarinic, opioid, and sedative drugs. Hyperactive bowel sounds, abdominal cramping, and diarrhea are common in poisoning with organophosphates, iron, arsenic, theophylline, *A phalloides*, and *A muscaria*.

6. Nervous system—A careful neurologic examination is essential. Focal seizures or motor deficits suggest a structural lesion (eg, intracranial hemorrhage due to trauma) rather than toxic or metabolic encephalopathy. Nystagmus, dysarthria, and ataxia are typical of phenytoin, carbamazepine, alcohol, and other sedative intoxication. Twitching and muscular hyperactivity are common with atropine and other anticholinergic agents, and cocaine and other sympathomimetic drugs. Muscular rigidity can be caused by haloperidol and other antipsychotic agents, and by strychnine or by tetanus. Generalized hypertonicity of muscles and lower extremity clonus are typical of serotonin syndrome. Seizures are

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often caused by overdose with antidepressants (especially tricyclic antidepressants and bupropion [as in the case study]), cocaine, amphetamines, theophylline, isoniazid, and diphenhydramine. Flaccid coma with absent reflexes and even an isoelectric electroencephalogram may be seen with deep coma due to sedative-hypnotic or other CNS depressant intoxication and may be mistaken for brain death.

Laboratory & Imaging Procedures

A. Arterial Blood Gases

Hypoventilation results in an elevated P_{CO_2} (hypercapnia) and a low P_{O_2} (hypoxia). The P_{O_2} may also be low in a patient with aspiration pneumonia or drug-induced pulmonary edema. Poor tissue oxygenation due to hypoxia, hypotension, or cyanide poisoning will result in metabolic acidosis. The P_{O_2} measures only oxygen dissolved in the plasma and not total blood oxygen content or oxyhemoglobin saturation and may appear normal in patients with severe carbon monoxide poisoning. Pulse oximetry may also give falsely normal results in carbon monoxide intoxication.

B. Electrolytes

Sodium, potassium, chloride, and bicarbonate should be measured. The anion gap is then calculated by subtracting the measured anions from cations:

$$\text{Anion gap} = (Na^+ + K^+) - (HCO_3^- + Cl^-)$$

Normally, the sum of the cations exceeds the sum of the anions by no more than 12–16 mEq/L (or 8–12 mEq/L if the formula used for estimating the anion gap omits the potassium level). A larger-than expected anion gap is caused by the presence of unmeasured anions (lactate, etc) accompanying metabolic acidosis. This may occur with numerous conditions, such as diabetic ketoacidosis, renal failure, or shock-induced lactic acidosis. Drugs that may induce an elevated anion gap metabolic acidosis (Table 58–1) include aspirin, metformin, methanol, ethylene glycol, isoniazid, and iron.

Alterations in the serum potassium level are hazardous because they can result in cardiac arrhythmias. Drugs that may cause hyperkalemia despite normal renal function include potassium itself, β blockers, digitalis glycosides, potassium-sparing diuretics, and fluoride. Drugs associated with hypokalemia include barium, β agonists, caffeine, theophylline, and thiazide and loop diuretics.

C. Renal Function Tests

Some toxins have direct nephrotoxic effects; in other cases, renal failure is due to shock or myoglobinuria. Blood urea nitrogen and creatinine levels should be measured and urinalysis performed. Elevated serum creatine kinase (CK) and myoglobin in the urine suggest muscle necrosis due to seizures or muscular rigidity. Oxalate crystals in large numbers in the urine suggest ethylene glycol poisoning.

D. Serum Osmolality

The calculated serum osmolality is dependent mainly on the serum sodium and glucose and the blood urea nitrogen and can be estimated from the following formula:

$$2 \times Na^+ \text{ (mEq/L)} + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{3}$$

This calculated value is normally 280–290 mOsm/L. Ethanol and other alcohols may contribute significantly to the measured serum osmolality but, since they are not included in the calculation, cause an osmol gap:

$$\text{Osmolar gap} = \text{Measured osmolality} - \text{Calculated osmolality}$$

Table 58–2 lists the concentration and expected contribution to the serum osmolality in ethanol, methanol, ethylene glycol, and isopropanol poisonings.

E. Electrocardiogram

Widening of the QRS complex duration (to more than 100 milliseconds) is typical of tricyclic antidepressant and quinidine overdoses (Figure 58–1). The QT_c interval may be prolonged (to more than 440 milliseconds) in many poisonings, including quinidine, antidepressants and antipsychotics, lithium, and arsenic (see also http://www.torsades.org/). Variable atrioventricular (AV) block and

TABLE 58–1 Examples of drug-induced anion gap acidosis.

Type of Elevation of the Anion Gap	Agents
Organic acid metabolites	Methanol, ethylene glycol, diethylene glycol
Lactic acidosis	Cyanide, carbon monoxide, ibuprofen, isoniazid, metformin, salicylates, valproic acid; any drug-induced seizures, hypoxia, or hypotension

Note: The normal anion gap calculated from $(Na^+ + K^+) - (HCO_3^- + Cl^-)$ is 12–16 mEq/L; calculated from $(Na^+) - (HCO_3^- + Cl^-)$, it is 8–12 mEq/L.

TABLE 58–2 Some substances that can cause an osmol gap.

Substance[1]	Serum Level (mg/dL)	Corresponding Osmol Gap (mOsm/kg)
Ethanol	350	75
Methanol	80	25
Ethylene glycol	200	35
Isopropanol	350	60

[1]Other substances that can increase the osmol gap include propylene glycol and other glycols, acetone, mannitol, and magnesium.

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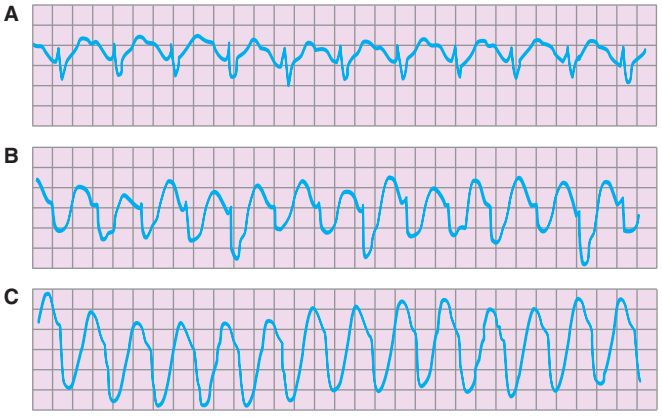

FIGURE 58–1 Changes in the electrocardiogram in tricyclic antidepressant overdosage. **A:** Slowed intraventricular conduction results in prolonged QRS interval (0.18 s; normal, 0.08 s). **B** and **C:** Supraventricular tachycardia with progressive widening of QRS complexes mimics ventricular tachycardia. (Reproduced, with permission, from Benowitz NL, Goldschlager N: Cardiac disturbances in the toxicologic patient. In: Haddad LM, Winchester JF [editors]. *Clinical Management of Poisoning and Drug Overdose*. WB Saunders, 1983.)

a variety of atrial and ventricular arrhythmias are common with poisoning by digoxin and other cardiac glycosides. Hypoxemia due to carbon monoxide poisoning may result in ischemic changes on the electrocardiogram.

F. Imaging Findings

A plain film of the abdomen may be useful because some tablets, particularly iron and potassium, may be radiopaque. Chest radiographs may reveal aspiration pneumonia, hydrocarbon pneumonia, or pulmonary edema. When head trauma is suspected, a computed tomography (CT) scan is recommended.

Toxicology Screening Tests

It is a common misconception that a broad toxicology "screen" is the best way to diagnose and manage an acute poisoning. Unfortunately, comprehensive toxicology screening is time-consuming and expensive and results of tests may not be available for days. Moreover, many highly toxic drugs such as calcium channel blockers, β blockers, and isoniazid are not included in the screening process. The clinical examination of the patient and selected routine laboratory tests are usually sufficient to generate a tentative diagnosis and an appropriate treatment plan. Although screening tests may be helpful in confirming a suspected intoxication or for ruling out intoxication as a cause of apparent brain death, they should not delay needed treatment.

When a specific antidote or other treatment is under consideration, quantitative laboratory testing may be indicated. For example, determination of the acetaminophen level is useful in assessing the need for antidotal therapy with acetylcysteine. Serum levels of salicylate (aspirin), ethylene glycol, methanol, theophylline, carbamazepine, lithium, valproic acid, and other drugs and poisons may indicate the need for hemodialysis (Table 58–3).

TABLE 58–3 Hemodialysis in drug overdose and poisoning.[1]

Hemodialysis may be indicated depending on the severity of poisoning or the blood concentration:
Carbamazepine
Ethylene glycol
Lithium
Methanol
Metformin
Phenobarbital
Salicylate
Theophylline
Valproic acid
Hemodialysis is ineffective or is not useful:
Amphetamines
Antidepressants
Antipsychotic drugs
Benzodiazepines
Calcium channel blockers
Digoxin
Metoprolol and propranolol
Opioids

[1]This listing is not comprehensive.

Decontamination

Decontamination procedures should be undertaken simultaneously with initial stabilization, diagnostic assessment, and laboratory evaluation. Decontamination involves removing toxins from the skin or gastrointestinal tract.

A. Skin

Contaminated clothing should be completely removed and double-bagged to prevent illness in health care providers and for possible laboratory analysis. Wash contaminated skin with soap and water.

B. Gastrointestinal Tract

Controversy remains regarding the efficacy of gut emptying by emesis or gastric lavage, especially when treatment is initiated more than 1 hour after ingestion. For most ingestions, clinical toxicologists recommend simple administration of activated charcoal to bind ingested poisons in the gut before they can be absorbed (as in the case study). In unusual circumstances, induced emesis or gastric lavage may also be used.

1. Emesis—Emesis can be induced with ipecac *syrup* (never *extract* of ipecac), and this method was previously used to treat some childhood ingestions at home under telephone supervision of a physician or poison control center personnel. However, the risks involved with inappropriate use outweighed the unproven

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benefits, and this treatment is rarely used in the home or hospital. Ipecac should not be used if the suspected intoxicant is a corrosive agent, a petroleum distillate, or a rapid-acting convulsant. Previously popular methods of inducing emesis such as fingertip stimulation of the pharynx, salt water, and apomorphine are ineffective or dangerous and should not be used.

2. Gastric lavage—If the patient is awake or if the airway is protected by an endotracheal tube, gastric lavage may be performed using an orogastric or nasogastric tube—as large a tube as possible. Lavage solutions (usually 0.9% saline) should be at body temperature to prevent hypothermia.

3. Activated charcoal—Owing to its large surface area, activated charcoal can adsorb many drugs and poisons. It is most effective if given in a ratio of at least 10:1 of charcoal to estimated dose of toxin by weight. Charcoal does not bind iron, lithium, or potassium, and it binds alcohols and cyanide only poorly. It does not appear to be useful in poisoning due to corrosive mineral acids and alkali. Studies suggest that oral activated charcoal given alone may be just as effective as gut emptying (eg, ipecac-induced emesis or gastric lavage) followed by charcoal. Repeated doses of oral activated charcoal may enhance systemic elimination of some drugs (including carbamazepine, dapsone, and theophylline) by a mechanism referred to as "gut dialysis," although the clinical benefit is unproved.

4. Cathartics—Administration of a cathartic (laxative) agent may hasten removal of toxins from the gastrointestinal tract and reduce absorption, although no controlled studies have been done. Whole bowel irrigation with a balanced polyethylene glycol-electrolyte solution (GoLYTELY, CoLyte) can enhance gut decontamination after ingestion of iron tablets, enteric-coated medicines, illicit drug-filled packets, and foreign bodies. The solution is administered orally at 1–2 L/h (500 mL/h in children) for several hours until the rectal effluent is clear.

Specific Antidotes

There is a popular misconception that there is an antidote for every poison. Actually, selective antidotes are available for only a few classes of toxins. The major antidotes and their characteristics are listed in Table 58–4.

Methods of Enhancing Elimination of Toxins

After appropriate diagnostic and decontamination procedures and administration of antidotes, it is important to consider whether measures for enhancing elimination, such as hemodialysis or urinary alkalinization, can improve the clinical outcome. Table 58–3 lists intoxications for which dialysis may be beneficial.

A. Dialysis Procedures

1. Peritoneal dialysis—Although it is a relatively simple and available technique, peritoneal dialysis is inefficient in removing most drugs.

2. Hemodialysis—Hemodialysis is more efficient than peritoneal dialysis and has been well studied. It assists in correction of fluid and electrolyte imbalance and may also enhance removal of toxic metabolites (eg, formic acid in methanol poisoning; oxalic and glycolic acids in ethylene glycol poisoning). The efficiency of both peritoneal dialysis and hemodialysis is a function of the molecular weight, water solubility, protein binding, endogenous clearance, and distribution in the body of the specific toxin. Hemodialysis is especially useful in overdose cases in which the precipitating drug can be removed and fluid and electrolyte imbalances are present and can be corrected (eg, salicylate intoxication).

B. Forced Diuresis and Urinary pH Manipulation

Previously popular but of unproved value, forced diuresis may cause volume overload and electrolyte abnormalities and is not recommended. Renal elimination of a few toxins can be enhanced by alteration of urinary pH. For example, urinary alkalinization is useful in cases of salicylate overdose. Acidification may increase the urine concentration of drugs such as phencyclidine and amphetamines but is not advised because it may worsen renal complications from rhabdomyolysis, which often accompanies the intoxication.

COMMON TOXIC SYNDROMES

ACETAMINOPHEN

Acetaminophen is one of the drugs commonly involved in suicide attempts and accidental poisonings, both as the sole agent and in combination with other drugs. Acute ingestion of more than 150–200 mg/kg (children) or 7 g total (adults) is considered potentially toxic. A highly toxic metabolite is produced in the liver (see Figure 4–5).

Initially, the patient is asymptomatic or has mild gastrointestinal upset (nausea, vomiting). After 24–36 hours, evidence of liver injury appears, with elevated aminotransferase levels and hypoprothrombinemia. In severe cases, fulminant liver failure occurs, leading to hepatic encephalopathy and death. Renal failure may also occur.

The severity of poisoning is estimated from a serum acetaminophen concentration measurement. If the level is greater than 150–200 mg/L approximately 4 hours after ingestion, the patient is at risk for liver injury. (Chronic alcoholics or patients taking drugs that enhance P450 production of toxic metabolites are at risk with lower levels.) The antidote acetylcysteine acts as a glutathione substitute, binding the toxic metabolite as it is produced. It is most effective when given early and should be started within 8–10 hours if possible. Liver transplantation may be required for patients with fulminant hepatic failure.

AMPHETAMINES & OTHER STIMULANTS

Stimulant drugs commonly abused in the USA include methamphetamine ("crank," "crystal"), methylenedioxymethamphetamine (MDMA, "ecstasy"), and cocaine ("crack") as well as pharmaceuticals such as pseudoephedrine (Sudafed) and ephedrine (as such

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TABLE 58–4 Examples of specific antidotes.

