7 Principles of Toxicology

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The discipline of toxicology considers the adverse effects of chemicals, including drugs, and other agents, such as biological toxins and radiation, on biological systems. Toxicity associated with drug action can generally be characterized as either an extension of the therapeutic effect, such as the fatal central nervous system (CNS) depression that may follow a barbiturate overdose, or as an effect that is unrelated to the therapeutic effect, such as the liver damage that may result from an acetaminophen overdose. This chapter focuses on the tissue response associated with the latter type of drug toxicity and on the toxicities associated with several important classes of nontherapeutic agents.

The target organ for the expression of xenobiotic toxicity is not necessarily the tissue or organ in which the drug produces its therapeutic effect, nor is it necessarily the tissue that has the highest concentration of the agent. For example, lead accumulates in bone but produces no toxicity there; certain chlorinated pesticides accumulate in adipose tissue but produce no local adverse effects. Drugs such as acetaminophen cause necrosis in the centrilobular portion of the liver at a site of the monooxygenase enzymes that bioactivate the analgesic.

It is necessary to distinguish between the intrinsic toxicity of a chemical and the hazard it poses. While a chemical may have high intrinsic toxicity, it may pose little or no hazard if exposure is low. In contrast, a relatively nontoxic chemical may be quite hazardous if exposure is large or the route of exposure is not physiological.

MANIFESTATIONS OF TOXICITY

Organ Toxicity

The events that initiate cell death are not completely understood. The common final stages of necrotic cell death are disruption of normal metabolic processes and ensuing inability to maintain intracellular electrolyte homeostasis. If the insult is severe or prolonged enough, the cell will not regain normal function. At the same time, other cells show apoptotic cell death, characterized by cell shrinkage, cleavage of DNA between nucleosomes, and formation of apoptotic bodies. Some chemicals are metabolized to reactive products that bind to cellular macromolecules. If such binding impairs the function of crucial macromolecules, cell viability is lost. How severely organ function will be impaired depends on the reserve capacity of that organ. The ultimate outcome will depend on the affected organ's regenerative capacity and response to damage.

Pulmonary Toxicity

Inhaled gases, solid particles, or liquid aerosols may deposit throughout the respiratory system, depending on their chemical and physical properties. The large surface area of the respiratory passages and alveolar region and the large volume of air delivered to that area (approximately 6–7 L/minute in a young man) provide great opportunity for interaction between inhaled materials and lung tissue. Examples of inhaled xenobiotics that cause

lung damage and those that have entered the body by ingestion, injection, or dermal absorption are presented in Figure 7.1.

Exposure of the lungs to xenobiotics may result in a number of disease conditions including bronchitis, emphysema, asthma, hypersensitivity pneumonitis, pneumoconiosis, and cancer. During repair, damaged lung alveolar epithelium may be replaced by fibrous tissue that does not allow for gas exchange, which intensifies the damage caused by the initial lesion.

Hepatotoxicity

The blood draining the stomach and small intestine is delivered directly to the liver via the hepatic portal vein, thus exposing the liver to relatively large concentrations of ingested drugs or toxicants (e.g., Fig. 7.1). Hepatic exposure to agents that undergo bioactivation to toxic species can be significant.

Hepatic necrosis can be classified by the zone of the liver tissue affected. Xenobiotics, such as acetaminophen or chloroform, that undergo bioactivation to toxic intermediates cause necrosis of the cells surrounding the central veins (*centrilobular*) because the components of the cytochrome P450 system are found in those cells in abundance. At higher doses or in the presence of agents that increase the synthesis of cytochrome P450 (inducers), the area of necrosis may incorporate the *midzonal* area (midway between the portal triad and central vein). Cells around the portal triad are exposed to the highest concentrations; necrosis occurs with direct-acting agents. A single large dose of a hepatotoxin may cause liver necrosis yet resolve with little or no tissue scarring. Continued exposure to the toxic agent, however, can result in hepatic cirrhosis and permanent scarring.

Allergic reactions to drugs produce foci of necrosis that are scattered throughout the liver. Other agents cause severe (chlorpromazine) or mild (estrogens) cholestatic liver damage, including cholestasis and inflammation of the portal triad and hepatocellular necrosis.

