

# Chapter 10

## CYANIDE POISONING

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## INTRODUCTION

Cyanide, long considered a toxic, deadly substance, has been used as a poison for thousands of years. It was not highly successful as a chemical warfare agent in World War I, possibly because of the way it was delivered. The effects of a high dose of cyanide are quick, and death occurs within minutes. Antidotes are effective if administered in time.

Cyanide is ubiquitous. It is present in some foods,

in the products of combustion of synthetic materials, and is widely used in industry. Much of the cyanide used is in the form of salts, such as sodium, potassium, or calcium cyanide. The cyanides of military interest are the volatile liquids hydrocyanic acid (hydrogen cyanide, HCN; North American Treaty Organization [NATO] designation: AC) and cyanogen chloride (NATO designation: CK) (Table 10-1).

**TABLE 10-1**  
**CHEMICAL, PHYSICAL, ENVIRONMENTAL, AND BIOLOGICAL PROPERTIES OF CYANIDES**

Properties	Hydrogen Cyanide (AC)	Cyanogen Chloride (CK)
Chemical and Physical		
Boiling Point	25.7°C	12.9°C
Vapor Pressure	740 mm Hg	1,000 mm Hg
Density:		
Vapor	0.99 at 20°C	2.1
Liquid	0.68 g/mL at 25°C	1.18 g/mL at 20°C
Solid		Crystal: 0.93 g/mL at -40°C
Volatility	1.1 × 10 <sup>6</sup> mg/m <sup>3</sup> at 25°C	2.6 × 10 <sup>6</sup> mg/m <sup>3</sup> at 12.9°C
Appearance and Odor	Gas: Odor of bitter almonds or peach kernels	Colorless gas or liquid
Solubility:		
In Water	Complete at 25°C	6.9 g/100 mL at 20°C
In Other Solvents	Completely miscible in almost all organic solvents	Most organic solvents (mixtures are unstable)
Environmental and Biological		
Detection	ICAD; M254A1 kit	M256A1 kit
Persistence:		
In Soil	< 1 h	Nonpersistent
On Materiel	Low	Nonpersistent
Skin Decontamination	Water; soap and water	Water; soap and water
Biologically Effective Amount:		
Vapor (mg • min/m <sup>3</sup> )	LC <sub>50</sub> : 2,500–5,000 (time-dependent)	LC <sub>50</sub> : 11,000
Liquid (mg/kg)	LD <sub>50</sub> (skin): 100	—

ICAD: individual chemical agent detector

LC<sub>50</sub>: the vapor or aerosol exposure [concentration • time] that is lethal to 50% of the exposed population

LD<sub>50</sub>: the dose that is lethal to 50% of the exposed population

## HISTORY AND USE OF CYANIDE

Although substances containing cyanide had been used for centuries as poisons, it was not until 1782 that cyanide itself was identified. It was first isolated by the Swedish chemist Scheele, who later may have died from cyanide poisoning in a laboratory accident.

### Military Uses

Since the days of ancient Rome, cyanide and the derivatives of this highly toxic substance have been used as weapons.<sup>1</sup> Nero used cherry laurel water, which contains cyanide as its chief toxic component, to poison members of his family and others who displeased him. Napoleon III proposed the use of cyanides to enhance the effectiveness of his soldiers' bayonets during the Franco-Prussian War.

During World War I, in late 1915 and early 1916, the French were the only proponents for using cyanide and its derivative, hydrocyanic acid. This was made by distilling a concentrated solution of potassium cyanide with dilute sulfuric acid. Its use, however, proved to produce less than its desired effect. A highly volatile gas and lighter than air, hydrocyanic acid persisted for only a few minutes in the open air; this made it difficult to disperse a lethal concentration (also, the munitions used had a small payload). The effects of cyanide were not cumulative. In addition, the Germans, on learning of its use, equipped their troops with a mask that was capable of filtering out the gas. These combined factors made hydrocyanic acid less effective as a weapon.

About September 1916, the French tried another cyanide-based poison, cyanogen chloride, which is heavier and less volatile than hydrocyanic acid and which had a cumulative effect on its victims. Cyanogen chloride was produced by chlorinating a saturated solution of potassium cyanide at 0°C (32°F). Its toxicity was similar to that of hydrocyanic acid, but cyanogen chloride was more effective at low concentrations (it irritated the eyes and lungs). Cyanogen chloride also had a delayed toxic effect similar to such lung irritants as chlorine and phosgene. At high concentrations, cyanogen chloride is capable of killing by rapidly paralyzing the respiratory system's nerve center.<sup>2</sup>

At about the same time that the French launched cyanogen chloride, the Austrians introduced their own poisonous gas, which was derived from potassium cyanide and bromine. The resulting cyanogen bromide was highly volatile, yet it had only a

quarter of the volatility of hydrocyanic acid and was less toxic. Cyanogen bromide had a strong irritating effect on the conjunctiva and on the mucous membranes of the respiratory system; however, because it corroded metals and was unstable in storage (gradually polymerizing into a toxicologically inert substance), the Austrians abandoned its use.<sup>2</sup>

During World War II, the Nazis employed hydrocyanic acid adsorbed onto a dispersible pharmaceutical base (Zyklon B) to exterminate millions of civilians and enemy soldiers in the death camps.<sup>3,4</sup> Zyklon B was a fumigant and rodenticide. One of its uses in the United States and other countries was to rid ships of rodents.

In the late 1980s, reports indicated that cyanide-like agents may have been used against the inhabitants of the Syrian city of Hama<sup>5</sup> and the inhabitants of the Kurdish city of Halabja, Iraq,<sup>6</sup> and possibly in Shahabad, Iran, during the Iran-Iraq War.<sup>7</sup> Based on this recent history, acute cyanide poisoning continues to constitute a threat for U.S. soldiers in future conventional or nonconventional conflicts.

### Nonmilitary Uses

There has been little use of cyanide by the military; most of the information on cyanide poisoning has been from civilian experience in poisoning, fires, and industrial accidents. Most people probably contact cyanide in some form almost every day. Hundreds of thousands of tons of cyanide are manufactured annually in this country. Cyanide is used in many chemical syntheses, electroplating, plastics processing, gold and silver extraction, tanning, metallurgy, and as a fumigant. Cyanides are in some foods; are pyrolysis products of many substances; and have gained notoriety for their use in executions, homicides, and suicides.

Cyanide poisoning has been reported<sup>8</sup> from eating chokecherries, bitter almonds, and apricot pits. In addition, cyanide is found in lima beans and cassava beans and roots. Cassava is a staple in certain countries and is blamed for the high incidence of tropical ataxic neuropathy in those areas.

Combustion of synthetic products that contain carbon and nitrogen, such as plastics and synthetic fibers, releases cyanide. Cigarette smoke contains cyanide; the nonsmoker averages 0.06 µg/mL of cyanide in blood, whereas the smoker has 0.17 µg/mL.<sup>9</sup> The effects of cyanide and of carbon monoxide, also formed in fires, are additive because they

**TABLE 10-2**  
**BLOOD CYANIDE LEVELS IN VICTIMS OF SMOKE INHALATION**

Total Subjects	Blood Cyanide Levels (Mean ± SD)
Fire Victims* (N = 109)	
Survivors (n = 66)	21.6 ± 36.4 μmol/L ( <i>P</i> < .001)
Fatalities (n = 43)	116.4 ± 89.6 μmol/L ( <i>P</i> < .001)
Controls (N = 114)	5.0 ± 5.5 μmol/L

\*Of the 66 fire victims who survived, 9 had blood cyanide levels above 40 μmol/L and 3 had levels above 100 μmol/L. Of the 43 fire victims who died, 32 had blood cyanide levels above 40 μmol/L and 20 had levels above 100 μmol/L. Data source: Baud FJ, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med.* 1991;325(25):Fig 1:1763.

both contribute to tissue hypoxia by different mechanisms. The two gases are major causes of combustion-related fatalities.<sup>10</sup> In residential fires, cyanide poisoning may be more significant than has previously been appreciated. The short half-life of cyanide in blood contributes to the low concentrations of cyanide found in fire victims when blood is drawn after the victims reach the hospital.

