

Cyanide (21)

acetylcholine at the postjunctional membrane of muscle fibers, reducing or blocking acetylcholine's transmitter action, are used as "muscle relaxants."

#### 6.2.2.2b Botulinum Toxins

Botulinum toxins are heat-labile neurotoxins produced by the microorganism *Clostridium botulinum*. Botulinum toxin binds irreversibly to the axon terminal, thus preventing release of acetylcholine. Botulism, one of the most dreaded of the bacterial foodborne diseases because it is so frequently fatal, results primarily from eating improperly preserved canned food in which the bacterium grew and produced the toxin.

#### 6.2.2.2c Tetrodotoxin

Tetrodotoxin has been responsible for deaths in humans as a result of consumption of improperly prepared puffer fish (Tetraodontidae). In Japan, puffer fish, known as fugu, are considered a great delicacy and are widely sold in restaurants. The toxins are found in the roe, liver, and skin of puffer fish, and workers must be specially trained in the preparation of this fish. It is thought that tetrodotoxin selectively blocks sodium channels along the nerve axon, preventing the inward sodium current of the action potential while leaving unaffected the outward potassium current. Approximately 60% of all cases of poisoning due to puffer fish result in death.

#### 6.2.2.2d Batrachotoxin

Batrachotoxin has been used as an arrow poison and is found in the skin of the South American frog *Phylllobates aurotaenia*. The action of batrachotoxin is opposite to the effects of tetrodotoxin on the sodium channels in that batrachotoxin increases the permeability of the resting membranes to sodium ions.

### 6.2.3 Inhibitors of Oxidative Phosphorylation

#### 6.2.3.1 Electron Transport Inhibitors

##### 6.2.3.1a Cyanide

Cyanide is one of the most rapidly acting of all poisons. It is readily absorbed through all routes, including skin and mucous membranes, and by inhalation. Ingestion of very small amounts of cyanide causes death within minutes or hours, depending on the route of exposure. Inhalation of hydrogen cyanide gas leads to death in a few minutes. The chemist, Karl Wilhelm Scheele, discoverer of hydrocyanic acid (prussic acid), was killed by its vapors. Cyanide is a common component in some rat and pest poisons, silver and metal polishes, ore refining processes, photographic solutions, and fumigating products. Cyanide is also present in the seeds of apples, peaches, plums, apricots, cherries, and almonds in the form of amygdalin, a cyanogenic glycoside.

Amygdalin, also an ingredient of Laetrile, an alleged anticancer drug, is composed of glucose, benzaldehyde, and cyanide moieties. Cyanide can be released from the glucoside by the action of  $\beta$ -glucosidase (emulsin), present in the pulp from crushed seeds and in mammalian intestinal microflora. For this reason, amygdalin may be much more toxic orally than intravenously (IV).



Laetrile has been responsible for cases of human cyanide poisoning, as have apricot kernels, the latter being widely available in health food stores.

Another potential source of cyanide poisoning is the drug sodium nitropruside, which is used in the treatment of hypertension. Overdoses of this drug have led to cyanide toxicity.

Cyanide exerts its toxic effect by interrupting electron transport in the mitochondrial cytochrome chain at the cytochromes  $a-a_3$  step (Figure 6.6). These cytochromes, which are isolated as a single, large protein molecule containing both cytochromes  $a$  and  $a_3$ , are referred to as cytochrome  $a_3$  or cytochrome oxidase. Cyanide complexes with the heme of cytochrome  $a_3$ , thus preventing the heme's binding with oxygen. As a result of cyanide inhibition, electron transfer from cytochrome  $a_3$  to molecular oxygen is blocked and cell death occurs. Death from cyanide poisoning is due to respiratory arrest.

The symptoms, which occur in quick succession, are salivation, giddiness, headache, palpitation, difficulty in breathing, and unconsciousness. Typically, cyanide has a bitter, burning taste; in addition, there is a faint odor of almonds. It has been estimated, however, that 20–40% of the population are genetically unable to detect the cyanide odor and thus are insensitive to this property.

The accepted treatment for cyanide poisonings is a three-step procedure. First, amyl nitrite is given to the patient by inhalation followed by IV administration of sodium nitrite. These chemicals oxidize the heme iron of hemoglobin from the ferrous ( $Fe^{2+}$ ) to the ferric ( $Fe^{3+}$ ) state; the resulting greenish-brown to black pigment is known as methemoglobin. The ferric iron of the methemoglobin combines with  $CN^-$  from the plasma, causing dissociation of cyanide already bound to cytochrome oxidase. After administration of nitrite, sodium thiosulfate is injected. Thiosulfate provides a substrate for the enzyme rhodanese (thiosulfate sulfur transferase) that catalyzes the conversion of cyanide to thiocyanate, which is nontoxic and readily excreted (Figure 6.6). For additional discussion of cyanide toxicity and treatment, see Section 11.4.2.2.