Nephrotoxicity

The kidneys are susceptible to toxicity from xenobiotics (Fig. 7.1) because they too have a high blood flow. Cells of the tubular nephron face double-sided exposure, to agents in the blood on the basolateral side and in the filtered urine on the luminal side. Proximal tubule cells are generally the site of nephrotoxicity, since these cells have an abundance of cytochrome P450 and can transport organic anions and cations from the blood into the cells, thereby concentrating these chemicals manyfold.

Chemically induced kidney damage is typically seen as acute tubular necrosis (ATN). The cells in the proximal tubule are affected. Reabsorption of water, elec-

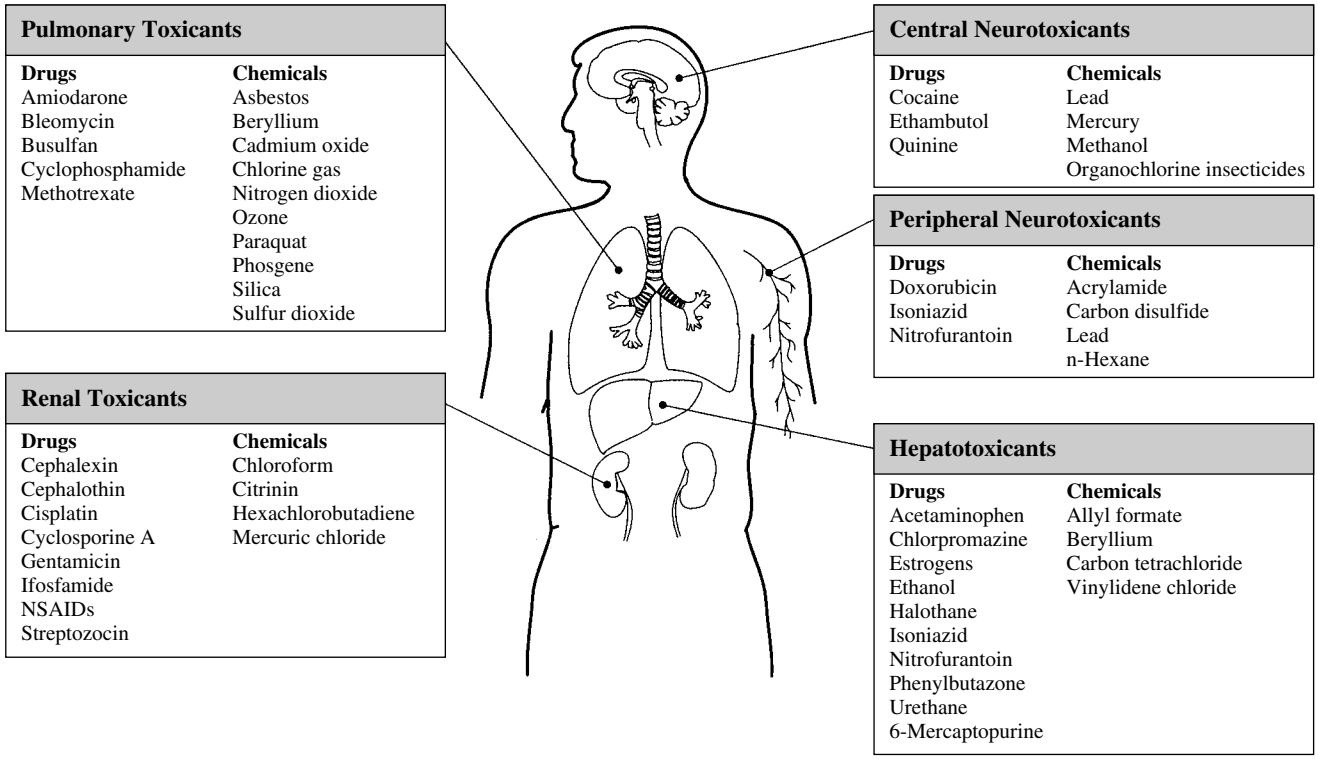

FIGURE 7.1
Organ toxicity of selected chemicals.

trolytes, glucose, and amino acids is impaired. Feedback mechanisms decrease glomerular filtration and thus prevent delivery of large volumes of water to nephron segments. Urine output may be increased, decreased, or unchanged. Markers of glomerular filtration, *blood urea nitrogen* (*BUN*) and *creatinine,* are increased only if filtration falls by 80%. The urine may contain glucose and protein, including proteinaceous casts formed in the nephron of tubular debris.