From April 1988 through April 1989, a team of French investigators<sup>11</sup> collected samples—on the scene—from 109 victims of residential fires in and around Paris, France. The data they gathered were compared with data from a control group (N = 114) of individuals whose injuries were not caused by fire.

Blood cyanide concentrations were much higher in the fire victims than in the control group (Table 10-2), and victims who died had significantly higher levels (> 5-fold) than victims who survived. Contrary to what previous researchers have concluded, the results from this study “suggest that cyanide poisoning may prevail over carbon monoxide poisoning as the cause of death in some fire victims.”<sup>11(p1765)</sup> Therefore, military medical officers

need to be aware that victims of smoke inhalation from fires may be suffering the effects of cyanide poisoning, and might benefit from early antidotal cyanide therapy.

In addition, cyanide is used by governments, terrorists, corporations, and individuals to achieve various economic, beneficial, humanitarian, or harmful ends:

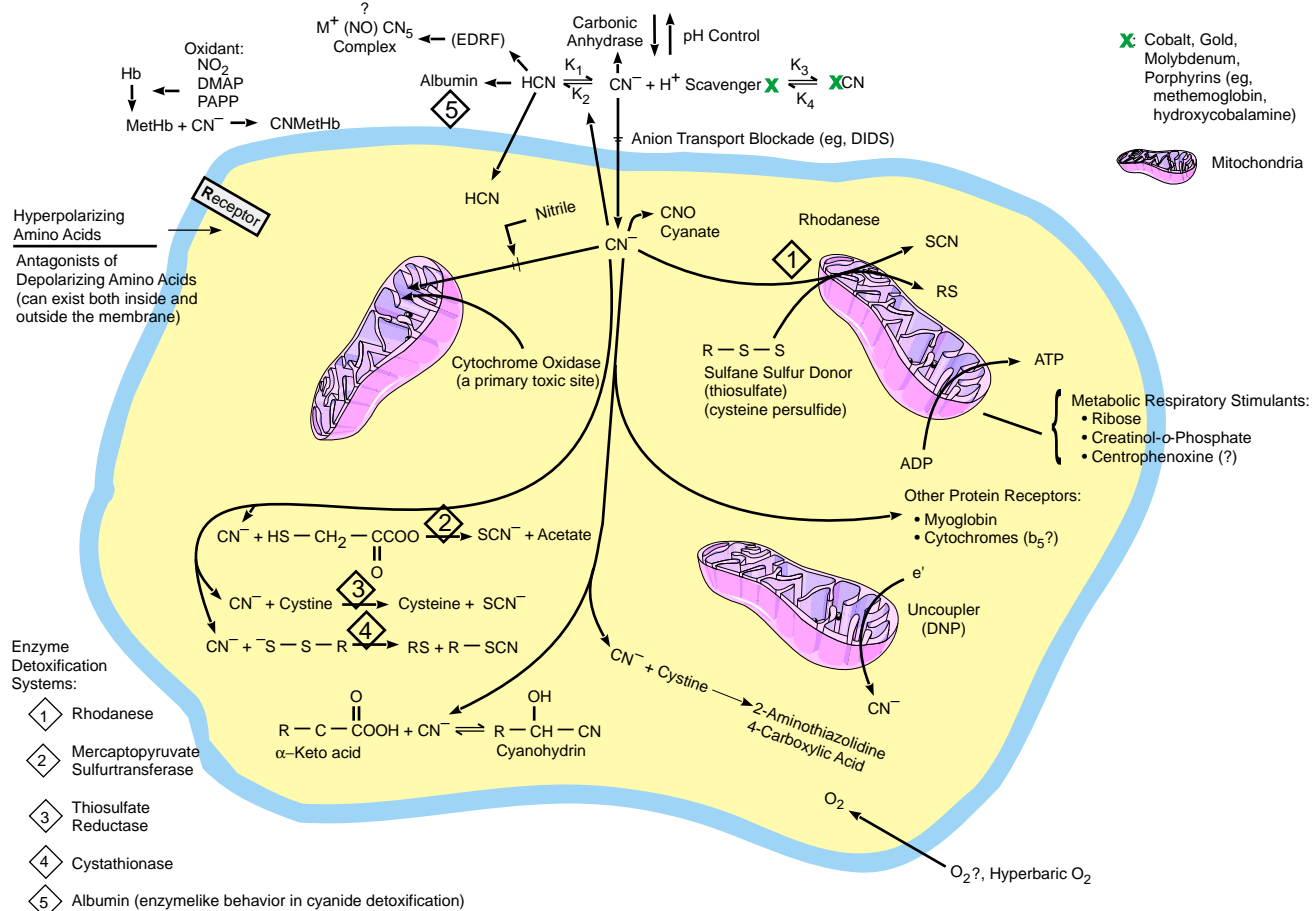
- Cyanide is the agent used in “gas chambers,” in which a cyanide salt is dropped into an acid to produce HCN. (These chemicals—an acid and a cyanide salt—were found in several subway restrooms in Tokyo, Japan, in the weeks following the release of nerve agents in Tokyo in March 1995.)<sup>12</sup>
- It was illicitly placed in bottles of Tylenol (acetaminophen, manufactured by McNeill Consumer Products Co., Fort Washington, Pa.) in the Chicago area in 1982, killing seven people.<sup>13</sup>
- In 1978 near Port Kaituma, Guyana, the followers of the Reverend Jim Jones drank a grape-flavored drink laced with cyanide, and more than 900 children and adult members of the People’s Temple committed mass suicide.<sup>14</sup>
- Furthermore, cyanide is a metabolic product of ingested Laetrile (an alleged cancer chemotherapeutic compound not available in this country) and may have been responsible for the deaths of some patients who took this substance.

Chronic ingestion of cyanide in the form of organic cyanogens is a public health problem in areas such as East Africa and Southeast Asia. Several common plants contain cyanogenic glycosides<sup>15,16</sup>; ingestion coupled with improper processing of such cyanogenic glycosides can result in death. Consumption of foodstuffs such as cassava result in tropical neuropathies in Africa<sup>17</sup> and in other diseases, such as tropical thyroid disease and tobacco amblyopia.

### BIOCHEMICAL BASIS FOR POISONING

Although cyanide is known to bind and inactivate several enzymes, it is thought to exert its ultimate lethal effect of histotoxic anoxia by binding to the active site of cytochrome oxidase (Figure 10-1), thereby stopping aerobic cell metabolism<sup>18,19</sup> after an initial effect on excitable tissue. The binding to

the cytochrome oxidase can occur over minutes. A more rapid effect appears to occur on neuronal transmission. No antagonists are known for the latter reaction, although it appears to be feasible to develop competitive antagonists for cyanide at a cytochrome oxidase-binding site.<sup>20</sup>



**Fig. 10-1.** The possible detoxification reactions for cyanide are shown for this hypothetical cell.

Cyanide can be removed by several processes before it can enter the cell. Perhaps of greatest importance is the formation of cyanomethemoglobin (CNMetHb), which is produced when the cyanide ion ( $\text{CN}^-$ ) reacts with MetHb. Methemoglobin is formed when hemoglobin (Hb) reacts with a variety of oxidants (eg, nitrite, dimethylaminopheno [DMAP], and *p*-aminopropiophenone [PAPP]). Cyanide may complex with endothelial-derived relaxing factor (EDRF, which is thought to be nitric oxide). Cyanide can interfere with the action of carbonic anhydrase and lower pH, thereby decreasing the concentration of  $\text{CN}^-$  in the extracellular space. Heavy metals (eg, gold, molybdenum, or cobalt salts) or organic compounds (eg, hydroxocobalamin) may scavenge  $\text{CN}^-$ , effectively removing it from the milieu of the cell. Finally, albumin can exhibit enzymelike behavior and use bound elemental sulfur<sup>1</sup> to detoxify cyanide. It is also theoretically possible to prevent entrance of cyanide ions into the cell by blocking transport mechanisms with substances such as DIDS.