Antidote	Poison(s)	Comments
Acetylcysteine (Acetadote, Mucomyst)	Acetaminophen	Best results if given within 8–10 hours of overdose. Follow liver function tests and acetaminophen blood levels. Acetadote is given intravenously; Mucomyst is given orally.
Atropine	Anticholinesterase intoxication: organophosphates, carbamates	An initial dose of 1–2 mg (for children, 0.05 mg/kg) is given IV, and if there is no response, the dose is doubled every 10–15 minutes, with decreased wheezing and pulmonary secretions as therapeutic end points.
Bicarbonate, sodium	Membrane-depressant cardiotoxic drugs (tricyclic antidepressants, quinidine, etc)	1–2 mEq/kg IV bolus usually reverses cardiotoxic effects (wide QRS, hypotension). Give cautiously in heart failure (avoid sodium overload).
Calcium	Fluoride; calcium channel blockers	Large doses may be needed in severe calcium channel blocker overdose. Start with 15 mg/kg IV.
Deferoxamine	Iron salts	If poisoning is severe, give 15 mg/kg/h IV. 100 mg of deferoxamine binds 8.5 mg of iron.
Digoxin antibodies	Digoxin and related cardiac glycosides	One vial binds 0.5 mg digoxin; indications include serious arrhythmias, hyperkalemia.
Esmolol	Theophylline, caffeine, metaproterenol	Short-acting β blocker. Infuse 25–50 mcg/kg/min IV.
Ethanol	Methanol, ethylene glycol	A loading dose is calculated so as to give a blood level of at least 100 mg/dL (42 g/70 kg in adults). Fomepizole (see below) is easier to use.
Flumazenil	Benzodiazepines	Adult dose is 0.2 mg IV, repeated as necessary to a maximum of 3 mg. *Do not give to patients with seizures, benzodiazepine dependence, or tricyclic overdose.*
Fomepizole	Methanol, ethylene glycol	More convenient than ethanol. Give 15 mg/kg; repeat every 12 hours.
Glucagon	β blockers	5–10 mg IV bolus may reverse hypotension and bradycardia.
Hydroxocobalamin	Cyanide	Adult dose is 5 g IV over 15 minutes. Converts cyanide to cyanocobalamin (vitamin B_{12}).
Naloxone	Narcotic drugs, other opioid derivatives	A specific antagonist of opioids; give 0.4–2 mg initially by IV, IM, or SC injection. Larger doses may be needed to reverse the effects of overdose with propoxyphene, codeine, or fentanyl derivatives. Duration of action (2–3 hours) may be significantly shorter than that of the opioid being antagonized.
Oxygen	Carbon monoxide	Give 100% by high-flow nonrebreathing mask; use of hyperbaric chamber is controversial but often recommended for severe poisoning.
Physostigmine	Suggested for delirium caused by anticholinergic agents	Adult dose is 0.5–1 mg IV slowly. The effects are transient (30–60 minutes), and the lowest effective dose may be repeated when symptoms return. May cause bradycardia, increased bronchial secretions, seizures. Have atropine ready to reverse excess effects. *Do not use for tricyclic antidepressant overdose.*
Pralidoxime (2-PAM)	Organophosphate (OP) cholinesterase inhibitors	Adult dose is 1 g IV, which should be repeated every 3–4 hours as needed or preferably as a constant infusion of 250–400 mg/h. Pediatric dose is approximately 250 mg. No proved benefit in carbamate poisoning; uncertain benefit in established OP poisoning.

and in the herbal agent *Ma-huang*) (see Chapter 32). Caffeine is often added to dietary supplements sold as "metabolic enhancers" or "fat-burners." Newer synthetic analogs of amphetamines such as 3,4-methylenedioxypyrovalerone (MDPV) and various derivatives of methcathinone are becoming popular drugs of abuse, often sold on the street as "bath salts" with names like "Ivory Wave," "Bounce," "Bubbles," "Mad Cow," and "Meow Meow."

At the doses usually used by stimulant abusers, euphoria and wakefulness are accompanied by a sense of power and well-being. At higher doses, restlessness, agitation, and acute psychosis may occur, accompanied by hypertension and tachycardia. Prolonged muscular hyperactivity or seizures may contribute to hyperthermia and rhabdomyolysis. Body temperatures as high as 42°C (107.6°F) have been recorded. Hyperthermia can cause brain damage, hypotension, coagulopathy, and renal failure.

Treatment for stimulant toxicity includes general supportive measures as outlined earlier. There is no specific antidote. Seizures and hyperthermia are the most dangerous manifestations and must be treated aggressively. Seizures are usually managed with intravenous benzodiazepines (eg, lorazepam). Temperature is

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reduced by removing clothing, spraying with tepid water, and encouraging evaporative cooling with fanning. For very high body temperatures (eg, > 40–41°C [104–105.8°F]), neuromuscular paralysis is used to abolish muscle activity quickly.

ANTICHOLINERGIC AGENTS

A large number of prescription and nonprescription drugs, as well as a variety of plants and mushrooms, can inhibit the effects of acetylcholine at muscarinic receptors. Some drugs used for other purposes (eg, antihistamines) also have anticholinergic effects, in addition to other potentially toxic actions. For example, antihistamines such as diphenhydramine can cause seizures; tricyclic antidepressants, which have anticholinergic, quinidine-like, and α-blocking effects, can cause severe cardiovascular toxicity.

The classic anticholinergic (technically, "antimuscarinic") syndrome is remembered as "red as a beet" (skin flushed), "hot as a hare" (hyperthermia), "dry as a bone" (dry mucous membranes, no sweating), "blind as a bat" (blurred vision, cycloplegia), and "mad as a hatter" (confusion, delirium). Patients usually have sinus tachycardia, and the pupils are usually dilated (see Chapter 8). Agitated delirium or coma may be present. Muscle twitching is common, but seizures are unusual unless the patient has ingested an antihistamine or a tricyclic antidepressant. Urinary retention is common, especially in older men.

Treatment for anticholinergic syndrome is largely supportive. Agitated patients may require sedation with a benzodiazepine or an antipsychotic agent (eg, haloperidol). The specific antidote for peripheral and central anticholinergic syndrome is physostigmine, which has a prompt and dramatic effect and is especially useful for patients who are very agitated. Physostigmine is given in small intravenous doses (0.5–1 mg) with careful monitoring, because it can cause bradycardia and seizures if given too rapidly. Physostigmine should not be given to a patient with suspected tricyclic antidepressant overdose because it can aggravate cardiotoxicity, resulting in heart block or asystole. Catheterization may be needed to prevent excessive distention of the bladder.

ANTIDEPRESSANTS

Tricyclic antidepressants (eg, amitriptyline, desipramine, doxepin, many others; see Chapter 30) are among the most common prescription drugs involved in life-threatening drug overdose. Ingestion of more than 1 g of a tricyclic (or about 15–20 mg/kg) is considered potentially lethal.

Tricyclic antidepressants are competitive antagonists at muscarinic cholinergic receptors, and anticholinergic findings (tachycardia, dilated pupils, dry mouth) are common even at moderate doses. Some tricyclics are also strong α blockers, which can lead to vasodilation. Centrally mediated agitation and seizures may be followed by depression and hypotension. Most important is the fact that tricyclics have quinidine-like cardiac depressant effects on the sodium channel that cause slowed conduction with a wide QRS interval and depressed cardiac contractility. This cardiac toxicity may result in serious arrhythmias (Figure 58–1), including ventricular conduction block and ventricular tachycardia.

Treatment of tricyclic antidepressant overdose includes general supportive care as outlined earlier. Endotracheal intubation and assisted ventilation may be needed. Intravenous fluids are given for hypotension, and dopamine or norepinephrine is added if necessary. Many toxicologists recommend norepinephrine as the initial drug of choice for tricyclic-induced hypotension. The antidote for quinidine-like cardiac toxicity (manifested by a wide QRS complex) is sodium bicarbonate: a bolus of 50–100 mEq (or 1–2 mEq/kg) provides a rapid increase in extracellular sodium that helps overcome sodium channel blockade. *Do not use physostigmine!* Although this agent does effectively reverse anticholinergic symptoms, it can aggravate depression of cardiac conduction and cause seizures.

Monoamine oxidase inhibitors (eg, tranylcypromine, phenelzine) are older antidepressants that are occasionally used for resistant depression. They can cause severe hypertensive reactions when interacting foods or drugs are taken (see Chapters 9 and 30), and they can interact with the selective serotonin reuptake inhibitors (SSRIs).

Newer antidepressants (eg, fluoxetine, paroxetine, citalopram, venlafaxine) are mostly SSRIs and are generally safer than the tricyclic antidepressants and monoamine oxidase inhibitors, although they can cause seizures. **Bupropion** (not an SSRI) has caused seizures even in therapeutic doses. Some antidepressants have been associated with QT prolongation and torsades de pointes arrhythmia. SSRIs may interact with each other or especially with monoamine oxidase inhibitors to cause the **serotonin syndrome,** characterized by agitation, muscle hyperactivity, and hyperthermia (see Chapter 16).

ANTIPSYCHOTICS

Antipsychotic drugs include the older phenothiazines and butyrophenones, as well as newer atypical drugs. All of these can cause CNS depression, seizures, and hypotension. Some can cause QT prolongation. The potent dopamine D_2 blockers are also associated with parkinsonian movement disorders (dystonic reactions) and in rare cases with the neuroleptic malignant syndrome, characterized by "lead-pipe" rigidity, hyperthermia, and autonomic instability (see Chapters 16 and 29).

ASPIRIN (SALICYLATE)

Salicylate poisoning (see Chapter 36) is a much less common cause of childhood poisoning deaths since the introduction of child-resistant containers and the reduced use of children's aspirin. It still accounts for numerous suicidal and accidental poisonings. Acute ingestion of more than 200 mg/kg is likely to produce intoxication. Poisoning can also result from chronic overmedication; this occurs most commonly in elderly patients using salicylates for chronic pain who become confused about their dosing. Poisoning causes uncoupling of oxidative phosphorylation and disruption of normal cellular metabolism.

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The first sign of salicylate toxicity is often hyperventilation and respiratory alkalosis due to medullary stimulation. Metabolic acidosis follows, and an increased anion gap results from accumulation of lactate as well as excretion of bicarbonate by the kidney to compensate for respiratory alkalosis. Arterial blood gas testing often reveals a mixed respiratory alkalosis and metabolic acidosis. Body temperature may be elevated owing to uncoupling of oxidative phosphorylation. Severe hyperthermia may occur in serious cases. Vomiting and hyperpnea as well as hyperthermia contribute to fluid loss and dehydration. With very severe poisoning, profound metabolic acidosis, seizures, coma, pulmonary edema, and cardiovascular collapse may occur. Absorption of salicylate and signs of toxicity may be delayed after very large overdoses or ingestion of enteric coated tablets.

General supportive care is essential. After massive aspirin ingestions (eg, more than 100 tablets), aggressive gut decontamination is advisable, including gastric lavage, repeated doses of activated charcoal, and consideration of whole bowel irrigation. Intravenous fluids are used to replace fluid losses caused by tachypnea, vomiting, and fever. For moderate intoxications, intravenous sodium bicarbonate is given to alkalinize the urine and promote salicylate excretion by trapping the salicylate in its ionized, polar form. For severe poisoning (eg, patients with severe acidosis, coma, and serum salicylate level > 100 mg/dL), emergency hemodialysis is performed to remove the salicylate more quickly and restore acid-base balance and fluid status.

BETA BLOCKERS

In overdose, β blockers inhibit both β_1 and β_2 adrenoceptors; selectivity, if any, is lost at high dosage. The most toxic β blocker is propranolol. As little as two to three times the therapeutic dose can cause serious toxicity. This may be because propranolol in high doses may cause sodium channel blocking effects similar to those seen with quinidine-like drugs, and it is lipophilic, allowing it to enter the CNS (see Chapter 10).

Bradycardia and hypotension are the most common manifestations of toxicity. Agents with partial agonist activity (eg, pindolol) can cause tachycardia and hypertension. Seizures and cardiac conduction block (wide QRS complex) may be seen with propranolol overdose.

General supportive care should be provided as outlined earlier. The usual measures used to raise the blood pressure and heart rate, such as intravenous fluids, β-agonist drugs, and atropine, are generally ineffective. Glucagon is a useful antidote that—like β agonists—acts on cardiac cells to raise intracellular cAMP but does so independent of β adrenoceptors. It can improve heart rate and blood pressure when given in high doses (5–20 mg intravenously).

CALCIUM CHANNEL BLOCKERS

Calcium antagonists can cause serious toxicity or death with relatively small overdoses. These channel blockers depress sinus node automaticity and slow AV node conduction (see Chapter 12). They also reduce cardiac output and blood pressure. Serious hypotension is mainly seen with nifedipine and related dihydropyridines, but in severe overdose all of the listed cardiovascular effects can occur with any of the calcium channel blockers.

Treatment requires general supportive care. Since most ingested calcium antagonists are in sustained-release form, it may be possible to expel them before they are completely absorbed; initiate whole bowel irrigation and oral activated charcoal as soon as possible, before calcium antagonist-induced ileus intervenes. Calcium, given intravenously in doses of 2–10 g, is a useful antidote for depressed cardiac contractility but less effective for nodal block or peripheral vascular collapse. Other treatments reported to be helpful in managing hypotension associated with calcium channel blocker poisoning include glucagon and high-dose insulin (0.5–1 unit/kg/h) plus glucose supplementation to maintain euglycemia. Recently case reports have suggested benefit from administration of lipid emulsion (Intralipid, normally used as an intravenous dietary fat supplement) for severe verapamil overdose.

CARBON MONOXIDE & OTHER TOXIC GASES

Carbon monoxide (CO) is a colorless, odorless gas that is ubiquitous because it is created whenever carbon-containing materials are burned. Carbon monoxide poisoning is the leading cause of death due to poisoning in the USA. Most cases occur in victims of fires, but accidental and suicidal exposures are also common. The diagnosis and treatment of carbon monoxide poisoning are described in Chapter 56. Many other toxic gases are produced in fires or released in industrial accidents (Table 58–5).

CHOLINESTERASE INHIBITORS

Organophosphate and carbamate cholinesterase inhibitors (see Chapter 7) are widely used to kill insects and other pests. Most cases of serious organophosphate or carbamate poisoning result from intentional ingestion by a suicidal person, but poisoning has also occurred at work (pesticide application or packaging) or, rarely, as a result of food contamination or terrorist attack (eg, release of the chemical warfare nerve agent sarin in the Tokyo subway system in 1995).

Stimulation of muscarinic receptors causes abdominal cramps, diarrhea, excessive salivation, sweating, urinary frequency, and increased bronchial secretions (see Chapters 6 and 7). Stimulation of nicotinic receptors causes generalized ganglionic activation, which can lead to hypertension and either tachycardia or bradycardia. Muscle twitching and fasciculations may progress to weakness and respiratory muscle paralysis. CNS effects include agitation, confusion, and seizures. The mnemonic DUMBELS (diarrhea, urination, miosis and muscle weakness, bronchospasm, excitation, lacrimation, and seizures, sweating, and salivation) helps recall the common findings. Blood testing may be used to document depressed activity of red blood cell (acetylcholinesterase) and plasma (butyrylcholinesterase) enzymes, which provide an indirect estimate of synaptic cholinesterase activity.