Neurotoxicity

Although the CNS is protected from a number of xenobiotics by the blood-brain barrier, the barrier is not effective against lipophilic compounds, such as solvents or insecticides (Fig. 7.1). Similarly, the peripheral nervous system is protected by a blood-neural barrier. The barriers are less well developed in the immature nervous system, rendering the fetus and neonate even more susceptible to neurotoxicants. Neural tissue susceptibility is due in large part to its high metabolic rate, high lipid content, and for the CNS, high rate of blood flow.

Since damaged neural tissue cannot easily replicate, glial and other nonconducting cells may proliferate and occupy the space of the dead neurons, and the damage may be expressed as deficits of sensory and motor functions and behavior. Alternatively, other neurons may take on the functions of the damaged neurons such that there is little or no perceptible damage.

Immunotoxicity

A number of drugs and environmentally and occupationally important chemicals can impair the activity of one or more components of the immune system. Immunodeficiency may result in increased susceptibility to infection, decreased surveillance against precancerous or cancerous cells, or tissue-damaging reactions (Table 7.1). Allergic and autoimmune reactions are examples of this form of toxicity.

Clinical expressions of cutaneous allergic reactions include eczematous, indurate–inflammatory, and urticarial eruptions. Irritant responses causing direct damage to the skin may be confused with allergic responses involving immune mechanisms. An important difference is that allergic reactions require an initial exposure to sensitize the individual; dermatitis is then elicited by minimal subsequent exposure to the agent.

Toxic Effects on Genetic Material and Cell Replication

Mutagenesis, teratogenesis, and carcinogenesis are different manifestations of damage to genetic material (*genotoxicity*). Chemically induced genotoxicity occurs in several steps, and at each step there is opportunity for repair. Generally, xenobiotics are not themselves mutagenic, but rather they must be bioactivated to metabolites that are sufficiently reactive to bind to DNA and disrupt its coding. The reactive intermediates must be formed close enough to the DNA to interact with it before interacting with other less important macromolecules or before being further metabolized to inactive forms. Nongenotoxic carcinogens act by altering cell replication control.

TABLE 7.1 Chemicals that Suppress the Immune System in Humans and Animals

Drugs	Chemicals
Azathioprine	Arsenic
Corticosteroids	Benzene
Cyclophosphamide	Dibenzodioxins (TCDD)
Cyclosporine A	Lead
Methotrexate	Organophosphate and organochlorine insecticides
	Ozone
	Polybrominated and polychlorinated biphenyls

Reproductive Toxicity

Most drugs and chemicals pose a threat to the developing fetus. An estimated 4 to 5% of developmental defects in humans result from prenatal exposure to drugs or environmental chemicals. This is particularly important, since women with irregular menstrual cycles may be exposed to teratogens and enter the sensitive period of *organogenesis* before pregnancy is suspected.

Gestation is generally considered to consist of three periods of development, each with differing sensitivities to chemicals. During the *preimplantation* or predifferentiation phase, expression of toxicity is an all-or-none phenomenon; damage to the embryo results in either death or no effect. *Organogenesis* occurs during the embryonic period (the first 3 months of pregnancy), and therefore, susceptibility to teratogenesis is high; the embryo is particularly vulnerable to teratogens on days 25 through 40. The *fetal period* consists of the last 6 months of gestation and is a time of reduced susceptibility to teratogenic alterations. Certain organs, such as the genitals and the nervous system, however, are still undergoing differentiation during this period. Functional impairment in tissues without marked structural damage and growth retardation is the most common effect of chemical exposure during the fetal period.

Chemicals such as 1,2-dibromo-3-chloropropane can disrupt spermatogenesis, leading to impaired reproductive function, including sterility. Men and women undergoing cancer chemotherapy with alkylating drugs are at increased risk for sterility.

TREATMENT OF POISONINGS

Specific antidotes are available for only a few toxic agents (Table 7.2). Even these are not always effective, particularly if the poisoning is severe. The best treatment begins with supportive care. This includes resuscitation (if necessary) and maintenance of respiratory and cardiovascular functions. Imbalances in fluid and electrolytes may have to be corrected. An approach to the treatment of victims of poisoning is presented in Table 7.3.

EXPOSURE TO NONTHERAPEUTIC TOXICANTS

Worldwide production of chemicals has increased dramatically in recent decades, resulting in increased human exposure. This applies not only to workers who manufacture the chemicals and final products but also to those who use the products or are exposed through contamination of surface and ground water and air.