At least four intracellular enzymes may be involved for cyanide detoxification. The generalized reactions of rhodanese, mercaptopyruvate sulfurtransferase, thiosulfate reductase, and cystathionase are shown within the cell.

Several broad classes of reactions may serve to ameliorate cyanide toxicity. They include but are not limited to the following. Metabolic respiratory stimulants may cross into the cell and stimulate adenosine triphosphate (ATP) production through a scavenger-ATP pathway (ie, ribose) or substrate augmentation (ie, creatinol-*o*-phosphate) or a free radical mechanism (ie, centrophenoxine). Hyperbaric oxygen or perhaps oxygen itself can reduce cyanide toxicity by competing with cyanide at some site (such as cytochrome oxidase in the mitochondria, which is thought to be a primary site for cyanide poisoning). Substances that act as hyperpolarizing agents or that antagonize depolarizing amino acids at ion channel receptors may ameliorate the convulsions from cyanide. Other possible reactions are formation of cyanohydrin with  $\alpha$ -keto acids, competitive blockade by other nitriles, and reaction with other sites such as myoglobin, cytochrome  $b_5$ , or other electron transport system (ETS) compounds (eg, dinitrophenol [DNP]).

(1) Source for this statement: Lieske CN, Clark CR, Zoefel LD, et al. Temperature effects in cyanolysis using elemental sulfur. *J Appl Toxicol.* 1996;16:171-175.

DIDS: 4,4'-diisothiocyano-2,2'-disulfonic stilbene

Cyanide is readily diffusible through epithelium. This property contributes to its lethal toxicity after inhalation of hydrogen cyanide (HCN) gas (the usual route of military exposure), ingestion of cyanide salts or cyanogens, or percutaneous absorption of cyanide from high-concentration solutions. Because cyanides are present at low concentrations in several naturally occurring environmental sources, it is not surprising that most animals have intrinsic biochemical pathways for detoxification of the cyanide ion.

The most important route of cyanide excretion is by formation of thiocyanate ( $\text{SCN}^-$ ), which is subsequently excreted in the urine.<sup>17</sup> Thiocyanate possesses a less inherent toxicological hazard than cyanide, cyanate, or isocyanate. Thiocyanate formation is catalyzed directly by the enzyme rhodanese (EC 2.8.1.1) and indirectly via a spontaneous reaction between cyanide and the persulfide sulfur products of the enzymes 3-mercaptopyruvate sulfurtransferase (EC 2.8.1.2)<sup>21</sup> and thiosulfate reductase (EC number unassigned) (see Figure 10-1). The mechanisms of all three enzymes<sup>22</sup> as well as the pharmacokinetics of thiocyanate formation<sup>23</sup> have been studied. Although 3-mercaptopyruvate functions to convert cyanide to this cyanate, its instability and self-oxidation at a basic pH may mask this effect.<sup>24</sup> The enzymatic routes are efficient but have an insufficient capacity for detoxification in acute poisoning because of lack of sulfur donors. The mitochondrial sulfurtransferase reactions are exploited by the administration of sodium thiosulfate (used in therapy and discussed later in this chapter) in the treatment of acute poisonings. It is still not known with any certainty, however, what specific endogenous sulfur sources participate in the formation of thiocyanate from cyanide.<sup>25</sup>

A minor route of metabolism is the oxidation of cyanide to cyanate ( $\text{CNO}^-$ ), which occurs via enzymatic and nonenzymatic pathways. The interaction of cystine and cyanide to form 2-amino thiazoline 4-carboxylic acid and its tautomer accounts for approximately 20% of cyanide metabolism. This increases with toxic doses of cyanide. However, the protection conferred by forming cyanate derivatives is limited because of the cell's inability to utilize oxygen during cyanide intoxication.

Combined, these metabolic routes detoxify 0.017 mg of cyanide per kilogram of body weight per minute in the average human. Cyanide is one of the few chemical agents that does not follow Haber's law, which states that the  $Ct$  (the product of concentration and time) necessary to cause a given biological effect is constant over a range of concentrations and times. For this reason, the  $LCt_{50}$  (the vapor

or aerosol exposure that is lethal to 50% of the exposed population) for a short exposure to a high concentration is different from a long exposure to a low concentration.

### Cyanide Pharmacokinetics and Pharmacodynamics

Cyanide appears to display first-order kinetics during the period of initial toxicity.<sup>23</sup> The volume of distribution for cyanide appears to change as the blood levels of the chemical change,<sup>26</sup> but these alterations probably reflect the marked intracellular sequestration of the molecule. Animal studies<sup>27,28</sup> show a differential disposition of inhaled HCN, with the highest tissue levels found in the lung, heart, and brain. These data seem to corroborate the evidence from other animal studies and from clinical reports that emphasize the importance of these organs in cyanide toxicity. Ingestion of cyanide results in much higher levels in the liver than does inhalation; this is a useful differential point in forensic investigations. Cyanide also has wide-ranging cardiovascular effects, including a poorly understood increase in vascular resistance in the early phases of poisoning<sup>29</sup> and a marked increase in cerebral blood flow in dogs.<sup>30</sup>

Data from rodent studies suggest that a single, acute administration of a cyanide salt leads either to death or to complete recovery. However, data from HCN inhalational studies in dogs, rabbits, monkeys, and humans suggests that death may be delayed for up to 8 days.<sup>31,32</sup> The neurological sequelae of cyanide intoxication may be delayed for up to a year.<sup>1</sup> These delayed changes in regional sensitivities of the brain are thought to be due to hypoxic stress and are analogous to those seen following sublethal carbon monoxide poisoning.

### Toxicity

Although they are generally considered to be very toxic substances, when compared with other lethal chemical warfare agents, cyanides are among the least toxic. The  $LCt_{50}$  for hydrogen cyanide (hydrocyanic acid) is generally stated to be 2,500–5,000  $\text{mg}\cdot\text{min}/\text{m}^3$ ; for cyanogen chloride, about 11,000  $\text{mg}\cdot\text{min}/\text{m}^3$ . (Comparable values for the nerve agents are 10–200  $\text{mg}\cdot\text{min}/\text{m}^3$ ; for sulfur mustard, 1,500  $\text{mg}\cdot\text{min}/\text{m}^3$ ; and for phosgene, 3,000  $\text{mg}\cdot\text{min}/\text{m}^3$ .)

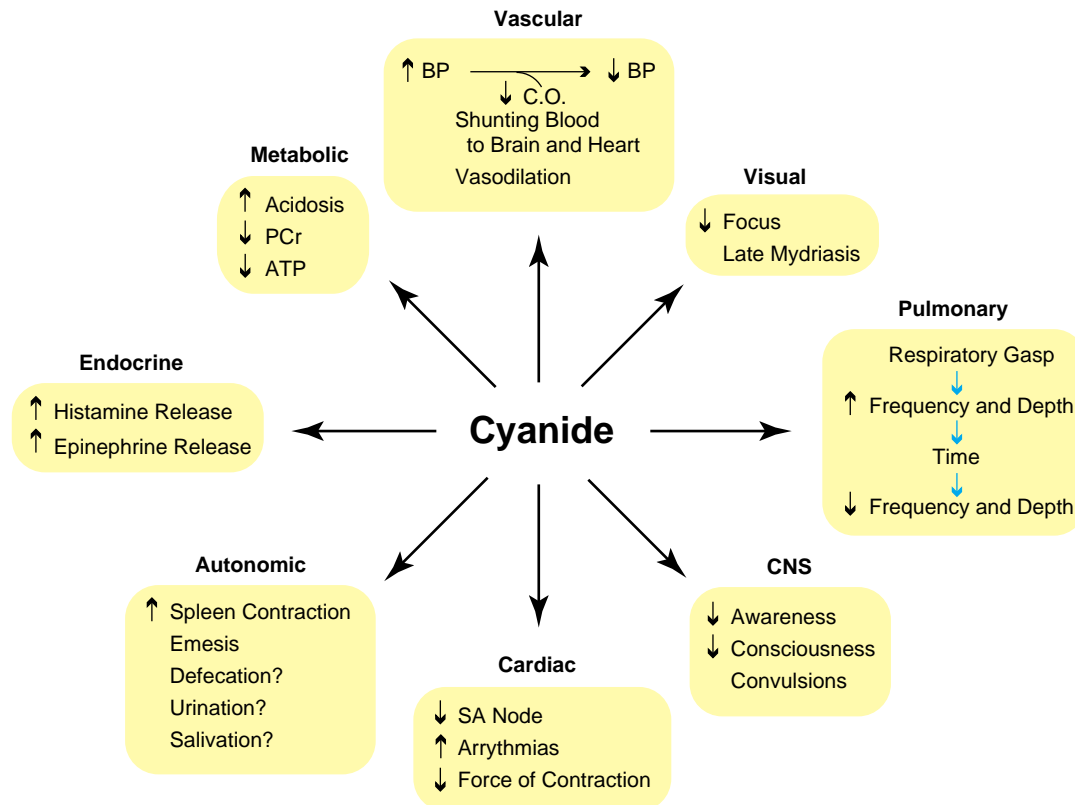
The estimated intravenous dose that is lethal to 50% of the exposed population ( $LD_{50}$ ) of hydrogen cyanide for man is 1.0 mg/kg, and the estimated  $LD_{50}$  for liquid on the skin is about 100 mg/kg.