#### 6.2.3.1b Other Inhibitors

Azide, like cyanide, inhibits cytochrome oxidase and produces similar biochemical lesions. Hydrogen sulfide is also an inhibitor of cytochrome oxidase in vitro and is thought to have the same mode of action as hydrogen cyanide.

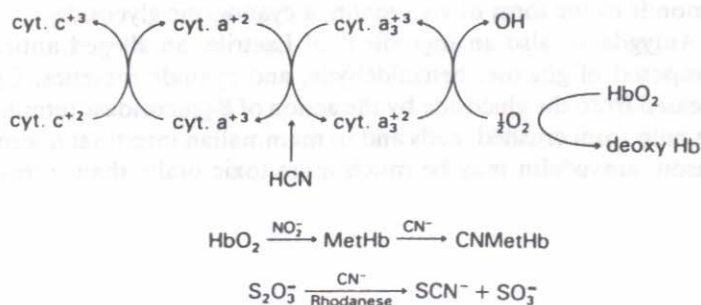


FIGURE 6.6.  
Cyanide poisoning and treatment.

TABLE 11.3  
Examples of Therapy Related to Mode of Action of Specific Toxicants

Mechanism	Poison	Therapeutic Agent
A. Metabolism of toxicant		
Competition for activation reaction	Methanol	Ethanol
Stimulation of detoxication mechanism	Cyanide	Thiosulfate
B. Direct effect of toxicant		
Complexing agents	Lead	CaEDTA
C. Effects on receptor site		
Competition for receptor	CO	O <sub>2</sub>
Receptor blocking	Carbaryl	Atropine
D. Repair mechanism		
Reversal of toxic effect	Parathion	2-PAM
	Nitrite	Methylene blue
Bypass of toxic effect	Methotrexate	Thymidine adenine and glycine
E. Facilitation of excretion		
Administration of physiologically similar molecules	Bromide	Chloride

2-PAM, *N*-methypiridinium 2 aldoxime.

#### 11.4.2.1 Methanol

Methanol is a common cause of poisoning and results in a number of deaths annually. The acute effects appear to be due to the formation of formaldehyde by the action of alcohol dehydrogenase and subsequently formic acid by the action of aldehyde oxidase. Formaldehyde has been shown to affect the retina and is probably the cause of the blindness associated with methanol poisoning, whereas formic acid causes the acute acidosis also associated with this toxicant.

Various nonspecific treatments include induction of vomiting with syrup of ipecac and the use of gastric lavage; acidosis is countered by administration of sodium bicarbonate, and urine flow is maintained by oral or IV fluids. If the patient fails to respond to specific or nonspecific therapy, dialysis is performed.

The specific therapy for methanol poisoning is the administration of ethanol, initially orally and subsequently IV. The ethanol acts by competition for alcohol-metabolizing enzymes, thus permitting the excretion of methanol before it is activated to formaldehyde and formic acid. The toxicity of the acetaldehyde and acetic acid formed from ethanol is low as compared with that of formaldehyde and formic acid.

#### 11.4.2.2 Cyanide

Hydrogen cyanide and its salts have a variety of uses, and cyanide ion may be released metabolically from a number of secondary plant chemicals. It acts primarily by inhibiting cytochrome oxidase, thus blocking cellular respiration (see Section 6.2.3.1a). Other enzymes are also inhibited by cyanide, but the effects are relatively unimportant as compared with those caused by the rapid,