Air Pollution

Industrial activity has polluted the outdoor air with a number of chemicals known to be hazardous to human health. These include a variety of gases, such as carbon monoxide, ozone, and the oxides of sulfur and nitrogen. Unacceptable levels of air pollutants can occur indoors as well. While some of these pollutants may be the same as for the outdoor air, they also include biological agents (e.g., fungal spores, viruses, bacteria, actinomycetes), volatile organic compounds, carbon dioxide, and formaldehyde.

Gases

Carbon monoxide arises from the incomplete combustion of organic material. Of principal concern is its generation by the internal combustion engine and by home heating units, particularly in poorly ventilated areas. Carbon monoxide emission by automobiles in closed garages and by unvented space heaters results in numerous deaths each year. Following inhalation, carbon monoxide binds to hemoglobin, displacing oxygen and forming carboxyhemoglobin. This decreases the oxygen-carrying capacity of the blood and impairs the blood cells' ability to release bound oxygen. The resulting hypoxia is the principal mechanism of carbon monoxide toxicity.

Nitrogen oxides, principally nitrogen dioxide, and ozone are classified as oxidizing pollutants. The major source of nitrogen dioxide is the internal combustion engine. Photolysis of nitrogen dioxide by ultraviolet radiation liberates oxygen atoms, which can then combine with molecular oxygen to form ozone. Both gases cause irritation of the deep lung and can result in increased susceptibility to respiratory infection, pulmonary edema, and impaired lung function.

Oxides of sulfur (principally sulfur dioxide) are generated during the burning of fossil fuels, most notably coal, and are classified as reducing pollutants because of

TABLE 7.2 Some Specific Antidotes for Toxic Drugs and Chemicals

Agent	Antidote	Mechanism of Action
Drugs		
Heparin	Protamine	Ionically neutralizes heparin
Acetaminophen	*N*-acetylcysteine	Inactivates toxic metabolite
Narcotics and opioids	Naloxone	Displaces drugs from receptors
Insulin, oral hypoglycemics	Glucose	Reverses glucose depletion
Chemicals		
Methanol	Ethanol	Blocks metabolism to toxic metabolite
Ethylene glycol	Ethanol	Blocks metabolism to toxic metabolite
Botulinum toxin	Antiserum	Immunologically neutralizes toxicant
Cyanide	Sodium nitrate	Forms methemoglobin, which binds cyanide, thus removing it from active pool
	Sodium thiosulfate	Provides a source of sulfur to detoxify cyanide
Organophosphates	Atropine	Displaces acetylcholine from its receptor
	Pralidoxime	Reactivates acetylcholinesterase
Carbon monoxide	Oxygen	Displaces toxicant from hemoglobin
Nitrites	Methylene blue	Reduces methemoglobin to hemoglobin
Arsenic	Dimercaprol	Forms inactive complex with metal
Iron	Deferoxamine	Forms inactive complex with metal
Lead	Calcium disodium edetate	Forms inactive complete with metal
Warfarin	Vitamin K_1	Stimulates coagulation factor synthesis

TABLE 7.3 A General Approach to the Treatment of Acute Poisoning

- Provide emergency management
  - Perform cardiopulmonary resuscitation if necessary
  - If victim is in a coma, administer naloxone hydrochloride (in narcotic or opioid overdose) and 50% glucose (in case of insulin shock)
- Evaluation
  - Identify the toxic agent and dose if possible
  - Assess vital signs and level of consciousness
  - Conduct laboratory tests
- Reduce absorption and enhance removal of poison
  - Irrigate eyes and skin if involved
  - Induce emesis with syrup of ipecac if victim is conscious and has not ingested acids, alkali, hydrocarbons, or petroleum distillates
  - Perform gastric lavage if victim is unconscious or in some instances when conscious
  - Administer activated charcoal to bind poison
  - Administer milk or water if alkali, acid, hydrocarbon, or petroleum distillates have been ingested
  - Administer antidote, if one exists, that is specific for the poison
  - Consider forced diuresis, urine acidification, or alkalinization if specific antidotes are not available
  - Hemodialysis or charcoal hemoperfusion may be appropriate for rapid elimination if antidotes are not available

the types of reactions they undergo. Particulate matter associated with most emissions promotes the conversion of sulfur dioxide to the more toxic sulfuric acid and facilitates deposition in the deep lungs. The acid can cause bronchospasm and lung damage, including alveolitis. Asthmatic episodes can be exacerbated by sulfur dioxide and sulfuric acid.