## CLINICAL PRESENTATION AND MANAGEMENT

The effects from cyanide poisoning are those of progressive histotoxic tissue hypoxia (Figure 10-2). The symptoms, signs, and physical findings are directly related to the dose of cyanide, the route of exposure, and the type of cyanide compound. In addition to the effects described below, cyanogen chloride also produces irritation of the eyes and

mucous membranes similar to that produced by riot control agents.

On a military battlefield, casualties will be from exposure to cyanide gas; this can be fatal within minutes after exposure to high concentrations. An initial hyperpnea (15 sec after exposure), due to the effect of cyanide on the chemoreceptor bodies, is



**Fig. 10-2.** Cyanide can affect many functions in the body, including the vascular, visual, pulmonary, central nervous, cardiac, autonomic, endocrine, and metabolic systems. The toxicodynamic effects can vary depending on the dose, route and speed of administration, chemical form of the cyanide, and other factors including the gender, age, weight, stress level, and general physical condition of the recipient. Proceeding clockwise from the top of the diagram: **Vascular** effects for cyanide can include an initial transient increase, followed by a decrease, in cardiac output. Blood pressure falls as the cardiac inotropic effect decreases and as vasodilation occurs. **Visual** effects can include a decrease in the capacity to focus, with late-onset mydriasis secondary to hypoxia. One of the first **pulmonary** effects from cyanide is a respiratory gasp, which is caused by stimulation of chemoreceptor bodies near the aortic bifurcation. Hyperventilation follows this response. Over time (the response is dose-dependent, but seconds to minutes), the frequency and depth of breathing diminish. **Central nervous system** effects initially manifest as decreased awareness and increased release of enkephalins followed by loss of consciousness and convulsions. **Cardiac** effects after cyanide exposure are an increase in heart rate, then a decrease; both are accompanied by arrhythmias and negative inotropy. Cyanide produces a number of **autonomic nervous system** effects, based on the route and dose of the agent. Cyanide can also produce multiple **endocrine** effects including epinephrine and histamine release, and **metabolic** actions that decrease energy production by the inhibition of the use of cytochrome oxidase.

PCr: phosphocreatine

ATP: adenosine triphosphate

C.O.: cardiac output

closely followed by a loss of consciousness (30 sec after exposure). This progresses to apnea (3–5 min after exposure), cessation of cardiac activity (5–8 min after exposure), and death.

After exposure to lower concentrations, or exposure to lethal amounts via the oral or percutaneous routes, the effects are slower to develop. For example, after ingestion of a lethal dose of a cyanide salt, the casualty might have 15 to 30 minutes of survival time during which an antidote could be administered.

Prominent early signs and symptoms of cyanide poisoning include a transient hyperpnea, headache, dyspnea, and findings of general central nervous system (CNS) excitement, including anxiety, personality changes, and agitation progressing to seizures.<sup>33</sup> Diaphoresis, flushing, weakness, and vertigo may also be present. Late-appearing indications of CNS depression, such as coma and dilated, unresponsive pupils, are prominent signs of cyanide intoxication.<sup>33–35</sup> These signs are not specific for cyanide poisoning, which makes the distinction from other types of poisoning very difficult without a history of exposure. The telltale odor of bitter almonds cannot be used as a guide because 40% to 60% of the population is unable to detect the odor.<sup>36</sup>

Because the toxic effect of cyanide is to block tissue uptake and utilization of oxygen, the casualty is transiently flushed and may have other, related signs of poor tissue oxygen extraction. For example, fundoscopic examination shows an equally bright red color for retinal arteries and veins because of poor oxygen extraction. Increased oxygenation of venous blood is also responsible for a “cherry-red” skin color, but this sign may not always be present.

### Laboratory Findings

Relevant laboratory findings include an early decreased arteriovenous difference in the partial pressure of oxygen (P<sub>O</sub><sub>2</sub>) with progressive lactic acidosis.

Timely measurements of blood and urine concentrations for suspected intoxicants are useful in guiding clinical therapy, especially when there is toxicity associated with the treatment agents. Unfortunately, analysis of cyanide in biological fluids is a difficult task for a variety of reasons.<sup>37</sup> Also, measurements of blood cyanide concentrations are almost never available during the treatment phase. Blood concentrations of cyanide and associated clinical effects are shown in Table 10-3.

Documentation of blood cyanide levels is useful in confirming the clinical diagnosis and in subsequent follow-up investigations. The red blood cells

TABLE 10-3

### BLOOD CONCENTRATIONS OF CYANIDE AND ASSOCIATED CLINICAL EFFECTS

Cyanide Concentration (µg/mL)	Signs and Symptoms
0.2–0.5	None
0.5–1.0	Flushing, tachycardia
1.0–2.5	Obtunded
2.5–3.0	Coma
≥ 3.0	Death

Reprinted from Rumack BH. Cyanide poisoning. In: Newball HH, ed. Respiratory care of chemical casualties. In: *Proceedings of the Symposium on Respiratory Care of Chemical Casualties*. Fort Detrick, Frederick, Md: US Army Medical Research and Development Command; 28–30 November 1983: 186.

contain most of the cyanide in the blood, so an assay of whole blood is necessary. Furthermore, cyanide levels tend to fall in stored samples because of the compound’s short half-life, and this process can only partially be limited by optimal storage conditions. Therefore, the time of sampling and the conditions of storage are very important factors to consider and record.

Cyanide concentrations in tissue, such as liver, lung, spleen, and heart, may be more accurate indicators of the blood cyanide intoxication levels. Estimates of tissue levels are necessary adjunctive studies in forensic cases.<sup>38</sup> For details on collecting and analyzing blood and tissue for cyanide, see *Assay Techniques for Detection of Exposure to Sulfur Mustard, Cholinesterase Inhibitors, Sarin, Soman, GF, and Cyanide*, Technical Bulletin Medical 296.<sup>39</sup>

### Principles of Therapy

An understanding of the toxicology and pathophysiology of cyanide poisoning leads directly to the principles of therapy: eliminate further exposure, and institute supportive and specific antidotal therapy. (The specific antidotes are discussed separately in the section that follows.) In addition to the difficulties of diagnosing cyanide poisoning, each of the specific antidotal therapies discussed in this chapter has its own inherent toxicity. This knowledge should temper their use in the typical field medical treatment facility and other emergency setting.



### Elimination of Further Exposure

The first principle of therapy is the obvious one: eliminate any potential source of continuing cyanide poisoning:

- Remove the patient from an environment containing cyanide.
- Remove all contaminated clothing; rinse skin with soap and water or water alone if there is liquid on the skin.
- Gavage and administer activated charcoal if cyanide was ingested.

Following these steps can significantly decrease the amount of poison that has to be eliminated from the body.<sup>40</sup>

### Supportive Therapy

Possibly the most important elements of therapy are general supportive actions, which, by themselves, can effect the recovery of most casualties without further risk from specific antidotal therapy.<sup>41</sup> They are probably the only indicated therapies for casualties of cyanide poisoning who arrive conscious at the emergency medical treatment station.