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TABLE 58–5 Characteristics of poisoning with some gases.

Gas	Mechanism of Toxicity	Clinical Features and Treatment
Irritant gases (eg, chlorine, ammonia, sulfur dioxide, nitrogen oxides)	Corrosive effect on upper and lower airways	Cough, stridor, wheezing, pneumonia *Treatment:* Humidified oxygen, bronchodilators
Carbon monoxide	Binds to hemoglobin, reducing oxygen delivery to tissues	Headache, dizziness, nausea, vomiting, seizures, coma *Treatment:* 100% oxygen; consider hyperbaric oxygen
Cyanide	Binds to cytochrome, blocks cellular oxygen use	Headache, nausea, vomiting, syncope, seizures, coma *Treatment:* Conventional antidote kit consists of nitrites to induce methemoglobinemia (which binds cyanide) and thiosulfate (which hastens conversion of cyanide to less toxic thiocyanate); a newer antidote kit (Cyanokit) consists of concentrated hydroxocobalamin, which directly converts cyanide into cyanocobalamin
Hydrogen sulfide	Similar to cyanide	Similar to cyanide. Smell of rotten eggs *Treatment:* No specific antidote; some authorities recommend the nitrite portion of the conventional cyanide antidote kit.
Oxidizing agents (eg, nitrogen oxides)	Can cause methemoglobinemia	Dyspnea, cyanosis (due to brown color of methemoglobin), syncope, seizures, coma *Treatment:* Methylene blue (which hastens conversion back to normal hemoglobin)

General supportive care should be provided as outlined above. Precautions should be taken to ensure that rescuers and health care providers are not poisoned themselves by exposure to contaminated clothing or skin. This is especially critical for the most potent substances such as parathion or nerve gas agents. Antidotal treatment consists of atropine and pralidoxime (see Table 58–4). Atropine is an effective competitive inhibitor at muscarinic sites but has no effect at nicotinic sites. Pralidoxime given early enough may be capable of restoring the cholinesterase activity and is active at both muscarinic and nicotinic sites.

CYANIDE

Cyanide (CN^-) salts and hydrogen cyanide (HCN) are highly toxic chemicals used in chemical synthesis, as rodenticides (eg, "gopher getter"), formerly as a method of execution, and as agents of suicide or homicide. Hydrogen cyanide is formed from the burning of plastics, wool, and many other synthetic and natural products. Cyanide is also released after ingestion of various plants (eg, cassava) and seeds (eg, apple, peach, and apricot).

Cyanide binds readily to cytochrome oxidase, inhibiting oxygen utilization within the cell and leading to cellular hypoxia and lactic acidosis. Symptoms of cyanide poisoning include shortness of breath, agitation, and tachycardia followed by seizures, coma, hypotension, and death. Severe metabolic acidosis is characteristic. The venous oxygen content may be elevated because oxygen is not being taken up by cells.

Treatment of cyanide poisoning includes rapid administration of activated charcoal (although charcoal binds cyanide poorly, it can reduce absorption) and general supportive care. The conventional antidote kit available in the USA includes two forms of nitrite (amyl nitrite and sodium nitrite) and sodium thiosulfate. The nitrites induce methemoglobinemia, which binds to free CN^- creating the less toxic cyanomethemoglobin; thiosulfate is a cofactor in the enzymatic conversion of CN^- to the much less toxic thiocyanate (SCN^-).

In 2006 the FDA approved a new cyanide antidote, a concentrated form of hydroxocobalamin, which is now available as the Cyanokit (EMD Pharmaceuticals, Durham, North Carolina). Hydroxocobalamin (one form of vitamin B_{12}) combines rapidly with CN^- to form cyanocobalamin (another form of vitamin B_{12}).

DIGOXIN

Digitalis and other cardiac glycosides and cardenolides are found in many plants (see Chapter 13) and in the skin of some toads. Toxicity may occur as a result of acute overdose or from accumulation of digoxin in a patient with renal insufficiency or from taking a drug that interferes with digoxin elimination. Patients receiving long-term digoxin treatment are often also taking diuretics, which can lead to electrolyte depletion (especially potassium).

Vomiting is common in patients with digitalis overdose. Hyperkalemia may be caused by acute digitalis overdose or severe poisoning, whereas hypokalemia may be present in patients as a result of long-term diuretic treatment. (Digitalis does not cause hypokalemia.) A variety of cardiac rhythm disturbances may occur, including sinus bradycardia, AV block, atrial tachycardia with block, accelerated junctional rhythm, premature ventricular beats, bidirectional ventricular tachycardia, and other ventricular arrhythmias.

General supportive care should be provided. Atropine is often effective for bradycardia or AV block. The use of digoxin antibodies (see Chapter 13) has revolutionized the treatment of digoxin toxicity; they should be administered intravenously in the dosage indicated in the package insert. Symptoms usually improve within

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30–60 minutes after antibody administration. Digoxin antibodies may also be tried in cases of poisoning by other cardiac glycosides (eg, digitoxin, oleander), although larger doses may be needed due to incomplete cross-reactivity.

ETHANOL & SEDATIVE-HYPNOTIC DRUGS

Overdosage with ethanol and sedative-hypnotic drugs (eg, benzodiazepines, barbiturates, γ-hydroxybutyrate [GHB], carisoprodol [Soma]; see Chapters 22 and 23) occurs frequently because of their common availability and use.

Patients with ethanol or other sedative-hypnotic overdose may be euphoric and rowdy ("drunk") or in a state of stupor or coma ("dead drunk"). Comatose patients often have depressed respiratory drive. Depression of protective airway reflexes may result in pulmonary aspiration of gastric contents leading to pneumonia. Hypothermia may be present because of environmental exposure and depressed shivering. Ethanol blood levels greater than 300 mg/dL usually cause deep coma, but regular users are often tolerant to the effects of ethanol and may be ambulatory despite even higher levels. Patients with GHB overdose are often deeply comatose for 3–4 hours and then awaken fully in a matter of minutes.

General supportive care should be provided. With careful attention to protecting the airway (including endotracheal intubation) and assisting ventilation, most patients recover as the drug effects wear off. Hypotension usually responds to intravenous fluids, body warming if cold, and, if needed, dopamine. Patients with isolated benzodiazepine overdose may awaken after intravenous flumazenil, a benzodiazepine antagonist. However, this drug is not widely used as empiric therapy for drug overdose because it may precipitate seizures in patients who are addicted to benzodiazepines or who have ingested a convulsant drug (eg, a tricyclic antidepressant). There are no antidotes for ethanol, barbiturates, or most other sedative-hypnotics.

ETHYLENE GLYCOL & METHANOL

Ethylene glycol and methanol are alcohols that are important toxins because of their metabolism to highly toxic organic acids (see Chapter 23). They are capable of causing CNS depression and a drunken state similar to ethanol overdose. In addition, their products of metabolism—formic acid (from methanol) or hippuric, oxalic, and glycolic acids (from ethylene glycol)—cause a severe metabolic acidosis and can lead to coma and blindness (in the case of formic acid) or renal failure (from oxalic acid and glycolic acid). Initially, the patient appears drunk, but after a delay of up to several hours, a severe anion gap metabolic acidosis becomes apparent, accompanied by hyperventilation and altered mental status. Patients with methanol poisoning may have visual disturbances ranging from blurred vision to blindness.

Metabolism of ethylene glycol and methanol to their toxic products can be blocked by inhibiting the enzyme alcohol dehydrogenase with a competing drug, such as fomepizole (4-methylpyrazole). Ethanol is also an effective antidote, but it can be difficult to achieve a safe and effective blood level.

IRON & OTHER METALS

Iron is widely used in over-the-counter vitamin preparations and is a leading cause of childhood poisoning deaths. As few as 10–12 prenatal multivitamins with iron may cause serious illness in a small child. Poisoning with other metals (lead, mercury, arsenic) is also important, especially in industry. See Chapters 33, 56, and 57 for detailed discussions of poisoning by iron and other metals.

OPIOIDS

Opioids (opium, morphine, heroin, meperidine, methadone, etc) are common drugs of abuse (see Chapters 31 and 32), and overdose is a common result of using the poorly standardized preparations sold on the street. See Chapter 31 for a detailed discussion of opioid overdose and its treatment.

RATTLESNAKE ENVENOMATION

In the USA, rattlesnakes are the most common venomous reptiles. Bites are rarely fatal, and 20% do not involve envenomation. However, about 60% of bites cause significant morbidity due to the destructive digestive enzymes found in the venom. Evidence of rattlesnake envenomation includes severe pain, swelling, bruising, hemorrhagic bleb formation, and obvious fang marks. Systemic effects include nausea, vomiting, muscle fasciculations, tingling and metallic taste in the mouth, shock, and systemic coagulopathy with prolonged clotting time and reduced platelet count.

Studies have shown that emergency field remedies such as incision and suction, tourniquets, and ice packs are far more damaging than useful. Avoidance of unnecessary motion, on the other hand, does help to limit the spread of the venom. Definitive therapy relies on intravenous antivenom (also known as antivenin) and this should be started as soon as possible.

THEOPHYLLINE

Although it has been largely replaced by inhaled β agonists, theophylline continues to be used for the treatment of bronchospasm by some patients with asthma and bronchitis (see Chapter 20). A dose of 20–30 tablets can cause serious or fatal poisoning. Chronic or subacute theophylline poisoning can also occur as a result of accidental overmedication or use of a drug that interferes with theophylline metabolism (eg, cimetidine, ciprofloxacin, erythromycin; see Chapter 4).

In addition to sinus tachycardia and tremor, vomiting is common after overdose. Hypotension, tachycardia, hypokalemia, and hyperglycemia may occur, probably owing to β_2-adrenergic activation. The cause of this activation is not fully understood, but the

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effects can be ameliorated by β blockers (see below). Cardiac arrhythmias include atrial tachycardias, premature ventricular contractions, and ventricular tachycardia. In severe poisoning (eg, acute overdose with serum level > 100 mg/L), seizures often occur and are usually resistant to common anticonvulsants. Toxicity may be delayed in onset for many hours after ingestion of sustained-release tablet formulations.

General supportive care should be provided. Aggressive gut decontamination should be carried out using repeated doses of activated charcoal and whole bowel irrigation. Propranolol or other β blockers (eg, esmolol) are useful antidotes for β-mediated hypotension and tachycardia. Phenobarbital is preferred over phenytoin for convulsions; most anticonvulsants are ineffective. Hemodialysis is indicated for serum concentrations greater than 100 mg/L and for intractable seizures in patients with lower levels.

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CASE STUDY ANSWER

Overdose of bupropion can cause seizures that are often recurrent or prolonged. Drug-induced seizures are treated with an intravenous benzodiazepine such as lorazepam or diazepam. If this is not effective, phenobarbital or another more efficacious central nervous system depressant may be used. To prevent ingested drugs and poisons from being absorbed systemically, a slurry of activated charcoal is often given orally or by nasogastric tube.

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SECTION X SPECIAL TOPICS

CHAPTER 59

Special Aspects of Perinatal & Pediatric Pharmacology

Gideon Koren, MD*

The effects of drugs on the fetus and newborn infant are based on the general principles set forth in Chapters 1–4 of this book. However, the physiologic contexts in which these pharmacologic laws operate are different in pregnant women and in rapidly maturing infants. At present, the special pharmacokinetic factors operative in these patients are beginning to be understood, whereas information regarding pharmacodynamic differences (eg, receptor characteristics and responses) is still incomplete.

DRUG THERAPY IN PREGNANCY

Pharmacokinetics

Most drugs taken by pregnant women can cross the placenta and expose the developing embryo and fetus to their pharmacologic and teratogenic effects. Critical factors affecting placental drug transfer and drug effects on the fetus include the following: (1) the physicochemical properties of the drug; (2) the rate at which the drug crosses the placenta and the amount of drug reaching the fetus; (3) the duration of exposure to the drug; (4) distribution characteristics in different fetal tissues; (5) the stage of placental and fetal development at the time of exposure to the drug; and (6) the effects of drugs used in combination.

A. Lipid Solubility

As is true also of other biologic membranes, drug passage across the placenta is dependent on lipid solubility and the degree of drug ionization. Lipophilic drugs tend to diffuse readily across the placenta and enter the fetal circulation. For example, thiopental, a drug commonly used for cesarean sections, crosses the placenta almost immediately and can produce sedation or apnea in the newborn infant. Highly ionized drugs such as succinylcholine and tubocurarine, also used for cesarean sections, cross the placenta slowly and achieve very low concentrations in the fetus. Impermeability of the placenta to polar compounds is relative rather than absolute. If high enough maternal-fetal concentration gradients are achieved, polar compounds cross the placenta in measurable amounts. Salicylate, which is almost completely ionized at physiologic pH, crosses the placenta rapidly. This occurs because the small amount of salicylate that is not ionized is highly lipid-soluble.

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B. Molecular Size and pH

The molecular weight of the drug also influences the rate of transfer and the amount of drug transferred across the placenta. Drugs with molecular weights of 250–500 can cross the placenta easily, depending upon their lipid solubility and degree of ionization; those with molecular weights of 500–1000 cross the placenta with more difficulty; and those with molecular weights greater than 1000 cross very poorly. An important clinical application of this property is the choice of heparin as an anticoagulant in pregnant women. Because it is a very large (and polar) molecule, heparin is unable to cross the placenta. Unlike warfarin, which is teratogenic and should be avoided during the first trimester and even beyond (as the brain continues to develop), heparin may be safely given to pregnant women who need anticoagulation. Yet the placenta contains drug transporters, which can carry larger molecules to the fetus. For example, a variety of maternal antibodies cross the placenta and may cause fetal morbidity, as in Rh incompatibility.

Because maternal blood has a pH of 7.4 and that of the fetal blood is 7.3, weakly basic drugs with pK_a above 7.4 will be more ionized in the fetal compartment, leading to ion trapping and, hence, to higher fetal levels (see Chapter 1).

C. Placental Transporters

During the last decade, many drug transporters have been identified in the placenta, with increasing recognition of their effects on drug transfer to the fetus. For example, the P-glycoprotein transporter encoded by the *MDR1* gene pumps back into the maternal circulation a variety of drugs, including cancer drugs (eg, vinblastine, doxorubicin) and other agents. Similarly, viral protease inhibitors, which are substrates of P-glycoprotein, achieve only low fetal concentrations—an effect that may increase the risk of vertical HIV infection from the mother to the fetus. The hypoglycemic drug glyburide shows much lower concentrations in the fetus as compared to the mother. Recent work has documented that this agent is effluxed from the fetal circulation by the BCRP transporter as well as by the MRP3 transporter located in the placental brush border membrane.