Particulates

Industrial processes, such as milling and mining, construction work, and the burning of wood or fossil fuel, generate particulates that can be directly toxic or can serve as vectors for the transfer of bound material, such as sulfuric acid, metals, and hydrocarbons, into the lungs. Natural products such as pollen, anthrax spores, and animal dander can elicit toxic reactions on inhalation or skin contact. The inhalation of asbestos, silica, or coal dust can cause pneumoconiosis, which may develop into serious lung disease. The size of the particle, ventilatory rate, and depth of breathing will determine the extent of pulmonary deposition.

Food Additives and Contaminants

Thousands of substances are added to foods to enhance their marketability (appearance, taste, texture, etc.), storage properties, or nutritive value, any of which may cause toxicity in susceptible individuals (Table 7.4). Microbial or fungal contamination of food, either during processing or storage, can introduce potent toxins into food.

Metals

Characteristics of toxicity for a number of metals are presented in Table 7.5. While the exact tissue and molecular site of the toxic action of each metal is different, toxicity generally results from interaction of the metal with specific functional groups on macromolecules in the cell. These groups include sulfhydryl, carboxyl, amino, phosphoryl, and phenolic moieties. Interactions of such groups with metals can lead to disruption of enzyme activities and transport processes and eventually

TABLE 7.4 Examples of Toxic Food Additives and Contaminants

Agent	Type	Source and Effects
Nitrate, nitrite	Preservative	Present in vegetables; form carcinogenic nitrosamines
Sulfites	Preservative	Antioxidants used to reduce spoilage; can produce allergic reactions, especially in asthmatics
Tartrazine	Food color	Can cause urticaria in sensitive individuals
Botulinum toxin	Contaminant	Produced by *Clostridium botulinum* in improperly canned vegetables; nausea, vomiting, diarrhea, paralysis
Salmonella	Contaminant	Improper processing of food allows *Salmonella* from intestinal tract to survive; the most common cause of gastroenteritis
Aflatoxins	Contaminant (mycotoxin)	Produced by *Aspergillus flavus,* especially grains, corn, and peanuts; carcinogenic and hepatotoxic
Ochratoxin, citrinin	Contaminant (mycotoxin)	Produced by *Penicillium* strains; nephropathy (endemic Balkan nephropathy)
Polybrominated biphenyls (PBBs)	Contaminant	Fire retardant inadvertently substituted for feed supplement in Michigan; livestock loss, undetermined effect on human health

TABLE 7.5 Characteristics of Toxicity of Selected Metals*

Metal	Selected features of toxicity
Arsenic	
Inorganic	Diarrhea, hyperkeratosis, garlic breath, Mees' lines on fingernails
Arsine gas	Hemolysis
Beryllium	Pneumonitis, chronic granulomatous disease, contact dermatitis
Cadmium	Pneumonitis, emphysema, kidney damage
Iron	Gastric irritation, liver damage
Lead	Peripheral and central neurotoxicity, kidney damage, anemia
Mercury	Pneumonitis, neuropsychiatric toxicity (excitability, emotional instability, depression, insomnia), motor dysfunction (tremors)
Elemental	
Organic	Sensory neuropathy (dysarthia, paresthesia, constriction of visual field, loss of taste, hearing, smell), motor dysfunction (tremors)
Inorganic	Kidney damage, irritation of oral cavity and gastrointestinal tract

*Representative toxicities are presented; for most metals, other symptoms of toxicity may be demonstrated. Nature of the toxicities is dependent on level of exposure, whether the exposure is acute or chronic, and the route of exposure.

to loss of such cellular functions as energy production and ion regulation. In general, toxicity is related to the form of the metal (inorganic, organic, or elemental), the route of exposure, and the route of excretion.

Solvents

Solvents are generally classified as aliphatic or aromatic, and either type may be halogenated, most commonly with chlorine. The toxicity of representative solvents is summarized in Table 7.6. Occupational exposure to solvents occurs in cleaning, degreasing, painting, and gluing. Exposure to solvents is generally through inhalation of vapors, although direct skin contact also occurs. The concentration of solvent in air is determined by the vapor pressure of the solvent, the ambient temperature, and the effectiveness of ventilation systems. These factors and the rate of pulmonary air exchange will affect the extent of exposure. Sniffing glue fumes is one form of substance abuse.