As early as 1840, Blake<sup>42</sup> found that the lethal effects of cyanide are neutralized by mechanical resuscitation. The use of hyperbaric oxygen in cyanide intoxication is still controversial. Supplemental oxygen with or without assisted ventilation clearly augments the effect of specific antidotes in animal studies; however, despite encouraging reports,<sup>43,44</sup> there is inconclusive evidence of further benefit from the use of hyperbaric oxygen.

Lactic acidosis resulting from anaerobic metabolism should be treated by intravenous administration of sodium bicarbonate, and seizures should be controlled by the administration of anticonvulsants such as diazepam.<sup>45</sup> Because correction of deficiencies in tissue perfusion and oxygenation is the ultimate goal of supportive therapy and is also important for the success of specific antidotal therapy, it is critically important to maintain an effective cardiac rhythm; this can be accomplished with cardiopulmonary resuscitation, if necessary, in the early stages of treatment.

### Specific Antidotal Therapy

Casualties with advanced toxicity from a large amount of cyanide may require specific antidotal therapy in addition to the vigorous supportive therapy outlined above. The recommended agents or components of specific antidotal therapies for cyanide

poisoning vary according to country and medical custom (Table 10-4). This diversity seems to be based, in part, on where the drugs were initially developed and used. The aims of the recommended therapies are generally similar, however, in that one drug is given for immediate relief from the histotoxic effect of cyanide complexed with cytochrome oxidase.

In most of the regimens discussed below, the action of displacing cyanide from cytochrome oxidase is accomplished by the formation of methemoglobin. Methemoglobin removes cyanide from the extracellular fluid space and, by so doing, displaces cyanide from the intracellular fluid. The second component of most regimens is sodium thiosulfate, which is given as a specific antidote to augment the systemic clearance of cyanide via thiocyanate formation by sulfur transferases.

**TABLE 10-4**  
**CYANIDE ANTIDOTAL COMPOUNDS IN USE**

Antidote (Route of Administration)	Country
Sodium nitrite and sodium thiosulfate (IV)	United States, <sup>1</sup> Yugoslavia <sup>2</sup>
4-Dimethylaminophenol (IV or IM) and sodium thiosulfate (IV)	Germany <sup>3,4</sup>
Dicobalt edetate (IV)	United States, <sup>5</sup> Netherlands <sup>6</sup>
Hydroxocobalamin (IV)	United States, <sup>7,8</sup> France <sup>9</sup>

IM: intramuscular; IV: intravenous

Sources: (1) Chen KK, Rose CL, Clowes GHA. Methylene blue, nitrites and sodium thiosulfate against cyanide poisoning. *Proc Soc Exp Biol Med.* 1933;31:250–251. (2) Binenfeld Z. Antidote therapy in cases of poisoning by some heavy metals and cyanides and its risks. *Farm Glas.* 1971;27:1–6. (3) Bright JE, Marrs TC. A model for the induction of moderate levels of methaemoglobinaemia in man using 4-methylaminophenol. *Arch Toxicol.* 1982;50:57–64. (4) Kiese M. *Methemoglobinemia: A Comprehensive Treatise.* Cleveland, Ohio: CRC Press; 1974. (5) Marrs TC, Swanston DW, Bright JE. 4-Dimethylaminophenol and dicobalt edetate (Kelocyanor) in the treatment of experimental cyanide poisoning. *Hum Toxicol.* 1985;4:591–600. (6) Nagler J, Provoost RA, Parizel G. Hydrogen cyanide poisoning: Treatment with cobalt EDTA. *J Occup Med.* 1978;20:414–416. (7) Cottrell JE, Casthely P, Brodie JD, Patel K, Klein A, Turndorf H. Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. *JAMA.* 1978;298:809–811. (8) Mushett CW, Kelley KL, Boxer GE, Rickards JC. Antidotal efficacy of vitamin B<sub>12a</sub> (hydroxocobalamin) in experimental cyanide poisoning. *Proc Soc Exp Biol Med.* 1952;81:234–237. (9) Yacoub J, Faure J, Morena H, Vincent M, Faure H. Acute cyanide poisoning: Current data on the metabolism of cyanide and treatment with vitamin B<sub>12a</sub>. *Eur J Toxicol.* 1974;7:22–29.

## SPECIFIC ANTIDOTES

The clinical use of most antidotes is based on animal experiments<sup>46</sup> and on extrapolations made from a small number of clinical cases. Comparing results from animal studies has limitations because of the differences in experimental design from one study to another as well as marked interspecies differences in cyanide and drug metabolism. Moreover, the studies were not designed to resemble the usual emergency medical or battlefield scenario. The disparity of antidotes for cyanide is due to the following factors<sup>47,48</sup>:

- the small number of patients;
- the fact that most cyanide victims understandably receive several treatment agents;
- the lack of readily available, adequate analysis of blood and tissue concentrations; and
- the limited comparison studies that are available in animal models.

Antidotes are usually unnecessary if the casualty is conscious.

### Drugs Used in the United States

#### Nitrites

Amyl nitrite and sodium nitrite, with or without sodium thiosulfate, are used as antidotes for cyanide.<sup>49</sup> The antidotal action of amyl nitrite was first noted as early as 1888.<sup>50</sup>

The oxidized form of heme iron ( $\text{Fe}^{3+}$ ) in methemoglobin has a higher binding affinity for cyanide than does cytochrome oxidase. The preferential binding of cyanide to methemoglobin to form cyanomethemoglobin frees cytochrome oxidase to resume its role in aerobic metabolism.<sup>51</sup> In the United States and other countries, sodium nitrite has been used as the methemoglobin-inducing drug of choice.

In addition to methemoglobin formation, both sodium and amyl nitrite cause significant vasodilation, which warrants careful monitoring of blood pressure. Marked vasodilation with orthostatic hypotension, dizziness, and headache, in addition to the unpredictable levels of methemoglobin formed,<sup>52</sup> limit the utility of amyl nitrite in an upright casualty. Therefore, if a casualty is conscious and able to stand, he should not receive any nitrite. These factors, together with other concerns, have caused amyl nitrite to be removed from the cyanide antidote kit in the U.S. Army formulary for field units.

Sodium nitrite is available in the Lilly Cyanide Antidote Kit (manufactured by Eli Lilly and Company, Indianapolis, Ind.) in 10-mL ampules containing 300 mg for intravenous administration. (The kit also contains amyl nitrite encased in glass "pearls," which are meant to be broken so the drug can be inhaled.) The solution of sodium nitrite (30 mg/mL) should be given to an adult intravenously over 5 to 15 minutes, with careful monitoring of blood pressure. A single dose is sufficient to raise the methemoglobin level to 20% in an adult,<sup>53</sup> and a second dose, up to half as large as the initial one, can be given. Methemoglobin levels should be monitored if possible and kept below 35% to 40%, the range that is associated with oxygen-carrying deficits caused by methemoglobin itself.<sup>54</sup>

Because most automated clinical analyzers do not detect cyanomethemoglobin, the residual normal hemoglobin capable of oxygen transport can be overestimated by measuring total hemoglobin only. Methemoglobin-inducing substances should not be given to fire victims, even if cyanide intoxication is suspected, because neither methemoglobin nor carboxyhemoglobin (formed by carbon monoxide) transport oxygen. Alternative therapy in this situation consists of administering oxygen, thiosulfate, and other standard supportive measures.

In children, sodium nitrite can cause lethal methemoglobin levels if the dose is too high. The recommended dose for children is 0.33 mL of the 10% solution per kilogram of body weight.<sup>34,55</sup>

Some data indicate that nitrites exert their action by a mechanism other than methemoglobin formation. It has been suggested that the protective effect is due to the vasodilating effect of nitrite.<sup>52</sup> Several  $\alpha$ -adrenergic antagonists (eg, chlorpromazine, promethazine, promazine, and phenoxybenzamine) that cause vasodilation also antagonize cyanide toxicity.<sup>56,57</sup> Further information is needed to determine the mechanism or mechanisms by which chlorpromazine and phenoxybenzamine reverse cyanide intoxication.<sup>57</sup>

Several alternative methemoglobin-forming drugs that have different pharmacological properties from sodium nitrite have been investigated and used in other countries (see Table 10-4).