D. Protein Binding

The degree to which a drug is bound to plasma proteins (particularly albumin) may also affect the rate of transfer and the amount transferred. However, if a compound is very lipid-soluble (eg, some anesthetic gases), it will not be affected greatly by protein binding. Transfer of these more lipid-soluble drugs and their overall rates of equilibration are more dependent on (and proportionate to) placental blood flow. This is because very lipid-soluble drugs diffuse across placental membranes so rapidly that their overall rates of equilibration do not depend on the free drug concentrations becoming equal on both sides. If a drug is poorly lipid-soluble and is ionized, its transfer is slow and will probably be impeded by its binding to maternal plasma proteins. Differential protein binding is also important since some drugs exhibit greater protein binding in maternal plasma than in fetal plasma because of a lower binding affinity of fetal proteins. This has been shown for sulfonamides, barbiturates, phenytoin, and local anesthetic agents. In addition, very high maternal protein binding of glyburide (> 98.8%) also contributes to lower fetal levels as compared to maternal concentrations, as mentioned above.

E. Placental and Fetal Drug Metabolism

Two mechanisms help protect the fetus from drugs in the maternal circulation: (1) The placenta itself plays a role both as a semipermeable barrier and as a site of metabolism of some drugs passing through it. Several different types of aromatic oxidation reactions (eg, hydroxylation, *N*-dealkylation, demethylation) have been shown to occur in placental tissue. Pentobarbital is oxidized in this way. Conversely, it is possible that the metabolic capacity of the placenta may lead to creation of toxic metabolites, and the placenta may therefore augment toxicity (eg, ethanol, benzpyrenes). (2) Drugs that have crossed the placenta enter the fetal circulation via the umbilical vein. Approximately 40–60% of umbilical venous blood flow enters the fetal liver; the remainder bypasses the liver and enters the general fetal circulation. A drug that enters the liver may be partially metabolized there before it enters the fetal circulation. In addition, a large proportion of drug present in the umbilical artery (returning to the placenta) may be shunted through the placenta back to the umbilical vein and into the liver again. It should be noted that metabolites of some drugs may be more active than the parent compound and may affect the fetus adversely.

Pharmacodynamics

A. Maternal Drug Actions

The effects of drugs on the reproductive tissues (breast, uterus, etc) of the pregnant woman are sometimes altered by the endocrine environment appropriate for the stage of pregnancy. Drug effects on other maternal tissues (heart, lungs, kidneys, central nervous system, etc) are not changed significantly by pregnancy, although the physiologic context (cardiac output, renal blood flow, etc) may be altered, requiring the use of drugs that are not needed by the same woman when she is not pregnant. For example, cardiac glycosides and diuretics may be needed for heart failure precipitated by the increased cardiac workload of pregnancy, or insulin may be required for control of blood glucose in pregnancy-induced diabetes.

B. Therapeutic Drug Actions in the Fetus

Fetal therapeutics is an emerging area in perinatal pharmacology. This involves drug administration to the pregnant woman with the fetus as the target of the drug. At present, corticosteroids are used to stimulate fetal lung maturation when preterm birth is expected. Phenobarbital, when given to pregnant women near term, can induce fetal hepatic enzymes responsible for the glucuronidation of bilirubin, and the incidence of jaundice is lower in newborns when mothers are given phenobarbital than when phenobarbital is not used. Before phototherapy became the preferred mode of therapy for neonatal indirect hyperbilirubinemia, phenobarbital was used for this indication. Administration of phenobarbital to the mother was suggested recently as a means of decreasing the risk of intracranial bleeding in preterm infants. However, large randomized studies failed to confirm this effect. Antiarrhythmic drugs have also been given to mothers for treatment of fetal cardiac arrhythmias. Although their efficacy has not yet

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been established by controlled studies, digoxin, flecainide, procainamide, verapamil, and other antiarrhythmic agents have been shown to be effective in case series. During the last two decades it has been shown that maternal use of zidovudine decreases by two thirds transmission of HIV from the mother to the fetus, and use of combinations of three antiretroviral agents can eliminate fetal infection almost entirely (see Chapter 49).

C. Predictable Toxic Drug Actions in the Fetus

Chronic use of opioids by the mother may produce dependence in the fetus and newborn. This dependence may be manifested after delivery as a neonatal withdrawal syndrome. A less well understood fetal drug toxicity is caused by the use of angiotensin-converting enzyme inhibitors during pregnancy. These drugs can result in significant and irreversible renal damage in the fetus and are therefore contraindicated in pregnant women. Adverse effects may also be delayed, as in the case of female fetuses exposed to diethylstilbestrol, who may be at increased risk for adenocarcinoma of the vagina after puberty.

D. Teratogenic Drug Actions

A single intrauterine exposure to a drug can affect the fetal structures undergoing rapid development at the time of exposure. Thalidomide is an example of a drug that may profoundly affect the development of the limbs after only brief exposure. This exposure, however, must be at a critical time in the development of the limbs. The thalidomide phocomelia risk occurs during the fourth through the seventh weeks of gestation because it is during this time that the arms and legs develop (Figure 59–1).

1. Teratogenic mechanisms—The mechanisms by which different drugs produce teratogenic effects are poorly understood and are probably multifactorial. For example, drugs may have a direct effect on maternal tissues with secondary or indirect effects on fetal tissues. Drugs may interfere with the passage of oxygen or nutrients through the placenta and therefore have effects on the most rapidly metabolizing tissues of the fetus. Finally, drugs may have important direct actions on the processes of differentiation in developing tissues. For example, vitamin A (retinol) has been shown to have important differentiation-directing actions in normal tissues. Several vitamin A analogs (isotretinoin, etretinate) are powerful teratogens, suggesting that they alter the normal processes of differentiation. Finally, deficiency of a critical substance appears to play a role in some types of abnormalities. For example, folic acid supplementation during pregnancy appears to reduce the incidence of neural tube defects (eg, spina bifida).

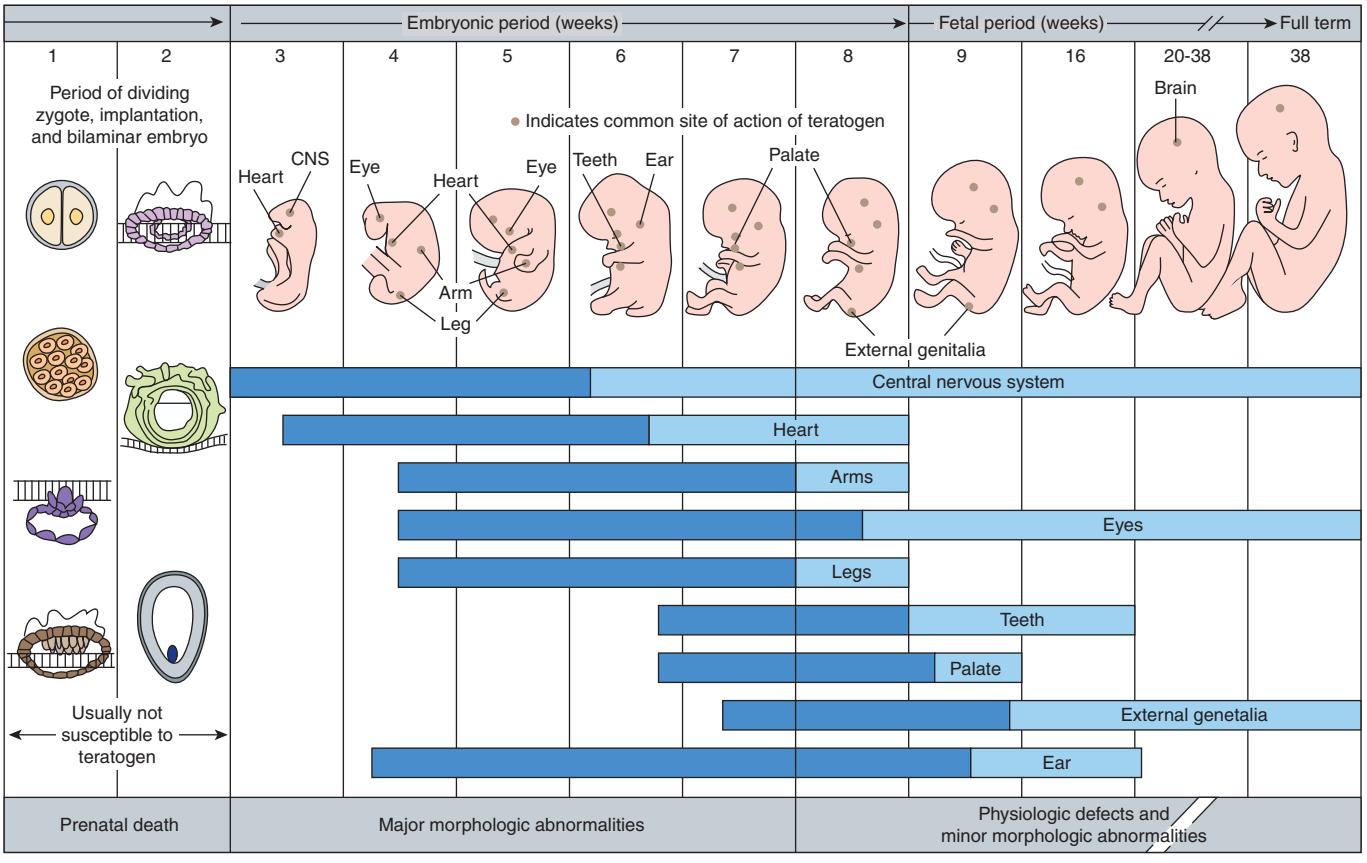

FIGURE 59–1 Schematic diagram of critical periods of human development. (Reproduced, with permission, from Moore KL: *The Developing Human: Clinically Oriented Embryology,* 4th ed. Saunders, 1988.)

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Continued exposure to a teratogen may produce cumulative effects or may affect several organs going through varying stages of development. Chronic consumption of high doses of ethanol during pregnancy, particularly during the first and second trimesters, may result in the fetal alcohol syndrome (see Chapter 23). In this syndrome, the central nervous system, growth, and facial development may be affected.

2. Defining a teratogen—To be considered teratogenic, a candidate substance or process should (1) result in a characteristic set of malformations, indicating selectivity for certain target organs; (2) exert its effects at a particular stage of fetal development, eg, during the limited time period of organogenesis of the target organs (Figure 59–1); and (3) show a dose-dependent incidence. Some drugs with known teratogenic or other adverse effects in pregnancy are listed in Table 59–1. Teratogenic effects are not limited only to major malformations, but also include intrauterine growth restriction (eg, cigarette smoking), miscarriage (eg, alcohol), stillbirth (eg, cigarette smoke), and neurocognitive delay (eg, alcohol).

The widely cited Food and Drug Administration (FDA) system for teratogenic potential (Table 59–2) is an attempt to quantify teratogenic risk from A (safe) to X (definite human teratogenic risk). This system has been criticized as inaccurate and impractical. For example, several drugs have been labeled "X" despite extensive opposite human safety data (eg, oral contraceptives). Diazepam and other benzodiazepines are labeled as "D" despite lack of positive evidence of human fetal risk. Presently the FDA is changing its system from the A, B, C grading system to narrative statements that will summarize evidence-based knowledge about each drug in terms of fetal risk and safety.

3. Counseling women about teratogenic risk—Since the thalidomide disaster, medicine has been practiced as if every drug were a potential human teratogen when, in fact, fewer than 30 such drugs have been identified, with hundreds of agents proved safe for the unborn. Owing to high levels of anxiety among pregnant women—and because half of the pregnancies in North America are unplanned—every year many thousands of women need counseling about fetal exposure to drugs, chemicals, and

TABLE 59–1 Drugs with significant teratogenic or other adverse effects on the fetus.

Drug	Trimester	Effect
ACE inhibitors	All, especially second and third	Renal damage
Aminopterin	First	Multiple gross anomalies
Amphetamines	All	Suspected abnormal developmental patterns, decreased school performance
Androgens	Second, third	Masculinization of female fetus
Antidepressants, tricyclic	Third	Neonatal withdrawal symptoms have been reported in a few cases with clomipramine, desipramine, and imipramine
Barbiturates	All	Chronic use can lead to neonatal dependence
Busulfan	All	Various congenital malformations; low birth weight
Carbamazepine	First	Neural tube defects
Chlorpropamide	All	Prolonged symptomatic neonatal hypoglycemia
Clomipramine	Third	Neonatal lethargy, hypotonia, cyanosis, hypothermia
Cocaine	All	Increased risk of spontaneous abortion, abruptio placentae, and premature labor; neonatal cerebral infarction, abnormal development, and decreased school performance
Cyclophosphamide	First	Various congenital malformations
Cytarabine	First, second	Various congenital malformations
Diazepam	All	Chronic use may lead to neonatal dependence
Diethylstilbestrol	All	Vaginal adenosis, clear cell vaginal adenocarcinoma
Ethanol	All	Risk of fetal alcohol syndrome and alcohol-related neurodevelopmental defects
Etretinate	All	High risk of multiple congenital malformations
Heroin	All	Chronic use leads to neonatal dependence
Iodide	All	Congenital goiter, hypothyroidism
Isotretinoin	All	Extremely high risk of CNS, face, ear, and other malformations
Lithium	First, third	Ebstein's anomaly, neonatal toxicity after third trimester
Methadone	All	Chronic use may lead to neonatal abstinence

(*continued*)

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TABLE 59–1 Drugs with significant teratogenic or other adverse effects on the fetus. (Continued)

Drug	Trimester	Effect
Methotrexate	First	Multiple congenital malformations
Methylthiouracil	All	Hypothyroidism
Metronidazole	First	May be mutagenic (from animal studies; there is no evidence for mutagenic or teratogenic effects in humans)
Misoprostol	First	Möbius sequence
Mycophenolate mofetil	First	Major malformations of the face, limbs, and other organs
Organic solvents	First	Multiple malformations
Penicillamine	First	Cutis laxa, other congenital malformations
Phencyclidine	All	Abnormal neurologic examination, poor suck reflex and feeding
Phenytoin	All	Fetal hydantoin syndrome
Propylthiouracil	All	Congenital goiter
Smoking (constituents of tobacco smoke)	All	Intrauterine growth retardation; prematurity; sudden infant death syndrome; perinatal complications
Selective serotonin reuptake inhibitors (SSRIs)	Third	Neonatal abstinence syndrome, persistent pulmonary hypertension of the newborn
Tamoxifen	All	Increased risk of spontaneous abortion or fetal damage
Tetracycline	All	Discoloration and defects of teeth and altered bone growth
Thalidomide	First	Phocomelia (shortened or absent long bones of the limbs) and many internal malformations
Trimethadione	All	Multiple congenital anomalies
Valproic acid	All	Neural tube defects, cardiac and limb malformations
Warfarin	First	Hypoplastic nasal bridge, chondrodysplasia
	Second	CNS malformations
	Third	Risk of bleeding. Discontinue use 1 month before delivery.

radiation. In the Motherisk program in Toronto, thousands of women are counseled every month, and the ability of appropriate counseling to prevent unnecessary abortions has been documented. Clinicians who wish to provide such counsel to pregnant women must ensure that their information is up-to-date and evidence-based and that the woman understands that the baseline teratogenic risk in pregnancy (ie, the risk of a neonatal abnormality in the absence of any known teratogenic exposure) is about 3%. It is also critical to address the maternal-fetal risks of the untreated condition if a medication is avoided. Recent studies show serious morbidity in women who discontinued selective serotonin reuptake inhibitor therapy for depression in pregnancy.