Solvents are generally lipid-soluble, and therefore they are readily absorbed across the skin. Once absorbed, they tend to concentrate in the brain, and CNS dysfunction is common at high exposures. Symptoms can range from confusion to unconsciousness. Solvents often undergo bioactivation and may cause systemic toxicity as a result of the formation of reactive intermediates.

Pesticides

Pesticides are chemicals used to eliminate unwanted organisms. Common targets for pesticides include insects, weeds (herbicides), fungi, and rodents. Poisoning from pesticides often affects professional exterminators, agricultural workers, and consumers (Table 7.7). More than half of the poisonings due to agricultural pesticides affect children.

Insecticides

The prototypical *organochlorine insecticide* is DDT. It was first used in World War II for vector control of malaria. The organochlorine insecticides are very stable in the environment. This persistence allows toxic concentrations to build up in nontarget organisms.

Organophosphate insecticides (e.g., malathion, parathion, diazinon) undergo metabolic activation to

TABLE 7.6 Toxicity of Selected Solvents

Solvent	Uses	Effect and Mechanism
Aliphatic solvents		
Chloroform	Drug purification	Hepatic centrilobular necrosis, likely from reactive metabolites
Trichloroethylene	Degreasing, dry cleaning	Sensitizes the myocardium to epinephrine, interferes with alcohol metabolism
Methylene chloride	Degreasing, paint stripping, aerosol propellant	Metabolized to CO, resulting in formation of carboxyhemoglobin
Hexane, methyl n-butyl ketone	Wood glue, plastics manufacturing	Polyneuropathy from their metabolite, 2,5-hexanedione
Aromatic solvents		
Benzene	Petroleum product, adhesives and coatings	Leukemia, aplastic anemia, likely from reactive intermediates
Toluene	Adhesives	Cerebellar degeneration with repeated high-dose exposure (glue sniffing)

TABLE 7.7 Toxicity of Selected Pesticides

Class and Examples	Effect and Mechanism
Organochlorine insecticides	Neuronal hyperactivity; convulsions; impaired vision, concentration, and memory
DDT, chlordane, aldrin, heptachlor	Altered membrane permeability to Na^+, K^+
	Block repolarization by inhibiting Na^+, K^+-ATPase
	Block GABA-stimulated chloride uptake
Organophosphate insecticides	Bronchoconstriction and secretion, muscular weakness or paralysis,
Bromophos, chlorpyrifos, parathion, malathion, diazinon	CNS depression, including respiratory centers
	Inhibition of acetylcholinesterase (reversible or irreversible)
Carbamate insecticides	Same as organophosphate insecticides
Carbaryl	Inhibition of acetylcholinesterase (reversible)
Pyrethrin and pyrethroid insecticides	Neuronal hyperactivity, incoordination, tremors with hyperthermia, seizures
Pyrethrin I, II; fenvalerate, permethrin	Delayed inactivation of channels in excitable tissues, causing repetitive firing and at high doses, depolarization
	Block GABA-stimulated chloride uptake
Chlorophenoxy herbicides	Muscle weakness, aching, and tenderness; hypotonia
2,4-D; 2,4,5-T	
Bipyridyl herbicides	Delayed respiratory distress, fibrosis, and atelectasis
Paraquat, diquat	Gastrointestinal, liver, and kidney toxicity
	Formation of reactive oxygen species
Rodenticides	Block tricarboxylic acid cycle (fluoroacetates)
Compound 1080, warfarin, strychnine	Prevent blood clotting
	Induce seizures

ATPase, adenosine triphosphatase; GABA, γ-aminobutyric acid; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid.

yield an oxygenated metabolite that will react with the active site of acetylcholinesterase (AChE), resulting in irreversible enzyme inhibition. Symptoms of poisoning are due to excessive stimulation of cholinergic receptors. In cases of lethal poisoning in humans, death is from respiratory failure. Distal neuropathy of the lower limbs also has been seen.

The *carbamate insecticides* also inhibit AChE. The mechanism of inhibition is similar, but the reaction is reversible.

Herbicides and Rodenticides

Herbicidal activity generally consists of interference with plant-specific biochemical reactions. Thus, mammalian toxicity is generally low and not predictable from the mechanism of herbicidal action. In contrast, rodenticide target selectivity is not based on differences in biochemistry between humans and rodents but rather on differences in physiology or behavior, especially feeding behavior. For example, an emetic may be included in a rodenticide formulation to promote vomiting in humans who accidentally consume the product; rodents do not have a vomit reflex.