#### Other Methemoglobin-Forming Drugs

4-Dimethylaminophenol (4-DMAP), *p*-aminopropiophenone (PAPP), *p*-aminoheptanoylphenone

(PAHP), and *p*-aminooctanoylphenone (PAOP) are also methemoglobin-forming compounds that have protective effects against cyanide. 4-DMAP was proposed as a fast-acting antidote with low toxicity.<sup>58,59</sup> This German-developed compound is used in the German military and by the civilian population. In humans, intravenous injection of 4-DMAP (3 mg/kg) can produce a level of 15% methemoglobin within 1 minute.<sup>60</sup> In dogs, a dose of 4-DMAP that produces a 30% level of methemoglobin will save animals that have received 2 to 3 LD<sub>50</sub> of cyanide.<sup>61</sup>

The disadvantages of 4-DMAP are (1) the appearance of necrosis in the area of injection after intramuscular administration and (2) the possibility that extremely high levels of methemoglobin may occasionally result. Increases in pain, fever, and muscle enzymes also occur after intramuscular administration of the drug. 4-DMAP has been reported to produce positive results in the Ames test, which suggests that the compound may be a mutagen. PAHP appears to be the safest phenone of the series.<sup>62</sup>

### Thiosulfate and Other Sulfur Donors

Thiosulfate has been used primarily with sodium nitrite in a fixed antidotal regimen. The standard dose of sodium thiosulfate, which is supplied in the Lilly Cyanide Antidote Kit in 50-mL ampules, is 50 mL of the 250 mg/mL (12.5 g), given intravenously. A second treatment with half of the initial dose may be given. The pediatric dose is 1.65 mL per kilogram of body weight.<sup>55</sup>

The utility of thiosulfate is limited because of its short biological half-life and its small volume of distribution.<sup>23</sup> This combination of pharmacological properties, in addition to the suggestion that the presence of cyanide increases the intracellular availability of the thiosulfate,<sup>63</sup> indicates that this compound probably cannot be used as a prophylactic but only as an antidote. Compounds containing the more-lipophilic sulfane sulfur (R—S—S<sup>-</sup>) or compounds that can be actively transported into the cells may be more beneficial as cyanide antagonists,<sup>64-66</sup> but none are commercially available.

### Other Therapeutic Drugs

#### Cobalt Salts

Cobalt salts have been shown to be an effective means for binding cyanide *in vitro* and *in vivo*.<sup>67,68</sup> Kelocyanor, the cobalt salt of ethylenediamine-

tetraacetic acid (EDTA), which is commercially available in Europe but not in the United States, is administered intravenously.<sup>69</sup> In comparison studies against nitrite and hyposulfite, the cobalt chelate was thought to be superior<sup>31</sup>; however, in other studies the nitrite-thiosulfate combination was found to be superior.<sup>70</sup>

The drawback of cobalt compounds is their rather severe toxicity. Cardiac effects such as angina pectoris and ventricular arrhythmias, edema around the eyes, vomiting, and death have been observed.<sup>71</sup> A clinical caveat is that severe toxicity from cobalt can be seen even after initial recovery from acute cyanide poisoning.

#### Hydroxocobalamin

Hydroxocobalamin (vitamin B<sub>12a</sub>) is an effective antagonist of cyanide intoxication that binds cyanide directly without forming methemoglobin. It is useful under certain conditions such as in fire victims who may already have a decreased concentration of functioning hemoglobin.<sup>72</sup> It has a low toxicity even at high doses.<sup>73</sup> In addition, *in vitro* cyanide studies<sup>74</sup> have shown a greater affinity for hydroxocobalamin than for cytochrome oxidase. Sodium thiosulfate can improve the protection provided by hydroxocobalamin alone.<sup>46</sup>

There are several disadvantages in the clinical use of this drug. In rare instances, urticaria can result from hydroxocobalamin administration. More importantly, hydroxocobalamin has a relatively short shelf life because it decomposes in light. It may cause tachyphylaxis, which may limit its usefulness.<sup>75</sup> The cost of the drug is high, in part because so much is needed on a molar basis. At 1,346 grams per mole of hydroxocobalamin, a dose of at least 4 g is needed to neutralize a lethal amount of cyanide.

### Investigational Drugs

#### Prophylactic Drugs

PAPP and PAOP are also aminophenol derivatives. PAPP may not be active against cyanide intoxication; its metabolite, *p*-hydroxylaminopropiophenone, may be the active compound. This could account, in part, for the fact that cyanide toxicity *itself* changes the pharmacokinetics of the antidote.<sup>76</sup> PAPP reduces cyanide levels within red blood cells,<sup>77</sup> and its effect is greatly enhanced in the presence of sodium thiosulfate.<sup>78</sup> PAPP, PAHP, and PAOP all have pharmacokinetics that may al-

low for prophylactic administration.<sup>62,79</sup> Prophylactic methemoglobin formation could present its own problems, however, for victims of smoke inhalation or in other settings where high levels of carbon monoxide occur.<sup>33,80</sup>

A number of 8-aminoquinoline analogs of primaquine have also been studied as potential prophylactic drugs because they create elevated methemoglobin levels of long duration. Only preliminary information is available regarding the methemoglobin-forming potential of these drugs in humans.<sup>62,81,82</sup>

### Cyanohydrin-Forming Drugs

Aldehydes and carbonyl-related compounds (such as pyruvate,  $\alpha$ -ketoglutaric acid, glyoxal, and reducing sugars) form cyanohydrins from cyanide. This action may be a mechanism for improving the protection provided by nitrites.<sup>83</sup> Steinberg and Thomas<sup>84</sup> found that glyoxal trimer may be the most effective compound of the group that they examined. The relatively short half-lives of these reversible reactions and the drug dose required<sup>85</sup> may limit the clinical utility of this class of compounds.<sup>24</sup>

### SUMMARY

Cyanide, an ancient compound, is often associated with murders and assassinations. Because of the high amount needed to cause death and the inefficient weapons in which it was used, cyanide was not an effective chemical weapon in World War I; however, it was possibly used by Iraq against the Kurds in the Iran–Iraq War during the late 1980s.

Cyanide causes intracellular hypoxia by inhibiting the intracellular electron transport mechanism,

the cytochrome enzymes. After inhalation of a large amount of cyanide—as either hydrocyanic acid or cyanogen chloride—the onset of effects is within seconds, symptoms are few, physical findings are scanty, and death occurs within minutes.

The antidotes used in the United States, sodium nitrite and sodium thiosulfate, are quite effective if given before cessation of cardiac activity.

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### REFERENCES

1. Sykes AH. Early studies on the toxicology of cyanide. In: Vennesland B, Conn EE, Knowles CJ, Westley J, Wissing F, eds. *Cyanide in Biology*. New York, NY: Academic Press; 1981: 1–9.
2. Prentiss AM. *Chemicals in War: A Treatise on Chemical War*. New York, NY: McGraw-Hill; 1937: 171–175.
3. Robinson JP. The problem of chemical and biological warfare. Vol 1. In: Robinson JP, ed. *The Rise of CB Weapons: A Study of the Historical, Technical, Military, Legal and Political Aspects of CBW, and Possible Disarmament Measures*. New York, NY: Humanities Press; 1971: 155–156.
4. Baskin SI. Zyklon. In: La Cleur W, ed. *Encyclopedia of the Holocaust*. New Haven, Conn: Yale University Press; 1998: in press.
5. Lang JS, Mullin D, Fenyvesi C, Rosenberg R, Barnes J. Is the “protector of lions” losing his touch? *US News & World Report*. November 1986;10:29.
6. Heylin M, ed. US decries apparent chemical arms attack. *Chem Eng News*. 1988;66:23.
7. Medical expert reports use of chemical weapons in Iran–Iraq War. *UN Chronicle*. 1985;22:24–26.
8. Hall AH, Rumack BH, Schaffer MI, Linden CH. Clinical toxicology of cyanide: North American clinical experiences. In: Ballantyne B, Marrs TC, eds. *Clinical and Experimental Toxicology of Cyanides*. Bristol, England: Wright; 1987: Chap 12: 313–314.