TABLE 59–2 FDA teratogenic risk categories.

Category	Description
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in late trimesters), and the possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

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DRUG THERAPY IN INFANTS & CHILDREN

Physiologic processes that influence pharmacokinetic variables in the infant change significantly in the first year of life, particularly during the first few months. Therefore, special attention must be paid to pharmacokinetics in this age group. Pharmacodynamic differences between pediatric and other patients have not been explored in great detail and are probably small except for those specific target tissues that mature at birth or immediately thereafter (eg, the ductus arteriosus).

Drug Absorption

Drug absorption in infants and children follows the same general principles as in adults. Unique factors that influence drug absorption include blood flow at the site of administration, as determined by the physiologic status of the infant or child; and, for orally administered drugs, gastrointestinal function, which changes rapidly during the first few days after birth. Age after birth also influences the regulation of drug absorption.

A. Blood Flow at the Site of Administration

Absorption after intramuscular or subcutaneous injection depends mainly, in neonates as in adults, on the rate of blood flow to the muscle or subcutaneous area injected. Physiologic conditions that might reduce blood flow to these areas are cardiovascular shock, vasoconstriction due to sympathomimetic agents, and heart failure. However, sick preterm infants requiring intramuscular injections may have very little muscle mass. This is further complicated by diminished peripheral perfusion to these areas. In such cases, absorption becomes irregular and difficult to predict, because the drug may remain in the muscle and be absorbed more slowly than expected. If perfusion suddenly improves, there can be a sudden and unpredictable increase in the amount of drug entering the circulation, resulting in high and potentially toxic concentrations of drug. Examples of drugs especially hazardous in such situations are cardiac glycosides, aminoglycoside antibiotics, and anticonvulsants.

B. Gastrointestinal Function

Significant biochemical and physiologic changes occur in the neonatal gastrointestinal tract shortly after birth. In full-term infants, gastric acid secretion begins soon after birth and increases gradually over several hours. In preterm infants, the secretion of gastric acid occurs more slowly, with the highest concentrations appearing on the fourth day of life. Therefore, drugs that are usually partially or totally inactivated by the low pH of gastric contents should not be administered orally.

Gastric emptying time is prolonged (up to 6 or 8 hours) in the first day or so after delivery. Therefore, drugs that are absorbed primarily in the stomach may be absorbed more completely than anticipated. In the case of drugs absorbed in the small intestine, therapeutic effect may be delayed. Peristalsis in the neonate is irregular and may be slow. The amount of drug absorbed in the small intestine may therefore be unpredictable; more than the usual amount of drug may be absorbed if peristalsis is slowed, and this could result in potential toxicity from an otherwise standard dose.

Table 59–3 summarizes data on oral bioavailability of various drugs in neonates compared with older children and adults. An increase in peristalsis, as in diarrheal conditions, tends to decrease the extent of absorption, because contact time with the large absorptive surface of the intestine is decreased.

Gastrointestinal enzyme activities tend to be lower in the newborn than in the adult. Activities of α-amylase and other pancreatic enzymes in the duodenum are low in infants up to 4 months of age. Neonates also have low concentrations of bile acids and lipase, which may decrease the absorption of lipid-soluble drugs.

Drug Distribution

As body composition changes with development, the distribution volumes of drugs are also changed. The neonate has a higher percentage of its body weight in the form of water (70–75%) than does the adult (50–60%). Differences can also be observed between the full-term neonate (70% of body weight as water) and the small preterm neonate (85% of body weight as water). Similarly, extracellular water is 40% of body weight in the neonate, compared with 20% in the adult. Most neonates will experience diuresis in the first 24–48 hours of life. Since many drugs are distributed throughout the extracellular water space, the size (volume) of the extracellular water compartment may be important in determining the concentration of drug at receptor sites. This is especially important for water-soluble drugs (such as aminoglycosides) and less crucial for lipid-soluble agents.

Preterm infants have much less fat than full-term infants. Total body fat in preterm infants is about 1% of total body weight, compared with 15% in full-term neonates. Therefore, organs that generally accumulate high concentrations of lipid-soluble drugs in adults and older children may accumulate smaller amounts of these agents in less mature infants.

Another major factor determining drug distribution is drug binding to plasma proteins. Albumin is the plasma protein with the greatest binding capacity. In general, protein binding of drugs is reduced in the neonate. This has been seen with local anesthetic drugs, diazepam, phenytoin, ampicillin, and phenobarbital. Therefore, the concentration of free (unbound) drug in plasma is

TABLE 59–3 Oral drug absorption (bioavailability) of various drugs in the neonate compared with older children and adults.

Drug	Oral Absorption
Acetaminophen	Decreased
Ampicillin	Increased
Diazepam	Normal
Digoxin	Normal
Penicillin G	Increased
Phenobarbital	Decreased
Phenytoin	Decreased
Sulfonamides	Normal

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increased initially. Because the free drug exerts the pharmacologic effect, this can result in greater drug effect or toxicity despite a normal or even low plasma concentration of total drug (bound plus unbound). Consider a therapeutic dose of a drug (eg, diazepam) given to a patient. The concentration of total drug in the plasma is 300 mcg/L. If the drug is 98% protein-bound in an older child or adult, then 6 mcg/L is the concentration of free drug. Assume that this concentration of free drug produces the desired effect in the patient without producing toxicity. However, if this drug is given to a preterm infant in a dosage adjusted for body weight and it produces a total drug concentration of 300 mcg/L—and protein binding is only 90%—then the free drug concentration will be 30 mcg/L, or five times higher. Although the higher free concentration may result in faster elimination (see Chapter 3), this concentration may be quite toxic initially.

Some drugs compete with serum bilirubin for binding to albumin. Drugs given to a neonate with jaundice can displace bilirubin from albumin. Because of the greater permeability of the neonatal blood-brain barrier, substantial amounts of bilirubin may enter the brain and cause kernicterus. This was in fact observed when sulfonamide antibiotics were given to preterm neonates as prophylaxis against sepsis. Conversely, as the serum bilirubin rises for physiologic reasons or because of a blood group incompatibility, bilirubin can displace a drug from albumin and substantially raise the free drug concentration. This may occur without altering the total drug concentration and would result in greater therapeutic effect or toxicity at normal concentrations. This has been shown to happen with phenytoin.

Drug Metabolism

The metabolism of most drugs occurs in the liver (see Chapter 4). The drug-metabolizing activities of the cytochrome P450-dependent mixed-function oxidases and the conjugating enzymes are substantially lower (50–70% of adult values) in early neonatal life than later. The point in development at which enzymatic activity is maximal depends upon the specific enzyme system in question. Glucuronide formation reaches adult values (per kilogram body weight) between the third and fourth years of life. Because of the neonate's decreased ability to metabolize drugs, many drugs have slow clearance rates and prolonged elimination half-lives. If drug doses and dosing schedules are not altered appropriately, this immaturity predisposes the neonate to adverse effects from drugs that are metabolized by the liver. Table 59–4 demonstrates how neonatal and adult drug elimination half-lives can differ and how the half-lives of phenobarbital and phenytoin decrease as the neonate grows older. The process of maturation must be considered when administering drugs to this age group, especially in the case of drugs administered over long periods.

Another consideration for the neonate is whether or not the mother was receiving drugs (eg, phenobarbital) that can induce early maturation of fetal hepatic enzymes. In this case, the ability of the neonate to metabolize certain drugs will be greater than expected, and one may see less therapeutic effect and lower plasma drug concentrations when the usual neonatal dose is given. During toddlerhood (12–36 months), the metabolic rate of many drugs exceeds adult values, often necessitating larger doses per kilogram than later in life.

TABLE 59–4 Comparison of elimination half-lives of various drugs in neonates and adults.

Drug	Neonatal Age	Neonates $t_{1/2}$ (hours)	Adults $t_{1/2}$ (hours)
Acetaminophen		2.2–5	0.9–2.2
Diazepam		25–100	40–50
Digoxin		60–70	30–60
Phenobarbital	0–5 days	200	64–140
	5–15 days	100	
	1–30 months	50	
Phenytoin	0–2 days	80	12–18
	3–14 days	18	
	14–50 days	6	
Salicylate		4.5–11	10–15
Theophylline	Neonate	13–26	5–10
	Child	3–4	

Drug Excretion

The glomerular filtration rate is much lower in newborns than in older infants, children, or adults, and this limitation persists during the first few days of life. Calculated on the basis of body surface area, glomerular filtration in the neonate is only 30–40% of the adult value. The glomerular filtration rate is even lower in neonates born before 34 weeks of gestation. Function improves substantially during the first week of life. At the end of the first week, the glomerular filtration rate and renal plasma flow have increased 50% from the first day. By the end of the third week, glomerular filtration is 50–60% of the adult value; by 6–12 months, it reaches adult values (per unit surface area). Therefore, drugs that depend on renal function for elimination are cleared from the body very slowly in the first weeks of life. Subsequently, during toddlerhood, it exceeds adult values, often necessitating larger doses per kilogram than in adults, as described previously for drug-metabolic rate.

Penicillins, for example, are cleared by preterm infants at 17% of the adult rate based on comparable surface area and 34% of the adult rate when adjusted for body weight. The dosage of ampicillin for a neonate less than 7 days old is 50–100 mg/kg/d in two doses at 12-hour intervals. The dosage for a neonate over 7 days old is 100–200 mg/kg/d in three doses at 8-hour intervals. A decreased rate of renal elimination in the neonate has also been observed with aminoglycoside antibiotics (kanamycin, gentamicin, neomycin, and streptomycin). The dosage of gentamicin for a neonate less than 7 days old is 5 mg/kg/d in two doses at 12-hour intervals. The dosage for a neonate over 7 days old is 7.5 mg/kg/d in three doses at 8-hour intervals. Total body clearance of digoxin is directly dependent upon adequate renal function, and accumulation of digoxin can occur when glomerular filtration is decreased. Since renal function in a sick infant may not improve at the predicted rate during the first

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weeks and months of life, appropriate adjustments in dosage and dosing schedules may be very difficult. In this situation, adjustments are best made on the basis of plasma drug concentrations determined at intervals throughout the course of therapy.

Although great focus is naturally concentrated on the neonate, it is important to remember that toddlers may have *shorter* elimination half-lives of drugs than older children and adults, due probably to *increased* renal elimination and metabolism. For example, the dose per kilogram of digoxin is much higher in toddlers than in adults. The mechanisms for these developmental changes are still poorly understood.

Special Pharmacodynamic Features in the Neonate

The appropriate use of drugs has made possible the survival of neonates with severe abnormalities who would otherwise die within days or weeks after birth. For example, administration of indomethacin (see Chapter 35) causes the rapid closure of a patent ductus arteriosus, which would otherwise require surgical closure in an infant with a normal heart. Infusion of prostaglandin E_1, on the other hand, causes the ductus to remain open, which can be lifesaving in an infant with transposition of the great vessels or tetralogy of Fallot (see Chapter 18). An unexpected effect of such infusion has been described. The drug caused antral hyperplasia with gastric outlet obstruction as a clinical manifestation in 6 of 74 infants who received it. This phenomenon appears to be dose-dependent. Neonates are also more sensitive to the central depressant effects of opioids than are older children and adults, necessitating extra caution when they are exposed to some narcotics (eg, codeine) through breast milk.

PEDIATRIC DOSAGE FORMS & COMPLIANCE

The form in which a drug is manufactured and the way in which the parent dispenses the drug to the child determine the actual dose administered. Many drugs prepared for children are in the form of elixirs or suspensions. **Elixirs** are alcoholic solutions in which the drug molecules are dissolved and evenly distributed. No shaking is required, and unless some of the vehicle has evaporated, the first dose from the bottle and the last dose should contain equivalent amounts of drug. **Suspensions** contain undissolved particles of drug that must be distributed throughout the vehicle by shaking. If shaking is not thorough each time a dose is given, the first doses from the bottle may contain less drug than the last doses, with the result that less than the expected plasma concentration or effect of the drug may be achieved early in the course of therapy. Conversely, toxicity may occur late in the course of therapy, when it is not expected. This uneven distribution is a potential cause of inefficacy or toxicity in children taking phenytoin suspensions. It is thus essential that the prescriber know the form in which the drug will be dispensed and provide proper instructions to the pharmacist and patient or parent.

Compliance may be more difficult to achieve in pediatric practice than otherwise, since it involves not only the parent's conscientious effort to follow directions but also such practical matters as measuring errors, spilling, and spitting out. For example, the measured volume of "teaspoons" ranges from 2.5 to 7.8 mL. The parents should obtain a calibrated medicine spoon or syringe from the pharmacy. These devices improve the accuracy of dose measurements and simplify administration of drugs to children.

When evaluating compliance, it is often helpful to ask if an attempt has been made to give a further dose after the child has spilled half of what was offered. The parents may not always be able to say with confidence how much of a dose the child actually received. The parents must be told whether or not to wake the infant for its every-6-hour dose day or night. These matters should be discussed and made clear, and no assumptions should be made about what the parents may or may not do. Noncompliance frequently occurs when antibiotics are prescribed to treat otitis media or urinary tract infections and the child feels well after 4 or 5 days of therapy. The parents may not feel there is any reason to continue giving the medicine even though it was prescribed for 10 or 14 days. This common situation should be anticipated so the parents can be told why it is important to continue giving the medicine for the prescribed period even if the child seems to be "cured."

Practical and convenient dosage forms and dosing schedules should be chosen to the extent possible. The easier it is to administer and take the medicine and the easier the dosing schedule is to follow, the more likely it is that compliance will be achieved.

Consistent with their ability to comprehend and cooperate, children should also be given some responsibility for their own health care and for taking medications. This should be discussed in appropriate terms both with the child and with the parents. Possible adverse effects and drug interactions with over-the-counter medicines or foods should also be discussed. Whenever a drug does not achieve its therapeutic effect, the possibility of noncompliance should be considered. There is ample evidence that in such cases parents' or children's reports may be grossly inaccurate. Random pill counts and measurement of serum concentrations may help disclose noncompliance. The use of computerized pill containers, which record each lid opening, has been shown to be very effective in measuring compliance.

Because many pediatric doses are calculated—eg, using body weight—rather than simply read from a list, major dosing errors may result from incorrect calculations. Typically, tenfold errors due to incorrect placement of the decimal point have been described. In the case of digoxin, for example, an intended dose of 0.1 mL containing 5 mcg of drug, when replaced by 1.0 mL—which is still a small volume—can result in fatal overdosage. A good rule for avoiding such "decimal point" errors is to use a leading "0" plus decimal point when dealing with doses less than "1" and to avoid using a zero after a decimal point (see Chapter 65).

DRUG USE DURING LACTATION

Despite the fact that most drugs are excreted into breast milk in amounts too small to adversely affect neonatal health, thousands of women taking medications do not breast-feed because

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of misperception of risk. Unfortunately, physicians contribute heavily to this bias. It is important to remember that formula feeding is associated with higher morbidity and mortality in all socioeconomic groups.