The *chlorophenoxy herbicides,* 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), were used in defoliating operations in Vietnam, and the adverse health effects of the contaminant 2,3,7,8-tetrachlorodibenzodioxin (dioxin) continue to be controversial.

The *bipyridyl herbicides* paraquat and diquat are broad-spectrum herbicides. As little as 10 mL of paraquat concentrate is lethal in adults. Paraquat damages the lungs and may result in the appearance of a respiratory distress syndrome appearing 1 or 2 weeks after poisoning. In contrast, diquat causes minimal lung damage because it does not selectively accumulate in the lung. Acute renal failure, liver toxicity, and gastrointestinal damage are sequelae to diquat poisoning.

Warfarin, a coumarin anticoagulant, is incorporated into cornmeal for use as a rat poison. Repeated exposure results in sufficient inhibition of prothrombin synthesis to cause fatal internal hemorrhage.

APPLICATIONS OF TOXICOLOGICAL PRINCIPLES

Health professionals may be asked to provide an opinion of the cause and effect relationship between exposure to a xenobiotic and an adverse health effect ranging from symptoms of toxicity to death. Certain principles, including an assessment of temporality, should be considered in such an evaluation. Do the

symptoms or disease follow the exposure within a proper time frame? In addition, an evaluation of the toxicological properties of the substance should be included. Does the xenobiotic possess properties that can logically be expected to cause the damage or disease in question? For many chemicals, the qualitative consideration of the types of symptoms, injury, or disease that may occur after exposure can be predicted based on the available toxicological data or known biological activity of the chemicals. If the toxicity or disease does not fit into this known profile, a causal relationship between the chemical and the problem should be questioned further. If the xenobiotic has the appropriate toxicological properties, quantitative consideration of the total dose received must be carefully evaluated. Was the dose high enough to produce health effects? Finally, the possibility of alternate causes of the health problems must be investigated carefully. Are there other more logical explanations for the symptoms? If appropriate, drug side effects should be considered as a possible cause of the adverse health effects. Lifestyle and avocations also must be evaluated. Alternate causation is ideally evaluated by a thorough and frequently tedious review of complete medical, occupational, and social records of the patient.

Study Questions

1. A dental technician begins to display symptoms, including tremors, depression, and insomnia. Which of the following chemicals present in the workplace may be responsible for the symptoms?
(A) Solvents used in dental adhesives
(B) Fluoride used in oral rinses
(C) Mercury used in the preparation of amalgams
(D) Lidocaine used as an anesthetic

2. A patient learned recently that she is about 5 weeks pregnant, but because she has been suffering from depression, she asks her physician for a prescription for a drug to treat this problem. Her physician refuses to prescribe a drug at this time because he is concerned that the fetus is at risk for toxicity from in utero exposure to the drug. What is the most likely adverse outcome if the woman began taking the drug at this time?
(A) The fetus would die.
(B) A teratogenic response would occur in the fetus.
(C) The growth of the fetus would be retarded.

3. Exposure to air pollutants can have adverse effects on human health. Exposure to one such pollutant, carbon monoxide, can result in which of the following conditions?
(A) Irritation of the deep lungs because of damage to the epithelium
(B) An increased susceptibility to respiratory infection due to impairment in phagocyte function
(C) Exacerbation of asthmatic episodes because of bronchoconstriction
(D) Hypoxia due to displacing oxygen from hemoglobin

4. A 4-year-old boy is taken to the emergency department by his parents in the afternoon the first Saturday in June. The family is moving into a house. They found the boy almost unconscious in a corner in the garage, having difficulty breathing. He was surrounded by chemical containers left by the previous owners. The labels had deteriorated and couldn't be read. On examination you noted bronchoconstriction and profuse airway secretion, weakness of the muscles, difficulty breathing, and CNS depression. Which of the following chemicals do you suspect was involved?
(A) Compound 1080
(B) Pyrethrin
(C) Parathion
(D) Diquat

5. You are a staff physician at a major chemical manufacturing company. A worker on the maintenance crew has complained of being light-headed and tired occasionally at work and that if it occurs, it clears up after he leaves for the day. He was asked to write down where he had worked on the days this occurred; these are listed below. In which of these areas is he most likely to have exposures that would cause these symptoms?
(A) Herbicide production area
(B) Insecticide packaging area
(C) Label printing area
(D) Kitchen area of the cafeteria