9. Clark CJ, Campbell D, Reid WH. Blood carboxyhaemoglobin and cyanide levels in fire survivors. *Lancet*. 1981;i:1332–1335. Quoted in: Hall AH, Rumack BH, Schaffer MI, Linden CH. Clinical toxicology of cyanide: North American clinical experiences. In: Ballantyne B, Marrs TC, eds. *Clinical and Experimental Toxicology of Cyanides*. Bristol, England: Wright; 1987; Chap 12: 321–333.
10. Anderson RA, Harland WA. Fire deaths in the Glasgow area, III: The role of hydrogen cyanide. *Med Sci Law*. 1982;22:35–40.
11. Baud FJ, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med*. 1991;325(25):1761–1766.
12. Sidell FR. Chemical Casualty Consultant, Bel Air, Md. Personal communication, August 1996.
13. Wolnick KA, Fricke FL, Bonnin E, Gaston CM, Satzger RD. The Tylenol tempering incident—Tracing the source. *Anal Chem*. 1984;56(3):466A–470A, 474A.
14. Thompson RL, Manders WW, Cowan RW. Postmortem findings of the victims of the Jonestown tragedy. *J Forensic Sci*. 1987;32(2):433–443.
15. Hibbs CM. Cyanide and nitrate toxicoses of cattle. *Vet Hum Toxicol*. 1979;21:401–403.
16. Conn EE. Introduction. In: Evered D, Harnett S, eds. *Cyanide Compounds in Biology*. London, England: Wiley; 1988: 1–2. CIBA Foundation Symposium 140.
17. Vennesland B, Castric PA, Conn EE, Solomonson LP, Volini M, Westley J. Cyanide metabolism. *Fed Proc*. 1982;41:2639–2648.
18. Warburg O. Inhibition of the action of prussic acid in living cells. *Hoppe-Seyler's Z Physiol Chem*. 1911;76:331–346.
19. Keilin D. Cytochrome and respiratory enzymes. *Proc R Soc Lond B Biol Sci*. 1929;104:206–251.
20. Alexander K, Baskin SI. The inhibition of cytochrome oxidase by diaminomalenitrile. *Biochem Biophys Acta*. 1987;912:41–47.
21. Jarabak R, Westley J. Steady-state kinetics of 3-mercaptopyruvate sulfurtransferase from bovine kidney. *Arch Biochem Biophys*. 1978;185:458–465.
22. Westley J. Cyanide and sulfane sulfur. In: Vennesland B, Conn EE, Knowles CJ, Westley J, Wissing F, eds. *Cyanide in Biology*. New York, NY: Academic Press; 1981: 61–76.
23. Sylvester DM, Hayton WL, Morgan RL, Way JL. Effects of thiosulfate on cyanide pharmacokinetics in dogs. *Toxicol Appl Pharmacol*. 1983;69:265–271.
24. Porter DW, Baskin SI. The effect of three  $\alpha$ -keto acids on 3-mercaptopyruvate sulfurtransferase activity. *J Biochem Toxicol*. 1996;11:45–50.
25. Sorbo B. Enzymatic conversion of cyanide to thiocyanate. In: *Proceedings of the 1st International Pharmacology Meeting*. Vol 6. Stockholm, Sweden; 1962: 121–136.
26. Marrs TC. Antidotal treatment of acute cyanide poisoning. *Adverse Drug React Acute Poisoning Rev*. 1988;4:179–206.
27. Ballantyne B, Bright J, Swanston DW, Williams P. Toxicity and distribution of free cyanide given intramuscularly. *Med Sci Law*. 1972;12:209–219.
28. Ballantyne B. Toxicology of cyanides. In: Ballantyne B, Marrs TC, eds. *Clinical and Experimental Toxicology of Cyanides*. Bristol, England: Wright; 1987: 41–126.
29. Baskin SI, Wilkerson G, Alexander K, Blitstein AG. Cardiac effects of cyanide. In: Ballantyne B, Marrs TC, eds. *Clinical and Experimental Toxicology of Cyanides*. Bristol, England: Wright; 1987: 138–155.

30. Pitt BR, Radford EP, Gurtner GH, Traystman RJ. Interaction of carbon monoxide and cyanide on cerebral circulation and metabolism. *Arch Environ Health*. 1979;34:354–359.
31. Paulet G, Chary R, Bocquet P. The comparative value of sodium nitrite and cobalt chelates in the treatment of cyanide intoxication in non-anesthetized animals. *Arch Int Pharmacodyn*. 1969;127:104–117.
32. Haymaker W, Ginzler AM, Ferguson RL. Residual neuropathological effects of cyanide poisoning in dogs: A study of the central nervous system of 23 dogs exposed to cyanide compounds. *Mil Surg*. 1952;3:231–246.
33. Hall AH, Rumack BH. Clinical toxicology of cyanide. *Ann Emerg Med*. 1986;15:1067–1074.
34. Egekeze JO, Oehme FW. Cyanides and their toxicity: A literature review. *Vet Q*. 1980;2:104–114.
35. Izraeli S, Israeli A, Danon Y. Pharmacological treatment of cyanide poisoning. *Harefuah*. 1988;114:338–342.
36. Kirk RL, Stenhaus NS. Ability to smell solutions of KCN. *Nature*. 1953;171:698–699.
37. Groff WA Sr, Stemler FW, Kaminskis A, Froehlich HL, Johnson RP. Plasma free cyanide and blood total cyanide: A rapid completely automated microdistillation assay. *Clin Toxicol*. 1985;23:133–163.
38. Sunshine I, Finkle B. The necessity for tissue studies in fatal cyanide poisoning. *Int Archiv Gewerbepathol Gewerbehyg*. 1964;20:558–561.
39. Department of the US Army. *Assay Techniques for Detection of Exposure to Sulfur Mustard, Cholinesterase Inhibitors, Sarin, Soman, GF, and Cyanide*. Washington, DC: Headquarters, DA; 22 May 1996. Technical Bulletin Medical 296.
40. Lambert RJ, Kindler BL, Schaeffer DJ. The efficacy of superactivated charcoal in treating rats exposed to a lethal oral dose of potassium cyanide. *Ann Emerg Med*. 1988;17:595–598.
41. Graham DL, Laman D, Theodore J, Robin ED. Acute cyanide poisoning complicated by lactic acidosis and pulmonary edema. *Arch Intern Med*. 1977;137:1051–1055.
42. Blake J. Observations and experiments on the mode in which various poisonous agents act on the animal body. *Edinb Med Surg*. 1840;53:35–49.
43. Taitelman UZ. Oxygen. In: Meredith TJ, Jacobsen D, Haines JA, Berger J-C, van Heijst ANP, eds. *Antidotes for Poisoning by Cyanide*. Vol 2. In: *International Program on Chemical Safety/Commission of the European Communities Evaluation of Antidotes Series*. Geneva, Switzerland: World Health Organization and Commission of the European Communities; 1993: 27–40. Publication EUR 14280 EN.
44. Takano T, Miyazaki Y, Nashimoto I. Effect of hyperbaric oxygen on cyanide intoxication: In situ changes in intracellular oxidation reduction. *Undersea Biomed Res*. 1980;7:191–197.
45. Brivet F, Delfraissy JF, Bertrand P, Dormont J. Acute cyanide poisoning: Recovery with non-specific supportive therapy. *Intensive Care Med*. 1983;9:33–35.
46. Way JL, Sylvester D, Morgan RL, et al. Recent perspectives on the toxicodynamic basis of cyanide antagonism. *Fundam Appl Toxicol*. 1984;4:S231–S239.
47. Tadic V. Terapija akutnog trovanja cijanidima [in Serbo-Croatian]. *Vojnosanit Pregl*. 1981;38:117–119.
48. Meredith TJ, Jacobsen D, Haines JA, Berger J-C, van Heijst ANP, eds. *Antidotes for Poisoning by Cyanide*. Vol 2. In: *International Program on Chemical Safety/Commission of the European Communities Evaluation of Antidotes Series*. Geneva, Switzerland: World Health Organization and Commission of the European Communities: 1993. Publication EUR 14280 EN.
49. Potter AL. The successful treatment of two recent cases of cyanide poisoning. *Br J Ind Med*. 1950;7:125–130.