Most drugs administered to lactating women are detectable in breast milk. Fortunately, the concentration of drugs achieved in breast milk is usually low (Table 59–5). Therefore, the total amount the infant would receive in a day is substantially less than what would be considered a "therapeutic dose." If the nursing mother must take medications and the drug is a relatively safe one, she should optimally take it 30–60 minutes after nursing and 3–4 hours before the next feeding. This allows time for many drugs to be cleared from the mother's blood, and the concentrations in breast milk will be relatively low. Drugs for which no data are available on safety during lactation should be avoided or breast-feeding discontinued while they are being given.

Most antibiotics taken by nursing mothers can be detected in breast milk. Tetracycline concentrations in breast milk are approximately 70% of maternal serum concentrations and present a risk of permanent tooth staining in the infant. Isoniazid rapidly reaches equilibrium between breast milk and maternal blood. The concentrations achieved in breast milk are high enough so that signs of pyridoxine deficiency may occur in the infant if the mother is not given pyridoxine supplements.

Most sedatives and hypnotics achieve concentrations in breast milk sufficient to produce a pharmacologic effect in some infants. Barbiturates taken in hypnotic doses by the mother can produce lethargy, sedation, and poor suck reflexes in the infant. Chloral hydrate can produce sedation if the infant is fed at peak milk concentrations. Diazepam can have a sedative effect on the nursing infant, but, most importantly, its long half-life can result in significant drug accumulation.

Opioids such as heroin, methadone, and morphine enter breast milk in quantities potentially sufficient to prolong the state of neonatal narcotic dependence if the drug was taken chronically by the mother during pregnancy. If conditions are well controlled and there is a good relationship between the mother and the physician, an infant could be breast-fed while the mother is taking methadone. She should not, however, stop taking the drug abruptly; the infant can be tapered off the methadone as the mother's dose is tapered. The infant should be watched for signs of narcotic withdrawal. Although codeine has been believed to be safe, a recent case of neonatal death from opioid toxicity revealed that the mother was an ultra rapid metabolizer of cytochrome 2D6 substrates, producing substantially higher amounts of morphine. Hence, polymorphism in maternal drug metabolism may affect neonatal exposure and safety. A subsequent case control study has shown that this situation is not rare. The FDA has published a warning to lactating mothers to exert extra caution while using painkillers containing codeine.

Minimal use of alcohol by the mother has not been reported to harm nursing infants. Excessive amounts of alcohol, however, can produce alcohol effects in the infant. Nicotine concentrations in the breast milk of smoking mothers are low and do not produce effects in the infant. Very small amounts of caffeine are excreted in the breast milk of coffee-drinking mothers.

Lithium enters breast milk in concentrations equal to those in maternal serum. Clearance of this drug is almost completely dependent upon renal elimination, and women who are receiving lithium may expose the infant to relatively large amounts of the drug.

Radioactive substances such as iodinated ^{125}I albumin and other forms of radioiodine can cause thyroid suppression in infants and may increase the risk of subsequent thyroid cancer as much as tenfold. Breast-feeding is contraindicated after large doses and should be withheld for days to weeks after small doses. Similarly, breast-feeding should be avoided in mothers receiving cancer chemotherapy or being treated with cytotoxic or immunomodulating agents for collagen diseases such as lupus erythematosus or after organ transplantation.

PEDIATRIC DRUG DOSAGE

Because of differences in pharmacokinetics in infants and children, simple proportionate reduction in the adult dose may not be adequate to determine a safe and effective pediatric dose. The most reliable pediatric dose information is usually that provided by the manufacturer in the package insert. However, such information is not available for the majority of products, even when studies have been published in the medical literature, reflecting the reluctance of manufacturers to label their products for children. Recently, the FDA has moved toward more explicit expectations that manufacturers test their new products in infants and children. Still, most drugs in the common formularies, eg, *Physicians' Desk Reference*, are not specifically approved for children, in part because manufacturers often lack the economic incentive to evaluate drugs for use in the pediatric market.

Most drugs approved for use in children have recommended pediatric doses, generally stated as milligrams per kilogram or per pound. In the absence of explicit pediatric dose recommendations, an approximation can be made by any of several methods based on age, weight, or surface area. These rules are not precise and should not be used if the manufacturer provides a pediatric dose. When pediatric doses are calculated (either from one of the methods set forth below or from a manufacturer's dose), the pediatric dose should never exceed the adult dose.

With the current epidemic of child obesity, a fresh and careful look at pediatric drug dosing will be needed. Studies in adults indicate that dosing based on per kilogram of body weight may constitute overdosing, because most drugs are distributed based on lean body weight, rather than total (obese) weight.

Surface Area, Age, & Weight

Calculations of dosage based on age or weight (see below) are conservative and tend to underestimate the required dose. Doses based on surface area (Table 59–6) are more likely to be adequate.

Age (Young's rule):

$$Dose = \text{Adult dose} \times \frac{\text{Age (years)}}{\text{Age} + 12}$$

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TABLE 59–5 Drugs often used during lactation and possible effects on the nursing infant.

Drug	Effect on Infant	Comments
Ampicillin	Minimal	No significant adverse effects; possible occurrence of diarrhea or allergic sensitization.
Aspirin	Minimal	Occasional doses probably safe; high doses may produce significant concentration in breast milk.
Caffeine	Minimal	Caffeine intake in moderation is safe; concentration in breast milk is low.
Chloral hydrate	Significant	May cause drowsiness if infant is fed at peak concentration in milk.
Chloramphenicol	Significant	Concentrations too low to cause gray baby syndrome; possibility of bone marrow suppression does exist; recommend not taking chloramphenicol while breast-feeding.
Chlorothiazide	Minimal	No adverse effects reported.
Chlorpromazine	Minimal	Appears insignificant.
Codeine	Variable, based on genetic polymorphism	Safe in most cases. Neonatal toxicity described when the mother is an ultra rapid 2D6 metabolizer, producing substantially more morphine from codeine.
Diazepam	Significant	Will cause sedation in breast-fed infants; accumulation can occur in newborns.
Dicumarol	Minimal	No adverse side effects reported; may wish to follow infant's prothrombin time.
Digoxin	Minimal	Insignificant quantities enter breast milk.
Ethanol	Moderate	Moderate ingestion by mother unlikely to produce effects in infant; large amounts consumed by mother can produce alcohol effects in infant.
Heroin	Significant	Enters breast milk and can prolong neonatal narcotic dependence.
Iodine (radioactive)	Significant	Enters milk in quantities sufficient to cause thyroid suppression in infant.
Isoniazid (INH)	Minimal	Milk concentrations equal maternal plasma concentrations. Possibility of pyridoxine deficiency developing in the infant.
Kanamycin	Minimal	No adverse effects reported.
Lithium	Variable	In some cases, large amounts in milk, but not in others.
Methadone	Significant	(See heroin.) Under close physician supervision, breast-feeding can be continued. Signs of opioid withdrawal in the infant may occur if mother stops taking methadone or stops breast-feeding abruptly.
Oral contraceptives	Minimal	May suppress lactation in high doses.
Penicillin	Minimal	Very low concentrations in breast milk.
Phenobarbital	Moderate	Hypnotic doses can cause sedation in the infant.
Phenytoin	Moderate	Amounts entering breast milk are not sufficient to cause adverse effects in infant.
Prednisone	Moderate	Low maternal doses (5 mg/d) probably safe. Doses 2 or more times physiologic amounts (> 15 mg/d) should probably be avoided.
Propranolol	Minimal	Very small amounts enter breast milk.
Propylthiouracil	Variable	Rarely may suppress thyroid function in infant.
Spironolactone	Minimal	Very small amounts enter breast milk.
Tetracycline	Moderate	Possibility of permanent staining of developing teeth in the infant. Should be avoided during lactation.
Theophylline	Moderate	Can enter breast milk in moderate quantities but not likely to produce significant effects.
Thyroxine	Minimal	No adverse effects in therapeutic doses.
Tolbutamide	Minimal	Low concentrations in breast milk.
Warfarin	Minimal	Very small quantities found in breast milk.

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TABLE 59–6 Determination of drug dosage from surface area.[1]

Weight (kg)	Weight (lb)	Approximate Age	Surface Area (m^2)	Percent of Adult Dose
3	6.6	Newborn	0.2	12
6	13.2	3 months	0.3	18
10	22	1 year	0.45	28
20	44	5.5 years	0.8	48
30	66	9 years	1	60
40	88	12 years	1.3	78
50	110	14 years	1.5	90
60	132	Adult	1.7	102
70	154	Adult	1.76	103

[1]For example, if adult dose is 1 mg/kg, dose for 3-month-old infant would be 0.18 mg/kg or 1.1 mg total.

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Weight (somewhat more precise is Clark's rule):

$$Dose = \text{Adult dose} \times \frac{\text{Weight (kg)}}{70}$$

or

$$Dose = \text{Adult dose} \times \frac{\text{Weight (lb)}}{150}$$

In spite of these approximations, only by conducting studies in children can safe and effective doses for a given age group and condition be determined.

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CHAPTER 60

Special Aspects of Geriatric Pharmacology

Bertram G. Katzung, MD, PhD

CASE STUDY

A 77-year-old man comes to your office at his wife's insistence. He has had documented moderate hypertension for 10 years but does not like to take his medications. He says he has no real complaints, but his wife remarks that he has become much more forgetful lately and has almost stopped reading the newspaper and watching television. A Mini-Mental Examination reveals that he is oriented as to name and place but is unable to give the month or year. He cannot remember the names of his three adult children nor three random words (tree, flag, chair) for more than 2 minutes. No cataracts are visible, but he is unable to read standard newsprint without a powerful magnifier. Why doesn't he take his antihypertensive medications? What therapeutic measures are available for the treatment of Alzheimer's disease? How might macular degeneration be treated?

Society has traditionally classified everyone over 65 as "elderly," but most authorities consider the field of geriatrics to apply to persons over 75—even though this too is an arbitrary definition. Furthermore, chronologic age is only one determinant of the changes pertinent to drug therapy that occur in older people. In addition to the chronic diseases of adulthood, the elderly have an increased incidence of many conditions, including Alzheimer's disease, Parkinson's disease, and vascular dementia; stroke; visual impairment, especially cataracts and macular degeneration; atherosclerosis, coronary heart disease, and heart failure; diabetes; arthritis, osteoporosis, and fractures; cancer; and incontinence. As a result, the need for drug treatment is great in this age group.

Important changes in responses to some drugs occur with increasing age in many individuals. For other drugs, age-related changes are minimal, especially in the "healthy old." Drug usage patterns also change as a result of the increasing incidence of disease with age and the tendency to prescribe heavily for patients in nursing homes. General changes in the lives of older people have significant effects on the way drugs are used. Among these changes are the increased incidence with advancing age of several simultaneous diseases, nutritional problems, reduced financial resources, and—in some patients—decreased dosing adherence (also called compliance) for a variety of reasons. The health practitioner should be aware of the changes in pharmacologic responses that may occur in older people and should know how to deal with these changes.

PHARMACOLOGIC CHANGES ASSOCIATED WITH AGING

In the general population, measurements of functional capacity of most of the major organ systems show a decline beginning in young adulthood and continuing throughout life. As shown in Figure 60–1, there is no "middle-age plateau" but rather a linear decrease beginning no later than age 45. However, these data reflect the mean and do not apply to every person above a certain age; approximately one third of healthy subjects have no age-related decrease in, for example, creatinine clearance up to the age of 75. Thus, the elderly do not lose specific functions at an accelerated rate compared with young and middle-aged adults but rather accumulate more deficiencies with the passage of time. Some of these changes result in altered pharmacokinetics. For the pharmacologist and the clinician, the most important of these is the decrease in renal function. Other changes and concurrent diseases may alter the pharmacodynamic characteristics of particular drugs in certain patients.

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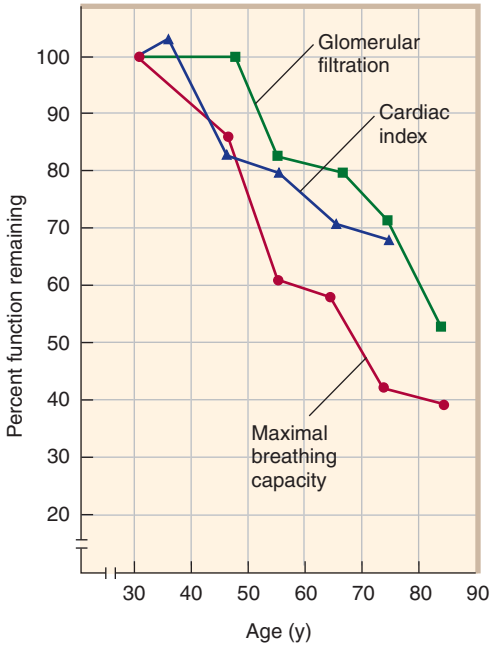

FIGURE 60–1 Effect of age on some physiologic functions. (Modified and reproduced, with permission, from Kohn RR: *Principles of Mammalian Aging*. Prentice-Hall, 1978.)

Pharmacokinetic Changes

A. Absorption

There is little evidence of any major alteration in drug absorption with age. However, conditions associated with age may alter the rate at which some drugs are absorbed. Such conditions include altered nutritional habits, greater consumption of nonprescription drugs (eg, antacids and laxatives), and changes in gastric emptying, which is often slower in older persons, especially in older diabetics.

B. Distribution

Compared with young adults, the elderly have reduced lean body mass, reduced body water, and increased fat as a percentage of body mass. Some of these changes are shown in Table 60–1. There is usually a decrease in serum albumin, which binds many drugs, especially weak acids. There may be a concurrent *increase* in serum orosomucoid (α-acid glycoprotein), a protein that binds many basic drugs. Thus, the ratio of bound to free drug may be significantly altered. As explained in Chapter 3, these changes may alter the appropriate loading dose of a drug. However since both the clearance and the effects of drugs are related to the free concentration, the steady-state effects of a maintenance dosage regimen should not be altered by these factors alone. For example, the loading dose of digoxin in an elderly patient with heart failure should be reduced (if used at all) because of the decreased apparent volume of distribution. The maintenance dose may have to be reduced because of reduced clearance of the drug.

C. Metabolism

The capacity of the liver to metabolize drugs does not appear to decline consistently with age for all drugs. Animal studies and some clinical studies have suggested that certain drugs are metabolized more slowly; some of these drugs are listed in Table 60–2. The greatest changes are in phase I reactions, ie, those carried out by microsomal P450 systems. There are much smaller changes in the ability of the liver to carry out conjugation (phase II) reactions (see Chapter 4). Some of these changes may be caused by decreased liver blood flow (Table 60–1), an important variable in the clearance of drugs that have a high hepatic extraction ratio. In addition, there is

TABLE 60–1 Some changes related to aging that affect pharmacokinetics of drugs.

Variable	Young Adults (20–30 years)	Older Adults (60–80 years)
Body water (% of body weight)	61	53
Lean body mass (% of body weight)	19	12
Body fat (% of body weight)	26–33 (women)	38–45
	18–20 (men)	36–38
Serum albumin (g/dL)	4.7	3.8
Kidney weight (% of young adult)	(100)	80
Hepatic blood flow (% of young adult)	(100)	55–60

TABLE 60–2 Effects of age on hepatic clearance of some drugs.