6. You have been told there has been a large spill at the chemical company but in the confusion you weren't told where it occurred. The exposed workers were agitated and irritable and said to be having difficulty walking in a coordinated manner. Some feel quite hot as if they are burning up, and one had a seizure. Which area do you suspect had the spill?
(A) Herbicide production area
(B) Insecticide packaging area
(C) Label printing area
(D) Kitchen area of the cafeteria

ANSWERS

1. **C.** The symptoms are characteristic of a person chronically exposed to vapors released from elemental mercury. Since the dental technician may handle elemental mercury, including mishandling, the symptoms presented may occur. While the technician may be exposed to solvent vapors released from dental adhesives, the symptoms are not characteristic of this type of exposure. Fluoride toxicity would not be expected because these are not symptoms associated with fluoride ingestion, and the patient and not the technician would be most likely exposed to quantities high enough to cause any symptoms. The technician has little exposure to lidocaine, and the symptoms are not typical of lidocaine toxicity.
2. **B.** The fetus is particularly vulnerable to teratogens between days 25 and 40 of gestation, and this patient is within this window of time. The fetus is at much greater risk for death if exposure occurs during the first 2 weeks of gestation. Growth retardation of the fetus is the principal outcome if exposure to drugs occurs during the last 6 months of gestation.
3. **D.** Carbon monoxide can cause hypoxia because it reduces the oxygen carrying capacity of the blood by displacing oxygen from hemoglobin as well as impairing the erythrocyte's ability to release oxygen. Particulate air pollutants and reactive air pollutant gases, such as ozone and nitrogen dioxide, can damage the lungs, including increasing susceptibility to respiratory infection and irritation of the deep lungs, while exposure to sulfur dioxide can exacerbate asthmatic episodes.
4. **C.** Bronchoconstriction and secretion and muscular weaknesses occur from acetylcholine accumulation after inhibition of acetylcholinesterase. Parathion is an organophosphate insecticide that inhibits acetylcholinesterase, and it is readily available. Poisoning with compound 1080 (fluorocitrate) inhibits mitochondrial respiration and causes seizures and cardiac arrhythmias. Pyrethrin and pyrethroids are generally low in toxicity and few poisonings have been reported; however, seizures are a symptom. Diquat causes gastrointestinal disturbances.
5. **C.** Symptoms that occur during the work day and clear up after work are often due to inhalation exposure of volatile or aerosol materials. The solvents used in printing inks cause light-headedness and sedation. The symptoms are not those of herbicide exposure and insecticide exposure.
6. **B.** Spills cause acute high-dose exposures. The symptoms are referable to an acute high exposure to an organochlorine or pyrethroid insecticide. While organochlorine pesticides are not used in this country, they are manufactured for export. An acute high exposure to herbicide would be primarily irritation of skin and mucous membranes. The solvents in printing ink would cause CNS depression.

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CASE Study A Case of Poisoning

A 5-year-old girl is taken to the doctor's office by her mother following a conference with her kindergarten teacher. The teacher is concerned because compared to her kindergarten classmates, she is hyperactive, restless, and easily distracted. Recent testing revealed that the child's vision was normal but hearing acuity was below normal. Recently the child has complained of abdominal pain and has had occasional constipation. About 3 years ago the parents moved into a 75-year-old house in the inner city and have been renovating it extensively. Within the past year, the parents separated and the father moved out of the house.

1. What is the most likely cause of the child's problems?
2. What tests should be run to help in the diagnosis?
3. What is the best treatment option?

ANSWERS:

1. These symptoms are consistent with childhood lead poisoning. The paint used originally in older homes usually contains lead. Since the parents have been renovating this older home, it is likely that they have removed some of the older paint, generating lead-containing dust and paint chips. Small children may exhibit pica, which is the compulsive eating of nonfood items, and this can occur during times of stress, such as the separation of parents. If the parents have not cleaned up adequately after removing the paint, it is probable that the child has had the opportunity to consume substantial quantities of lead.
2. Measuring the child's blood lead level will be very useful in assessing the possibility of lead poisoning. There is evidence that at blood lead levels of about 10 μg/dL, children are at risk for developmental impairment. Other tests that may be useful include examination for microcytic anemia and erythrocyte stippling and radiographic examination of the long bones for lead lines.
3. Several chelators can effectively lower the child's blood lead level. These include dimercaprol, edetate calcium disodium ($CaNa_2EDTA$) and succimer. Protocols are available for using the chelators depending upon the severity of symptoms.