50. Pedigo LG. Antagonism between amyl nitrite and prussic acid. *Trans Med Soc Virginia*. 1888;19:124–131.
51. Groff WA Sr, Kaminskis A, Cucinell SA. Simultaneous determination of methemoglobin and total hemoglobin by a continuous-flow method. *Clin Chem*. 1974;20:1116–1120.
52. Way JL. Cyanide intoxication and its mechanism of antagonism. *Annu Rev Pharmacol Toxicol*. 1984;24:451–481.
53. Chen KK, Rose CL. Nitrite and thiosulfate therapy in cyanide poisoning. *JAMA*. 1952;149:113–119.
54. Bunn HF. Disorders of hemoglobin. In: Braunwald E, Wilson JD, Martin JB, Fauci AS. *Harrison's Principles of Internal Medicine*. 11th ed. New York, NY: McGraw-Hill; 1987: 1518–1527.
55. Berlin CM. The treatment of cyanide poisoning in children. *Pediatrics*. 1970;6:793–796.
56. Guth PS, Sprites MA. Antagonism of cyanide intoxication by chlorpromazine. *Fed Proc*. 1958;17:374.
57. Pettersen JC, Cohen SD. Antagonism of cyanide poisoning by chlorpromazine and sodium thiosulfate. *Toxicol Appl Pharmacol*. 1985;81:265–273.
58. Weger NP. Treatment of cyanide poisoning with 4-DMAP—Experimental and clinical overview. *Fundam Appl Toxicol*. 1983;3:387–396.
59. Vick JA, Froehlich H. Treatment of cyanide poisoning. *J Toxicol Clin Exp*. 1988;25:125–138.
60. Kiese M, Weger N. Formation of ferrihaemoglobin with aminophenols in the human for the treatment of cyanide poisoning. *Eur J Pharmacol*. 1969;7:97–105.
61. Lorcher W, Weger N. Optimal concentration of ferrihemoglobin for the treatment of cyanide poisoning. *Naunyn-Schmiedeberg's Arch Exp Pathol Pharmacol*. 1971;270(suppl):R88.
62. Rockwood GA, Baskin SI, Romano JA Jr, et al. *Effects of p-Aminopropiophenone (PAPP), p-Aminoheptanoylphenone (PAHP), and p-Aminooctanoylphenone (PAOP) Exposure on Methemoglobin, Sulfhemoglobin, Oxyhemoglobin, Oxygen Content, Reduced Hemoglobin, Oxygen Saturation, Carboxyhemoglobin, and Oxygen Capacity in Mice*. Aberdeen Proving Ground, Md: US Army Medical Research Institute of Chemical Defense; April 1996. USAMRICD-TR-95-06.
63. Binenfeld Z. Antidote therapy in cases of poisoning by some heavy metals and cyanides and its risks. *Farm Glas*. 1971;27:1–6.
64. Frankenberg L, Sorbo B. Effect of cyanide antidotes on the metabolic conversion of cyanide to thiocyanate. *Arch Toxicol*. 1975;33:81–89.
65. Baskin SI, Legere RH, Kirby SD, et al. Biochemical and pharmacological approaches to the development of cyanide antidotes. In: *Proceedings of NATO Research Study Group 3, Panel VIII/RSG-3. Part 1*. Aberdeen Proving Ground, Edgewood, Md: US Army Medical Research Institute of Chemical Defense; 1988: 539–544.
66. Rockwood GA, Porter DW, Baskin SI, Romano JA Jr. An in vitro assessment of cyanide (CN) detoxifying sulfur compounds. *Toxicologist*. 1993;13:249.
67. Evans CL. Cobalt compounds as antidotes for hydrocyanic acid. *Br J Pharmacol*. 1964;23:455–475.
68. Hillman B, Bardhan KD, Bain JTB. 1974. The use of dicobalt edetate (Kelocyanor) in cyanide poisoning. *Postgrad Med J*. 1974;50:171–174.
69. Marrs TC. Dicobalt edetate (Kelocyanor). In: Meredith TJ, Jacobsen D, Haines JA, Berger J-C, van Heijst ANP, eds. *Antidotes for Poisoning by Cyanide*. Vol 2. In: *International Program on Chemical Safety/Commission of the European Communities Evaluation of Antidotes Series*. Geneva, Switzerland: World Health Organization and Commission of the European Communities; 1993: 79–94. Publication EUR 14280 EN.

70. Rose CL, Worth RM, Kikuchi K, Chen KK. Cobalt salts in acute cyanide poisoning. *Proc Soc Exp Biol Med.* 1965;120:780–783.
71. Reynolds JEF, Prasad AB, eds. Dicobalt edetate (1033-p). In: *Martindale: The Extra Pharmacopoeia*. 28th ed. London, England: Pharmaceutical Press; 1982: 382.
72. Rose CL, Worth RM, Chen KK. Hydroxocobalamin and acute cyanide poisoning in dogs. *Life Sci.* 1965;4:1785–1789.
73. Vesey CL, Cole PV, Linnell JC, Wilson J. Some metabolic effects of sodium nitroprusside in man. *Br Med J.* 1974;2:140–142.
74. Lopes LCV, Campello AP. Effect of hydroxocobalamin on the inhibition of cytochrome *c* oxidase by cyanide, II: In isolated cytochrome *c* oxidase. *Res Commun Chem Pathol Pharmacol.* 1976;14:177–191.
75. Posner MA, Rodkey FL, Tobey RE. Nitroprusside-induced cyanide poisoning: Antidotal effect of hydroxocobalamin. *Anesthesiology.* 1976;44:330–335.
76. Liu L, Huang R. Pharmacokinetics and pharmacodynamics of *p*-aminopropiophenone in rabbits. *Zhongguo Yaoli Xuebao.* 1988;9:178–181.
77. Marrs TC, Bright JE. Effect on blood and plasma cyanide levels and on methaemoglobin levels of cyanide administered with or without previous protection using PAPP. *Hum Toxicol.* 1987;6:139–145.
78. Rose CL, Welles JS, Fink RD, Chen KK. The antidotal action of *p*-aminopropiophenone with or without sodium thiosulfate in cyanide poisoning. *J Pharmacol Exp Ther.* 1947;89:109–114.
79. Rockwood GA, Romano JA Jr, Scharf BA, Baskin SI. The effects of *p*-aminopropiophenone (PAPP) and *p*-aminooctoylphenone (PAOP) against sodium cyanide (CN) challenge and on righting and motor activity in mice. *Toxicologist.* 1992;12:271.
80. Hall AH, Rumack BH. Management of cyanide poisoning. *Ann Emerg Med.* 1988;17:108–109.
81. Steinhaus RK, Baskin SI, Clark JH, Kirby SD. Formation of methemoglobin and metmyoglobin using 8-aminoquinoline derivatives or sodium nitrite and subsequent reaction with cyanide. *J Appl Toxicol.* 1990;10(5):345–351.
82. Levine BC, Wheeler CW, Tomlinson MJ. Acute and subchronic oral toxicity of the anticyanide drug WR242511 tartrate. *The Toxicologist.* 1996;16:106. Abstract.
83. Moore SJ, Norris JC, Ho IK. The efficacy of  $\alpha$ -ketoglutaric acid in the antagonism of cyanide intoxication. *Toxicol Appl Pharmacol.* 1986;82:40–44.
84. Steinberg GM, Thomas NC. *Aldehyde Treatment in Cyanide Poisoning in Mice*. Alexandria, Va: Defense Technical Information Center; 1974. Report AD-779540.
85. Johnson WD. *Effects of Methemoglobin Versus Potassium Cyanide Intoxication*. Fort Detrick, Frederick, Md: US Army Research and Development Command; 1987. USAMRDC Report 7583-14: 1–75.