Age-Related Decrease in Hepatic Clearance Found	No Age-Related Difference Found
Alprazolam	Ethanol
Barbiturates	Isoniazid
Carbenoxolone	Lidocaine
Chlordiazepoxide	Lorazepam
Chlormethiazole	Nitrazepam
Clobazam	Oxazepam
Desmethyldiazepam	Prazosin
Diazepam	Salicylate
Flurazepam	Warfarin
Imipramine	
Meperidine	
Nortriptyline	
Phenylbutazone	
Propranolol	
Quinidine, quinine	
Theophylline	
Tolbutamide	

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a decline with age of the liver's ability to recover from injury, eg, that caused by alcohol or viral hepatitis. Therefore, a history of recent liver disease in an older person should lead to caution in dosing with drugs that are cleared primarily by the liver, even after apparently complete recovery from the hepatic insult. Finally, malnutrition and diseases that affect hepatic function—eg, heart failure—are more common in the elderly. Heart failure may dramatically alter the ability of the liver to metabolize drugs by reducing hepatic blood flow. Similarly, severe nutritional deficiencies, which occur more often in old age, may impair hepatic function.

D. Elimination

Because the kidney is the major organ for clearance of drugs from the body, the age-related decline of renal functional capacity is very important. The decline in creatinine clearance occurs in about two thirds of the population. It is important to note that this decline is not reflected in an equivalent rise in serum creatinine because the production of creatinine is also reduced as muscle mass declines with age; therefore, serum creatinine alone is not an adequate measure of renal function. The practical result of this change is marked prolongation of the half-life of many drugs, and the possibility of accumulation to toxic levels if dosage is not reduced in size or frequency. Dosing recommendations for the elderly often include an allowance for reduced renal clearance. If only the young adult dosage is known for a drug that requires renal clearance, a rough correction can be made by using the **Cockcroft-Gault** formula, which is applicable to patients from ages 40 through 80:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{Age}) \times (\text{Weight in kg})}{72 \times \text{Serum creatinine in mg/dL}}$$

For women, the result should be multiplied by 0.85 (because of reduced muscle mass). It must be emphasized that this estimate is, at best, a *population* estimate and may not apply to a particular patient. If the patient has normal renal function (up to one third of elderly patients), a dose corrected on the basis of this estimate will be too low—but a low dose is initially desirable if one is uncertain of the renal function in any patient. If a precise measure is needed, a standard 12- or 24-hour creatinine clearance determination should be obtained. As indicated above, nutritional changes alter pharmacokinetic parameters. A patient who is severely dehydrated (not uncommon in patients with stroke or other motor impairment) may have an additional marked reduction in renal drug clearance that is completely reversible by rehydration.

The lungs are important for the excretion of volatile drugs. As a result of reduced respiratory capacity (Figure 60–1) and the increased incidence of active pulmonary disease in the elderly, the use of inhalation anesthesia is less common and parenteral agents more common in this age group. (See Chapter 25.)

Pharmacodynamic Changes

It was long believed that geriatric patients were much more "sensitive" to the action of many drugs, implying a change in the pharmacodynamic interaction of the drugs with their receptors. It is now recognized that many—perhaps most—of these apparent changes result from altered pharmacokinetics or diminished homeostatic responses. Clinical studies have supported the idea that the elderly are more sensitive to *some* sedative-hypnotics and analgesics. In addition, some data from animal studies suggest actual changes with age in the characteristics or numbers of a few receptors. The most extensive studies suggest a decrease in responsiveness to β-adrenoceptor agonists. Other examples are discussed below.

Certain homeostatic control mechanisms appear to be blunted in the elderly. Since homeostatic responses are often important components of the overall response to a drug, these physiologic alterations may change the pattern or intensity of drug response. In the cardiovascular system, the cardiac output increment required by mild or moderate exercise is successfully provided until at least age 75 (in individuals without obvious cardiac disease), but the increase is the result primarily of increased stroke volume in the elderly and not tachycardia, as in young adults. Average blood pressure goes up with age (in most Western countries), but the incidence of symptomatic orthostatic hypotension also increases markedly. It is thus particularly important to check for orthostatic hypotension on every visit. Similarly, the average 2-hour postprandial blood glucose level increases by about 1 mg/dL for each year of age above 50. Temperature regulation is also impaired, and hypothermia is poorly tolerated by the elderly.

Behavioral & Lifestyle Changes

Major changes in the conditions of daily life accompany the aging process and have an impact on health. Some of these (eg, forgetting to take one's pills) are the result of cognitive changes associated with vascular or other pathology. Others relate to economic stresses associated with greatly reduced income and, possibly, increased expenses due to illness. One of the most important changes is the loss of a spouse.

MAJOR DRUG GROUPS

CENTRAL NERVOUS SYSTEM DRUGS

Sedative-Hypnotics

The half-lives of many benzodiazepines and barbiturates increase by 50–150% between ages 30 and 70. Much of this change occurs during the decade from 60 to 70. For some of the benzodiazepines, both the parent molecule and its metabolites (produced in the liver) are pharmacologically active (see Chapter 22). The age-related decline in renal function and liver disease, if present, both contribute to the reduction in elimination of these compounds. In addition, an increased volume of distribution has been reported for some of these drugs. Lorazepam and oxazepam may be less affected by these changes than the other benzodiazepines. In addition to these pharmacokinetic factors, it is generally believed that the elderly vary more in their sensitivity to the sedative-hypnotic

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drugs on a pharmacodynamic basis as well. Among the toxicities of these drugs, ataxia and other signs of motor impairment should be particularly watched for in order to avoid accidents.

Analgesics

The opioid analgesics show variable changes in pharmacokinetics with age. However, the elderly are often markedly more sensitive to the respiratory effects of these agents because of age-related changes in respiratory function. Therefore, this group of drugs should be used with caution until the sensitivity of the particular patient has been evaluated, and the patient should then be dosed appropriately for full effect. Unfortunately, studies show that opioids are consistently *underutilized* in patients who require strong analgesics for chronic painful conditions such as cancer. There is no justification for underutilization of these drugs, especially in the care of the elderly, and good pain management plans are readily available (see Morrison, 2006; Rabow, 2011).

Antipsychotic & Antidepressant Drugs

The traditional antipsychotic agents (phenothiazines and haloperidol) have been very heavily used (and probably misused) in the management of a variety of psychiatric diseases in the elderly. There is no doubt that they are useful in the management of schizophrenia in old age, and also in the treatment of some symptoms associated with delirium, dementia, agitation, combativeness, and a paranoid syndrome that occurs in some geriatric patients (see Chapter 29). However, they are not fully satisfactory in these geriatric conditions, and dosage should not be increased on the assumption that full control is possible. There is no evidence that these drugs have any beneficial effects in Alzheimer's dementia, and on theoretical grounds the antimuscarinic effects of the phenothiazines might be expected to worsen memory impairment and intellectual dysfunction (see below).

Much of the apparent improvement in agitated and combative patients may simply reflect the sedative effects of the drugs. When a sedative antipsychotic is desired, a phenothiazine such as thioridazine is appropriate. If sedation is to be avoided, haloperidol or an atypical antipsychotic is more appropriate. Haloperidol has increased extrapyramidal toxicity, however, and should be avoided in patients with preexisting extrapyramidal disease. The phenothiazines, especially older drugs such as chlorpromazine, often induce orthostatic hypotension because of their α-adrenoceptor-blocking effects. They are even more prone to do so in the elderly. Dosage of these drugs should usually be started at a fraction of that used in young adults.

Lithium is often used in the treatment of mania in the aged. Because it is cleared by the kidneys, dosages must be adjusted appropriately and blood levels monitored. Concurrent use of thiazide diuretics reduces the clearance of lithium and should be accompanied by further reduction in dosage and more frequent measurement of lithium blood levels.

Psychiatric depression is thought to be underdiagnosed and undertreated in the elderly. The suicide rate in the over-65 age group (twice the national average) supports this view. Unfortunately, the apathy, flat affect, and social withdrawal of major depression may be mistaken for senile dementia. Clinical evidence suggests that the elderly are as responsive to antidepressants (of all types) as younger patients but are more likely to experience toxic effects. This factor along with the reduced clearance of some of these drugs underlines the importance of careful dosing and strict attention to the appearance of toxic effects. If a tricyclic antidepressant is to be used, a drug with reduced antimuscarinic effects should be selected, eg, nortriptyline or desipramine (see Table 30–2). To minimize autonomic effects, a selective serotonin reuptake inhibitor (SSRI) may be chosen.

Drugs Used in Alzheimer's Disease

Alzheimer's disease is characterized by progressive impairment of memory and cognitive functions and may lead to a completely vegetative state, resulting in massive socioeconomic disruption, and early death. Prevalence increases with age and may be as high as 20% in individuals over 85. Both familial and sporadic forms have been identified. Early onset of Alzheimer's disease is associated with several gene defects, including trisomy 21 (chromosome 21), a mutation of the gene for presenilin-1 on chromosome 14, and an abnormal allele, ε4, for the lipid-associated protein, ApoE, on chromosome 19. Unlike the normal form, ApoE ε2, the ε4 form facilitates the formation of amyloid β deposits.

Pathologic changes include increased deposits of amyloid β peptide in the cerebral cortex, which eventually forms extracellular plaques and cerebral vascular lesions, and intraneuronal fibrillary tangles consisting of the tau protein (Figure 60–2). There is a progressive loss of neurons, especially cholinergic neurons, and thinning of the cortex. The loss of cholinergic neurons results in a marked decrease in choline acetyltransferase and other markers of cholinergic activity. Patients with Alzheimer's disease are often exquisitely sensitive to the central nervous system toxicities of drugs with antimuscarinic effects. Some evidence implicates excess excitation by glutamate as a contributor to neuronal death. In addition, abnormalities of mitochondrial function may contribute to neuronal death.

Many methods of treatment of Alzheimer's disease have been explored (Table 60–3). Most attention has been focused on the cholinomimetic drugs because of the evidence of loss of cholinergic neurons. Monoamine oxidase (MAO) type B inhibition with selegiline (L-deprenyl) has been suggested to have some beneficial effects. One drug that inhibits *N*-methyl-D-aspartate (NMDA) glutamate receptors is available (see below), and "ampakines," substances that facilitate synaptic activity at glutamate AMPA receptors, are under intense study. Some evidence suggests that lipid-lowering statins are beneficial. Rosiglitazone, a PPAR-γ (peroxisome proliferator-activated receptor-gamma) agent, has also been reported to have beneficial effects in a preliminary study. Unfortunately, this drug is associated with increased cardiovascular risk and its use has been restricted (see Chapter 41). So-called cerebral vasodilators are ineffective.

Tacrine (tetrahydroaminoacridine, THA), a long-acting cholinesterase inhibitor and muscarinic modulator, was the first drug

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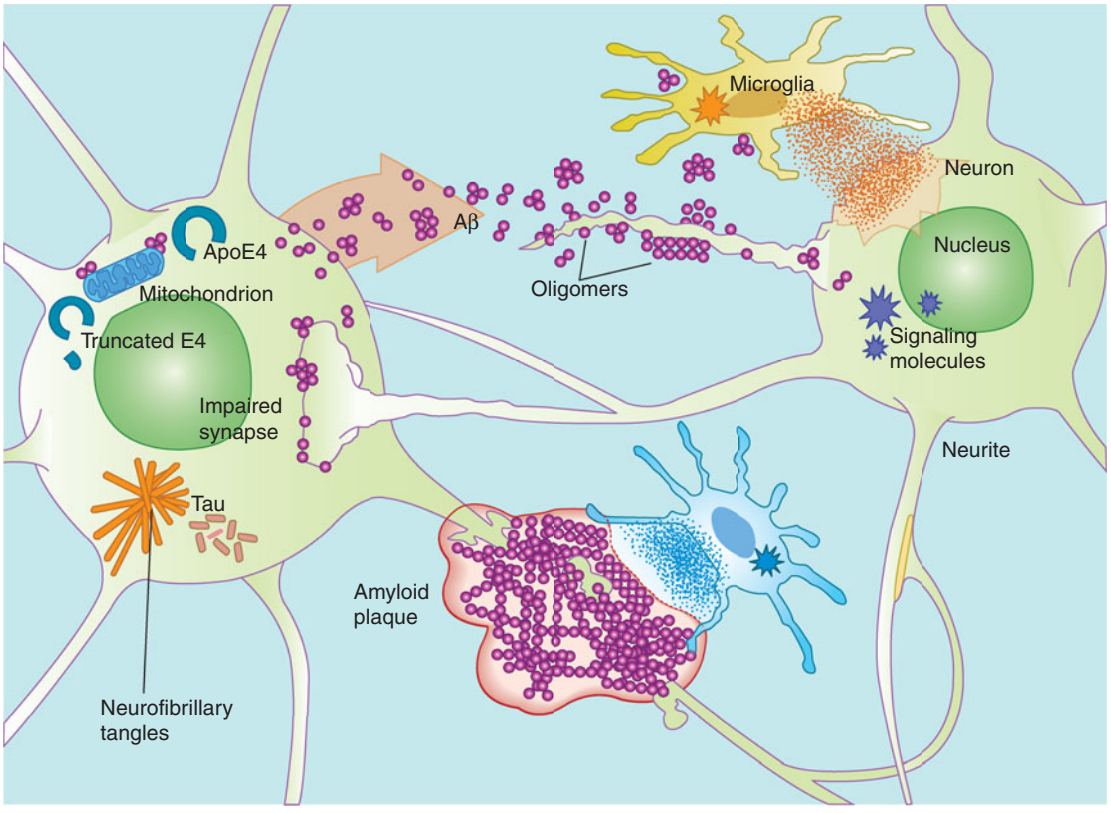

FIGURE 60–2 Some processes involved in Alzheimer's disease. From the left: mitochondrial dysfunction, possibly involving glucose utilization; synthesis of protein tau and aggregation in filamentous tangles; synthesis of amyloid β (Aβ) and secretion into the extracellular space, where it may interfere with synaptic signaling and accumulates in plaques. (Reproduced, with permission, from Robertson ED and Mucke L: 100 years and counting: Prospects for defeating Alzheimer's disease. Science 2006;314:781.)

shown to have any benefit in Alzheimer's disease. Because of its hepatic toxicity, tacrine has been almost completely replaced in clinical use by newer cholinesterase inhibitors: **donepezil, rivastigmine,** and **galantamine.** These agents are orally active, have adequate penetration into the central nervous system, and are much less toxic than tacrine. Although evidence for the benefit of cholinesterase inhibitors (and memantine; see below) is statistically significant, the clinical benefit from these drugs is modest and temporary.

The cholinesterase inhibitors cause significant adverse effects, including nausea and vomiting, and other peripheral cholinomimetic effects. These drugs should be used with caution in patients receiving other drugs that inhibit cytochrome P450 enzymes (eg, ketoconazole, quinidine; see Chapter 4). Preparations available are listed in Chapter 7.