Cyanide P-4

Toxicant	Antidote
$\text{CH}_3\text{OH}$ methanol	$\text{C}_2\text{H}_5\text{OH}$ ethanol
$\text{NaCN}$ sodium cyanide	$\text{NaNO}_2$ sodium nitrite $\text{Na}_2\text{S}_2\text{O}_3$ sodium thiosulfate
$\text{Pb, Hg}$ lead, mercury	$\begin{array}{c} \text{CH}_2\text{SH} \\   \\ \text{CHSH} \\   \\ \text{CH}_2\text{OH} \end{array}$ Dimercaprol (BAL) $(\text{HOOCCH}_2)_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{COOH})_2$ EDTA $\begin{array}{c} \text{CH}_3 \\   \\ \text{H}_3\text{CC}-\text{CH}-\text{COOH} \\   \quad   \\ \text{SH} \quad \text{NH}_2 \end{array}$ Penicillamine
$\text{CO}$ carbon monoxide	$\text{O}_2$ oxygen
$(\text{C}_2\text{H}_5\text{O})_2\text{P}(=\text{S})\text{C}_6\text{H}_4\text{NO}_2$ parathion	$\begin{array}{c} \text{pyridine ring}-\text{CH}=\text{NOH} \\   \\ \text{N}^+-\text{CH}_3 \end{array}$ 2-PAM $\begin{array}{c} \text{O}-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{OH} \\   \\ \text{N-methylpiperidine ring} \end{array}$ atropine
$\begin{array}{c} \text{O} \\    \\ \text{OCNH}(\text{CH}_3) \\   \\ \text{naphthalene ring} \end{array}$ carbaryl	atropine
$\text{Br}^-$ bromide ion	$\text{Cl}^-$ chloride ion

FIGURE 11.1.

Toxicants and antidotes used in examples of specific therapy.

extensive, and high-affinity binding to cytochrome oxidase. Although the toxic dose is very small and the resultant poisoning is rapid and often fatal, chronic poisoning due to prolonged exposure to very small amounts is known.

Emergency measures for either inhaled or ingested cyanide include amyl nitrite, artificial respiration, and 100%  $\text{O}_2$ . In the case of ingestion, gastric lavage may also be used.

There are two forms of specific therapy. Sodium nitrite is administered to convert hemoglobin to methemoglobin. The latter then combines with cyanide to form cyanomethemoglobin. Although the affinity of cyanide for methemoglobin is less than its affinity for cytochrome oxidase, the large amount of hemoglobin available makes this a useful therapy. Methemoglobinemia itself is hazardous, however, and the nitrite dose must be so calculated to cause no more than 25–40% conversion of hemoglobin. In the second form of specific therapy, thiosulfate is administered to provide a sulfur donor for the reaction, catalyzed by the enzyme cyanide-thiosulfate sulfur transferase, which converts cyanide to thiocyanate ( $\text{CN}^-$  to  $\text{SCN}^-$ ). Thus, the two specific therapies represent one case in which there is removal from the site of action by competition with another binding site, and one in which a detoxication mechanism is stimulated by providing a reactant that is normally rate-limiting in vivo. When these two specific antidotes are assessed in an experimental setting (eg, by their effect on the LD50 for cyanide) they are clearly synergistic, being much more than additive in their effect.

#### 114.2.3 Heavy Metals (Lead and Mercury)

Although chronic lead poisoning is thought of as the most common and dangerous form, particularly among children, acute lead poisoning is also a hazard. In acute lead poisoning, the unabsorbed lead compound must be removed either by gastric lavage with dilute magnesium or sodium sulfate solution or by emesis. Subsequently, urine flow must be maintained, and chelation therapy must be started. Dimercaprol and CaEDTA both function by chelating the lead and rendering it excretable. These two drugs are given by injection; subsequently, penicillamine can be given orally. The treatment is monitored by following blood and urine lead concentrations.

Inorganic mercury, particularly in the form of mercuric salts, can be acutely toxic or can give rise to chronic toxicity. In acute poisoning, gastric lavage or emesis is used to remove unabsorbed material. Subsequently, dimercaprol is used to complex the mercury and render it excretable. Dialysis can be used to speed elimination if necessary. Dimercaprol is also used to treat chronic mercury poisoning.

Organic compounds of heavy metals, such as tetraethyl lead and methyl mercury, can also cause serious poisoning. They differ from the inorganic ions in uptake, toxicokinetics, mode of action, and therapy and should be treated separately.

#### 114.2.4 Carbon Monoxide

Carbon monoxide (CO) is a common cause of poisoning, both deliberate, as in suicide attempts, and accidental. CO is produced by the incomplete combustion of fossil fuels, in automobiles, in industrial machinery, in home furnaces, etc., and exerts its toxic effects by binding reversibly, but with high affinity, to hemoglobin. It not only forms carboxyhemoglobin, thus occupying sites normally occupied by  $\text{O}_2$ , but also increases the affinity of unbound sites for  $\text{O}_2$ , thus impairing the release of  $\text{O}_2$  to the tissues. Because the affinity of CO is 250 times that of  $\text{O}_2$ , it is imperative to remove the victim from the source of CO.