Excitotoxic activation of glutamate transmission via NMDA receptors has been postulated to contribute to the pathophysiology of Alzheimer's disease. **Memantine** binds to NMDA receptor channels in a use-dependent manner and produces a noncompetitive blockade. This drug appears to be better tolerated and less toxic than the cholinesterase inhibitors. Memantine is available as Namenda in 5 and 10 mg oral tablets.

TABLE 60–3 Some potential strategies for the prevention or treatment of Alzheimer's disease.

Therapy	Comment
Cholinesterase inhibitors	Increase cholinergic activity; four drugs approved
N-methyl-D-aspartate glutamate antagonists	Inhibit glutamate excitotoxicity; 1 drug approved
Modifiers of glucose utilization	PPAR-γ agonists
Antilipid drugs	Statins (off-label use)
NSAIDs	Disappointing results with cyclooxygenase (COX)-2 inhibitors but interest continues
Anti-amyloid vaccines	In clinical trials
Anti-amyloid antibodies	Bapineuzumab in clinical trials
Inhibitors of amyloid β synthesis	γ-Secretase modulator studies in progress
Antioxidants	Disappointing results
Nerve growth factor	One very small trial

PPAR-γ, peroxisome proliferator-activated receptor-gamma.

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CARDIOVASCULAR DRUGS

Antihypertensive Drugs

Blood pressure, especially systolic pressure, increases with age in Western countries and in most cultures in which salt intake is high. In women, the increase is more marked after age 50. Although treated conservatively in the past, most clinicians now believe that hypertension should be treated vigorously in the elderly.

The basic principles of therapy are not different in the geriatric age group from those described in Chapter 11, but the usual cautions regarding altered pharmacokinetics and blunted compensatory mechanisms apply. Because of its safety, nondrug therapy (weight reduction in the obese and salt restriction) should be encouraged. Thiazides are a reasonable first step in drug therapy. The hypokalemia, hyperglycemia, and hyperuricemia caused by these agents are more relevant in the elderly because of the higher incidence in these patients of arrhythmias, type 2 diabetes, and gout. Thus, use of low antihypertensive doses—rather than maximum diuretic doses—is important. Calcium channel blockers are effective and safe if titrated to the appropriate response. They are especially useful in patients who also have atherosclerotic angina (see Chapter 12). Beta blockers are potentially hazardous in patients with obstructive airway disease and are considered less useful than calcium channel blockers in older patients unless heart failure is present. Angiotensin-converting enzyme inhibitors are also considered less useful in the elderly unless heart failure or diabetes is present. The most powerful drugs, such as minoxidil, are rarely needed. Every patient receiving antihypertensive drugs should be checked regularly for orthostatic hypotension because of the danger of cerebral ischemia and falls.

Positive Inotropic Agents

Heart failure is a common and particularly lethal disease in the elderly. Fear of this condition may be one reason why physicians overuse cardiac glycosides in this age group. The toxic effects of digoxin are particularly dangerous in the geriatric population, since the elderly are more susceptible to arrhythmias. The clearance of digoxin is usually decreased in the older age group, and although the volume of distribution is often decreased as well, the half-life of this drug may be increased by 50% or more. Because the drug is cleared mostly by the kidneys, renal function must be considered in designing a dosage regimen. There is no evidence that there is any increase in pharmacodynamic sensitivity to the therapeutic effects of the cardiac glycosides; in fact, animal studies suggest a possible decrease in therapeutic sensitivity. On the other hand, there is probably an increase in sensitivity to the toxic arrhythmogenic actions. Hypokalemia, hypomagnesemia, hypoxemia (from pulmonary disease), and coronary atherosclerosis all contribute to the high incidence of digitalis-induced arrhythmias in geriatric patients. The less common toxicities of digitalis such as delirium, visual changes, and endocrine abnormalities (see Chapter 13) also occur more often in older than in younger patients.

Antiarrhythmic Agents

The treatment of arrhythmias in the elderly is particularly challenging because of the lack of good hemodynamic reserve, the frequency of electrolyte disturbances, and the high prevalence of severe coronary disease. The clearances of quinidine and procainamide decrease and their half-lives increase with age. Disopyramide should probably be avoided in the geriatric population because its major toxicities—antimuscarinic action, leading to voiding problems in men; and negative inotropic cardiac effects, leading to heart failure—are particularly undesirable in these patients. The clearance of lidocaine appears to be little changed, but the half-life is increased in the elderly. Although this observation implies an increase in the volume of distribution, it has been recommended that the loading dose of this drug be reduced in geriatric patients because of their greater sensitivity to its toxic effects.

Recent evidence indicates that many patients with atrial fibrillation—a very common arrhythmia in the elderly—do as well with simple control of ventricular rate as with conversion to normal sinus rhythm. Measures (such as anticoagulant drugs) should be taken to reduce the risk of thromboembolism in chronic atrial fibrillation.

ANTIMICROBIAL DRUGS

Several age-related changes contribute to the high incidence of infections in geriatric patients. There appears to be a reduction in host defenses in the elderly, manifested in the increase in both serious infections and cancer. This may reflect an alteration in T-lymphocyte function. In the lungs, a major age and tobacco-dependent decrease in mucociliary clearance significantly increases susceptibility to infection. In the urinary tract, the incidence of serious infection is greatly increased by urinary retention and catheterization in men.

Since 1940, the antimicrobial drugs have contributed more to the prolongation of life than any other drug group because they can compensate to some extent for this deterioration in natural defenses. The basic principles of therapy of the elderly with these agents are no different from those applicable in younger patients and have been presented in Chapter 51. The major pharmacokinetic changes relate to decreased renal function; because most of the β-lactam, aminoglycoside, and fluoroquinolone antibiotics are excreted by this route, important changes in half-life may be expected. This is particularly important in the case of the aminoglycosides, because they cause concentration- and time-dependent toxicity in the kidney and in other organs. The half-lives of gentamicin, kanamycin, and netilmicin are more than doubled. The increase may not be so marked for tobramycin.

ANTI-INFLAMMATORY DRUGS

Osteoarthritis is a very common disease of the elderly. Rheumatoid arthritis is less exclusively a geriatric problem, but the same drug therapy is usually applicable. The basic principles laid down in

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Chapter 36 and the properties of the anti-inflammatory drugs described there apply fully here.

The nonsteroidal anti-inflammatory agents (NSAIDs) must be used with special care in geriatric patients because they cause toxicities to which the elderly are very susceptible. In the case of aspirin, the most important of these is gastrointestinal irritation and bleeding. In the case of the newer NSAIDs, the most important is renal damage, which may be irreversible. Because they are cleared primarily by the kidneys, these drugs accumulate more rapidly in the geriatric patient and especially in the patient whose renal function is already compromised beyond the average range for his or her age. A vicious circle is easily set up in which cumulation of the NSAID causes more renal damage, which causes more cumulation. There is no evidence that the cyclooxygenase (COX)-2 selective NSAIDs are safer with regard to renal function. Elderly patients receiving high doses of any NSAID should be carefully monitored for changes in renal function.

Corticosteroids are extremely useful in elderly patients who cannot tolerate full doses of NSAIDs. However, they consistently cause a dose- and duration-related increase in osteoporosis, an especially hazardous toxic effect in the elderly. It is not certain whether this drug-induced effect can be reduced by increased calcium and vitamin D intake, but it would be prudent to consider these agents (and bisphosphonates if osteoporosis is already present) and to encourage frequent exercise in any patient taking corticosteroids.

OPHTHALMIC DRUGS

Drugs Used in Glaucoma

Glaucoma is more common in the elderly, but its treatment does not differ from that of glaucoma of earlier onset. Management of glaucoma is discussed in Chapter 10.

Macular Degeneration

Age-related macular degeneration (AMD) is the most common cause of blindness in the elderly in the developed world. Two forms of advanced AMD are recognized: the neovascular "wet" form, which is associated with intrusion of new blood vessels in the subretinal space, and a more common "dry" form, which is not associated with abnormal vascularization. Although the cause of AMD is not known, smoking is a documented risk factor, and oxidative stress has long been thought to play a role. On this premise, antioxidants have been used to prevent or delay the onset of AMD. Proprietary oral formulations of vitamins C and E, β-carotene, zinc oxide, and cupric oxide are available. Evidence for the efficacy of these antioxidants is modest or absent. Oral drugs in clinical trials include the carotenoids lutein and zeaxanthin, and n-3 long-chain polyunsaturated fatty acids.

In advanced AMD, treatment has been moderately successful but only for the neovascular form. Neovascular AMD can now be treated with laser phototherapy or with antibodies against vascular endothelial growth factor (VEGF). Two antibodies are available: bevacizumab (Avastin, used off-label) and ranibizumab (Lucentis), as well as the oligopeptide pegaptanib (Macugen). The latter two are approved for neovascular AMD. These agents are injected into the vitreous for local effect. Ranibizumab is extremely expensive. Fusion proteins and RNA agents that bind VEGF are under study.

ADVERSE DRUG REACTIONS IN THE ELDERLY

The relation between the number of drugs taken and the incidence of adverse drug reactions has been well documented. In long-term care facilities, in which a high percentage of the population is elderly, the average number of prescriptions per patient varies between 6 and 8. Studies have shown that the percentage of patients with adverse reactions increases from about 10% when a single drug is being taken to nearly 100% when 10 drugs are taken. Thus, it may be expected that about half of patients in long-term care facilities will have recognized or unrecognized reactions at some time. Patients living at home may see several different practitioners for different conditions and accumulate multiple prescriptions for drugs with overlapping actions. It is useful to conduct a "brown bag" analysis in such patients. The brown bag analysis consists of asking the patient to bring to the practitioner a bag containing *all* the medications, supplements, vitamins, etc, that he or she is currently taking. Some prescriptions will be found to be duplicates, others unnecessary. The total number of medications taken can often be reduced by 30–50%.

The overall incidence of drug reactions in geriatric patients is estimated to be at least twice that in the younger population. Reasons for this high incidence undoubtedly include errors in prescribing on the part of the practitioner and errors in drug usage by the patient. Practitioner errors sometimes occur because the physician does not appreciate the importance of changes in pharmacokinetics with age and age-related diseases. Some errors occur because the practitioner is unaware of incompatible drugs prescribed by other practitioners for the same patient. For example, cimetidine, an H_2-blocking drug heavily prescribed (or recommended in its over-the-counter form) to the elderly, causes a much higher incidence of untoward effects (eg, confusion, slurred speech) in the geriatric population than in younger patients. It also inhibits the hepatic metabolism of many drugs, including phenytoin, warfarin, β blockers, and other agents. A patient who has been taking one of the latter agents without untoward effect may develop markedly elevated blood levels and severe toxicity if cimetidine is added to the regimen without adjustment of dosage of the other drugs. Additional examples of drugs that inhibit liver microsomal enzymes and lead to adverse reactions are described in Chapters 4 and 66.

Patient errors may result from nonadherence for reasons described below. In addition, they often result from use of nonprescription drugs taken without the knowledge of the physician. As noted in Chapters 63 and 64, many over-the-counter agents and herbal medications contain "hidden ingredients" with potent

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pharmacologic effects. For example, many antihistamines have significant sedative effects and are inherently more hazardous in patients with impaired cognitive function. Similarly, their antimuscarinic action may precipitate urinary retention in geriatric men or glaucoma in patients with a narrow anterior chamber angle. If the patient is also taking a metabolism inhibitor such as cimetidine, the probability of an adverse reaction is greatly increased. A patient taking an herbal medication containing gingko is more likely to experience bleeding while taking low doses of aspirin.

■ PRACTICAL ASPECTS OF GERIATRIC PHARMACOLOGY

The quality of life in elderly patients can be greatly improved and life span can be prolonged by the intelligent use of drugs. However, the prescriber must recognize several practical obstacles to compliance.

The expense of drugs can be a major disincentive in patients receiving marginal retirement incomes who are not covered or inadequately covered by health insurance. The prescriber must be aware of the cost of the prescription and of cheaper alternative therapies. For example, the monthly cost of arthritis therapy with newer NSAIDs may exceed $100, whereas that for generic aspirin is about $5 and for ibuprofen and naproxen, two older NSAIDs, about $20.

Nonadherence may result from forgetfulness or confusion, especially if the patient has several prescriptions and different dosing intervals. A survey carried out in 1986 showed that the population over 65 years of age accounted for 32% of drugs prescribed in the USA, although these patients represented only 11–12% of the population at that time. Since the prescriptions are often written by several different practitioners, there is usually no attempt to design "integrated" regimens that use drugs with similar dosing intervals for the conditions being treated. Patients may forget instructions regarding the need to complete a fixed duration of therapy when a course of anti-infective drug is being given. The disappearance of symptoms is often regarded as the best reason to halt drug taking, especially if the prescription was expensive.

Nonadherence may also be deliberate. A decision not to take a drug may be based on prior experience with it. There may be excellent reasons for such "intelligent" noncompliance, and the practitioner should try to elicit them. Such efforts may also improve compliance with alternative drug regimens, because enlisting the patient as a participant in therapeutic decisions increases the motivation to succeed.

Some errors in drug taking are caused by physical disabilities. Arthritis, tremor, and visual problems may all contribute. Liquid medications that are to be measured "by the spoonful" are especially inappropriate for patients with any type of tremor or motor disability. Use of a dosing syringe may be helpful in such cases. Because of decreased production of saliva, older patients often have difficulty swallowing large tablets. "Childproof" containers are often "elder-proof" if the patient has arthritis. Cataracts and macular degeneration occur in a large number of patients over 70. Therefore, labels on prescription bottles should be large enough for the patient with diminished vision to read or should be color-coded if the patient can see but can no longer read.

Drug therapy has considerable potential for both helpful and harmful effects in the geriatric patient. The balance may be tipped in the right direction by adherence to a few principles:

1. Take a careful drug history. The disease to be treated may be drug-induced, or drugs being taken may lead to interactions with drugs to be prescribed.
2. Prescribe only for a specific and rational indication. Do not prescribe omeprazole for "dyspepsia." Expert guidelines are published regularly by national organizations and websites such as UpToDate.com.
3. Define the goal of drug therapy. Then start with small doses and titrate to the response desired. Wait at least three half-lives (adjusted for age) before increasing the dose. If the expected response does not occur at the normal adult dosage, check blood levels. If the expected response does not occur at the appropriate blood level, switch to a different drug.
4. Maintain a high index of suspicion regarding drug reactions and interactions. Know what other drugs the patient is taking, including over-the-counter and botanical (herbal) drugs.
5. Simplify the regimen as much as possible. When multiple drugs are prescribed, try to use drugs that can be taken at the same time of day. Whenever possible, reduce the number of drugs being taken.

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CASE STUDY ANSWER

This patient has several conditions that warrant careful treatment. Hypertension is eminently treatable; the steps described in Chapter 11 are appropriate and effective in the elderly as well as in young patients. Patient education is critical in combating his reluctance to take his medications. Alzheimer's disease may respond temporarily to one of the anticholinesterase agents (donepezil, rivastigmine, galantamine). Alternatively, memantine may be tried. Unfortunately, age-related macular degeneration (the most likely cause of his visual difficulties) is not readily treated, but the "wet" (neovascular) variety may respond well to one of the drugs currently available (bevacizumab, ranibizumab, pegaptanib). However, these therapies are expensive.